RAPID RECOMMENDATIONS

RAPID RECOMMENDATIONS: IMPROVING THE EFFICIENCY AND TRUSTWORTHINESS OF SYSTEMATIC REVIEWS AND GUIDELINES

By REED A.C. SIEMIENIUK, B.Sc., M.D.

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AUTHOR: Reed Siemieniuk, B.Sc., M.D., (McMaster University)

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ABSTRACT

Healthcare workers rely on clinical practice guidelines to inform their practice. However, most guidelines are not trustworthy when judged by accepted standards and they typically take several years to produce. Guideline trustworthiness is undermined by panel members who often have conflicts of interest, by including representation from only a subset of stakeholders, by failing to examine the entirety of the evidence systematically, and by rapid obsolescence. Further, they are often difficult for users to understand in limited time.

Rather than updating guidance on a fixed schedule, the *Rapid Recommendations* approach involves continuous monitoring of the literature and produces guidelines in response to new potentially practice-changing evidence. A collaborative network of clinicians, methodologists, and patients respond by rapidly producing trustworthy evidence syntheses and guidance. We have identified efficiencies at every step of the guideline development process.

The guideline panel does not include anyone with a financial conflict of interest and there are strict limits professional and intellectual conflicts. Systematic reviews are produced on the relative effects of each option, on prognosis, and on patient values and preferences with the explicit intent to inform the question at hand. The panel also considers practical issues. *Rapid Recommendations* are published in a concise multilayered user-friendly format headed by an interactive infographic that contains all of the necessary information for users need to make informed decisions at the point of care. The guideline is published simultaneously in print and electronically, including decision aids that can be used at the point of care and integrated into electronic medical records.

In this thesis, you will find a selection of exemplary publications relevant to the *Rapid Recommendations* process. We show that a responsive approach to rapid and trustworthy guideline creation is possible. It represents a way forward from the current limitations that plague most current clinical practice guidelines.

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If I learned anything through this process it's that nothing great in medical science happens in a vacuum. The success of an undertaking fully depends on the team of great people you're working with, and the team of great people supporting those working on the project. With that, I'm deeply indebted to the incredible people that I'm lucky to have around me.

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This is a "sandwhich thesis" compromised of 14 chapters

Chapter 1 (introduction) is unpublished. Reed Siemieniuk is the sole author

Chapter 2 is published in *The BMJ.* RS wrote the first draft. All authors conceived the idea, provided critical input, and approved the final version.

Chapter 3 is commissioned by *The BMJ* and currently unpublished. RS wrote the first draft. All authors conceived the idea, provided critical input, and approved the final version.

Chapter 4 is published in *The BMJ*. RS wrote the first draft. Frederick Spencer, Per Vandvik, RS, Thomas Agoritsas, and Gordon Guyatt conceived the study idea. RS performed the literature search and data analysis. RS, TA, Veena Manja, and GG interpreted the data analysis. RS and VM wrote the first draft of the manuscript. TA, VM, Tahira Devji, Yaping Chang, and Malgorzata Bala acquired the data and judged risk of bias in the studies. Lehana Thebane provided statistical advice. TA, VM, TD, YC, MB, and GG critically revised the manuscript. RS had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. RS is guarantor.

Chapter 5 is published in *The BMJ.* RS chaired the guideline panel and wrote the first draft. All authors critically revised it and approved the final version. RS is the guarantor.

Chapter 6 is published in *BMJ Open*. RS, GG conceived the study idea. RS and GG wrote the first draft of the manuscript. Paul Alexander, Reza Mirza, RS designed the search strategy. RS, Farid Foroutan, RM, PA, Arnav Agarwal, Arnaud Merglen, YC, Yuan Zhang, Hassan Mir, Elliot Hepworth, Yung Lee, Dena Zeraatkar screened abstracts and full texts. RS, FF, RM, PA, AA, AM, YC, YZ, HM, EH, YL, DZ acquired the data and judged risk of bias in the studies. RS and FF performed the data analysis. All authors interpreted the data analysis and critically revised the manuscript. RS had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. RS is the guarantor.

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CHAPTER 1: INTRODUCTION

Clinical practice guidelines are recommendations about how to care for people facing specific health situations.[1] Healthcare workers increasingly rely on clinical practice guidelines.[2] Many healthcare workers wait for authoritative guidelines before they change how they practice, even in the face of practice-changing evidence.[3 4] As guidelines continue to gain influence on how healthcare is provided, its increasingly important to ensure that clinical practice guidelines meet the needs of all stakeholders.

Most guidelines have major limitations: limitations that unwittingly echo throughout most areas of healthcare.[5] As a result, patients suffer and resources are used inefficiently. Guidelines may be problematic because they seriously violate accepted trustworthy standards, or they may have previously met all of the key trustworthiness standards but are now out of date.

In 2011, the then Institute of Medicine published a seminal white paper titled "Clinical Practice Guidelines We Can Trust" that established 21 trustworthiness criteria.[6] Unfortunately, almost no guidelines meet all of the trustworthiness criteria, and most did not even meet half.[7] Even the guidelines that do initially meet most of the trustworthy standards are often out of date by the time that they're published because it usually takes several years to create a comprehensive trustworthy guideline.[8]

In this thesis, we explore a solution to these problems with traditional guidelines. The *Rapid Recommendations* approach is a new approach to guideline creation that is responsive instead of scheduled. By developing individual guidelines in a responsive manner, guidelines can be created quickly, and adhere to all trustworthy standards. The *Rapid Recommendations* steering committee and co-founders include Per Vandvik, Thomas Agoritsas, Gordon Guyatt, and myself, and work under the MAGIC (Making GRADE the Irresistable Choice) non-profit research program.

There are several problems with traditional clinical practice guidelines worth highlighting. First, trustworthy guidelines take too long. Typical guidelines are cumbersome with 10 to 40 recommendations, each requiring one or more systematic reviews. Further, most guidelines have accumulated bureaucracies that slow down the process. Perhaps most importantly, typical guidelines are updated on a pre-defined schedule – often every 5-10 years.[9] When new studies are published that should change practice, the corresponding guideline might not be published for many years. In the meantime, patients receive substandard care. The *Rapid Recommendation* approach overturns this paradigm, by creating guidelines in response to new evidence.[10]

Second, most guidelines do not include all key stakeholders. They are most often written by experts in the field – often subspecialists who have dedicated their careers to treating afflicted patients and researching the topic. While their input is valuable, input from other stakeholders with different perspectives is critical such as general practitioners, allied health care providers, clinicians from other medical specialties, and most importantly the patients impacted by the disease or condition.[11] Including patients who do not necessarily have medical training on guideline panels is a challenge.[12] We are extremely fortunate to have had Lyubov Lytvyn, who is

focusing her PhD research on patient public involvement in guidelines, lead the development of our world-leading patient involvement programme.

Third, guidelines are not always based on systematic reviews of all the best available data.[7] Reviewing the entirety of the literature systematically reduces the risk of introducing bias that often occurs when selecting relevant scientific studies unsystematically.[13] There are three key pieces of information needed to inform any recommendation: i) what are the relative effects of the intervention, ii) what is the baseline risk for each outcome, and iii) what are the values and preferences of the patients to whom the recommendation will apply. Each of these three issues has published literature, and often warrants a separate systematic review. In the *Rapid Recommendations,* we explicitly decide whether or not to pursue a systematic review for each of these and, in some cases, demonstrated the feasibility of doing all three.[14 15]

Fourth, typical guidelines are dense documents that are difficult to grasp.[16] MAGICapp has focused efforts over the years to develop an electronic, interactive, and multilayered tool to publish guidelines.[17] We have leveraged the work that Linn Brandt, Thomas Agoritsas, Per Vandvik, and many others spent developing MAGICapp to present all of our recommendations in digestible format. The hope is to make our guidelines "as simple as possible, but not simpler". In addition, with the help of *The BMJ's* lead graphic designer, Will Stahl-Timmins, we have created interactive infographics that contain all of the information necessary to implement our recommendations.

Even if we were able to succeed in all of the measures outlined above, would clinicians access and use guidelines created by a loose group of researchers without the endorsement of recognized a professional society or other organization?

In order to prove that the *Rapid Recommendation* approach to clinical practice guidelines was feasible, we needed an audience and publication platform. In 2016, we reached an agreement with *The BMJ* to co-publish the *BMJ Rapid Recommendation* series. We have worked closely with Helen Macdonald and others from *The BMJ* to develop and implement our approach. The recommendations are also co-published in a fully electronic version on MAGICapp. At the time of writing, we have published sixteen *BMJ Rapid Recommendations*, with several more in process. Several groups are already starting to emulate our process. In this thesis, you will find a selection of exemplary publications relevant to the *Rapid Recommendation process.* A short description puts each of these papers in context follows.

Chapter 2: *Introduction to BMJ Rapid Recommendations*[10]
This editorial introduces the *BMJ Rapid Recommendation* project. The electronic version is accompanied by a video describing the process to create a *Rapid Recommendation.* A table describes the problems with traditional guidelines that the *Rapid Recommendation* approach addresses.

Chapter 3: *Rapid Recommendations: how to create and disseminate trustworthy responsive clinical practice guidelines*

This paper goes into detail about how *Rapid Recommendations* work: it provides a roadmap for others who are interested in creating a similar product. It describes several of the advances in systematic review and guideline methodology that were necessary to develop *Rapid Recommendations.*

Chapter 4: *Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis: a systematic review*[18]
The paper presents a rapid systematic review informing the first *Rapid Recommendation.* This paper demonstrated the feasibility of creating and publishing a trustworthy systematic review in just a few months.
We were one of the first to use Kaplan-Meier curves to reconstruct time-based individual patient data for a detailed picture to estimate the time-changing nature of some outcomes. We were the first to successfully use GRADE to evaluate the quality of the evidence from such an exercise. In this study, the risk of death was higher with surgery, but the increased risk was limited to the first few months after surgery. This cautioned the panel to make a weak rather than strong recommendation, because it gave the panel a clue that the mortality benefit with TAVI might not last long term. The method has since been used much more widely in meta-analysis.

Chapter 5: *Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline*[19]
This is a *Rapid Recommendation* on the use of arthroscopy for degenerative knee disease. We made a strong recommendation against the use of arthroscopy.
Advances in this paper: we incorporated data on subjective patient-reported outcomes using a linked meta-analysis on minimally important differences (MIDs).[20] Making a strong recommendation implies that almost all informed patients would choose the same course of action, and that the evidence is unlikely to substantially change. Arthroscopy reduces pain and improves function in the short term, but the effects do not last. Based on the review of MIDs, the guideline panel unanimously agreed that almost no one would choose to go through the pain and recovery period for such a small short-term benefit. This approach to incorporating MIDs has since been successfully adopted by others.[21 22]

Chapter 6: *Antiretroviral therapy for pregnant women living with HIV or hepatitis B: a systematic review and meta-analysis*[23]
This is a network meta-analysis of medications used to treat HIV and hepatitis B in pregnancy showed that tenofovir probably increases the risk of stillbirth and early neonatal mortality. The focus of the guideline was women living with HIV, but we were guided by the linked guideline panel to look at indirect evidence from women with hepatitis B, and for adverse effects, from non-pregnant adults living with HIV.

Chapter 7: *Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline*[24]
This is a *Rapid Recommendation* on medications for pregnant women living with HIV. The review above found that a tenofovir probably increases risk of stillbirth. Another linked systematic review provided evidence that pregnant women living with HIV place an extremely high value on avoiding stillbirth. With these two key pieces of information, we were able to make a defensible

recommendation against tenofovir. This recommendation contradicted guidelines from the World Health Organization and others, which took a public health perspective and recommend tenofovir because of resource use and feasibility. A linked editorial called on the WHO to reprioritize the needs of women when making recommendations.

Chapter 8: *Corticosteroids for treatment of sore throat: systematic review and meta-analysis of randomised trials*[25]
A review showed that an ultra-short course of corticosteroids were more effective than placebo at reducing severity and duration of symptoms in patients with sore throat, without substantially increasing the risk of adverse effects.

Chapter 9: *Antibiotics after incision and drainage for uncomplicated skin abscesses: a clinical practice guideline*[26]
We recommended clindamycin or trimethoprim-sulfamethoxazole for patients with skin abscesses. The balance of desirable and undesirable consequences was close, and we therefore include a detailed description of what the shared-decision making process should look like.

Chapter 10: *Corticosteroid therapy for sepsis: a clinical practice guideline*[27]
Our guideline panel made a weak recommendation in favour of corticosteroids in patients with all severities of sepsis.

Chapter 11: *Oxygen therapy for acutely ill medical patients: a clinical practice guideline*[28]
Based on evidence that too much oxygen can be harmful, we were able to make recommendations for both when to initiate (or titrate up) and when to stop (or titrate down) oxygen therapy. We did this based on subsets of patients enrolled in the trials at the upper and lower ends of the oxygen saturation.

Chapter 12: *Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline*[15]
The decision to use GI bleeding prophylaxis or not depends on the baseline risk of bleeding, and on the relative efficacy and harms of the available options. We guided the panel through the complex decision making process, and came to recommendations that can be tailored based on a GI bleeding risk score that we developed. There was a lot of forethought put into the interactive graphical presentation of the complex decision-making process, to make the guideline as useable as possible for frontline clinicians.

Chapter 13: *The next frontier in critical care guidelines: rapid and trustworthy recommendations*
This editorial paper introduces a spin-off of the *Rapid Recommendations:* Rapid Recommendations in Intensive Care. This network produced *Rapid Recommendations* on two important topics in Critical Care. This provides one example of how the processes we developed can be adapted by other guideline developers.

References

1. Wilson MC, Hayward RSA, Tunis SR, et al. Users' Guides to the Medical Literature: VIII. How to Use Clinical Practice Guidelines B. What Are the Recommendations and Will They Help You in Caring for Your Patients? *JAMA* 1995;274(20):1630-32. doi: 10.1001/jama.1995.03530200066040
2. Nigam A. Changing health care quality paradigms: the rise of clinical guidelines and quality measures in American medicine. *Soc Sci Med* 2012;75(11):1933-7. doi: 10.1016/j.socscimed.2012.07.038 [published Online First: 2012/08/28]
3. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *Lancet* 1993;342(8883):1317-22. doi: 10.1016/0140-6736(93)92244-n [published Online First: 1993/11/27]
4. Lugtenberg M, Burgers JS, Westert GP. Effects of evidence-based clinical practice guidelines on quality of care: a systematic review. *Qual Saf Health Care* 2009;18(5):385-92. doi: 10.1136/qshc.2008.028043 [published Online First: 2009/10/09]
5. Lenzer J. Why we can't trust clinical guidelines. *Bmj* 2013;346:f3830. doi: 10.1136/bmj.f3830 [published Online First: 2013/06/19]
6. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice G. In: Graham R, Mancher M, Miller Wolman D, et al., eds. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US)

7. Kung J, Miller RR, Mackowiak PA. Failure of clinical practice guidelines to meet institute of medicine standards: Two more decades of little, if any, progress. *Arch Intern Med* 2012;172(21):1628-33. doi: 10.1001/2013.jamainternmed.56 [published Online First: 2012/10/24]
8. Martinez Garcia L, Sanabria AJ, Garcia Alvarez E, et al. The validity of recommendations from clinical guidelines: a survival analysis. *Cmaj* 2014;186(16):1211-9. doi: 10.1503/cmaj.140547 [published Online First: 2014/09/10]
9. Alonso-Coello P, Martinez Garcia L, Carrasco JM, et al. The updating of clinical practice guidelines: insights from an international survey. *Implement Sci* 2011;6:107. doi: 10.1186/1748-5908-6-107 [published Online First: 2011/09/15]
10. Siemieniuk RA, Agoritsas T, Macdonald H, et al. Introduction to BMJ Rapid Recommendations. *Bmj* 2016;354:i5191. doi: 10.1136/bmj.i5191 [published Online First: 2016/09/30]
11. Armstrong MJ, Bloom JA. Patient involvement in guidelines is poor five years after institute of medicine standards: review of guideline methodologies. *Res Involv Engagem* 2017;3:19. doi: 10.1186/s40900-017-0070-2 [published Online First: 2017/10/25]
12. Legare F, Boivin A, van der Weijden T, et al. Patient and public involvement in clinical practice guidelines: a knowledge synthesis of existing programs. *Med Decis Making* 2011;31(6):E45-74. doi: 10.1177/0272989x11424401 [published Online First: 2011/10/01]
13. Annane D, Jaeschke R, Guyatt G. Are systematic reviews and meta-analyses still useful research? Yes. *Intensive Care Med* 2018;44(4):512-14. doi: 10.1007/s00134-018-5102-3 [published Online First: 2018/04/18]
14. Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk:

a clinical practice guideline. *Bmj* 2016;354:i5085. doi: 10.1136/bmj.i5085 [published Online First: 2016/09/30]

15. Ye Z, Reintam Blaser A, Lytvyn L, et al. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. *Bmj* 2020;368:l6722. doi: 10.1136/bmj.l6722 [published Online First: 2020/01/08]
16. Kastner M, Bhattacharyya O, Hayden L, et al. Guideline uptake is influenced by six implementability domains for creating and communicating guidelines: a realist review. *J Clin Epidemiol* 2015;68(5):498-509. doi: 10.1016/j.jclinepi.2014.12.013 [published Online First: 2015/02/17]
17. Vandvik PO, Brandt L, Alonso-Coello P, et al. Creating clinical practice guidelines we can trust, use, and share: a new era is imminent. *Chest* 2013;144(2):381-89. doi: 10.1378/chest.13-0746 [published Online First: 2013/08/07]
18. Siemieniuk RA, Agoritsas T, Manja V, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis. *Bmj* 2016;354:i5130. doi: 10.1136/bmj.i5130 [published Online First: 2016/09/30]
19. Siemieniuk RAC, Harris IA, Agoritsas T, et al. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *Bmj* 2017;357:j1982. doi: 10.1136/bmj.j1982 [published Online First: 2017/05/12]
20. Devji T, Guyatt GH, Lytvyn L, et al. Application of minimal important differences in degenerative knee disease outcomes: a systematic review and case study to inform BMJ Rapid Recommendations. *BMJ Open* 2017;7(5):e015587. doi: 10.1136/bmjopen-2016-015587 [published Online First: 2017/05/13]
21. Busse JW, Craigie S, Juurlink DN, et al. Guideline for opioid therapy and chronic noncancer pain. *Cmaj* 2017;189(18):E659-e66. doi: 10.1503/cmaj.170363 [published Online First: 2017/05/10]
22. Vandvik PO, Lahdeoja T, Ardern C, et al. Subacromial decompression surgery for adults with shoulder pain: a clinical practice guideline. *Bmj* 2019;364:l294. doi: 10.1136/bmj.l294 [published Online First: 2019/02/08]
23. Siemieniuk RA, Foroutan F, Mirza R, et al. Antiretroviral therapy for pregnant women living with HIV or hepatitis B: a systematic review and meta-analysis. *BMJ Open* 2017;7(9):e019022. doi: 10.1136/bmjopen-2017-019022 [published Online First: 2017/09/13]
24. Siemieniuk RAC, Lytvyn L, Mah Ming J, et al. Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline. *Bmj* 2017;358:j3961. doi: 10.1136/bmj.j3961 [published Online First: 2017/09/13]
25. Sadeghirad B, Siemieniuk RAC, Brignardello-Petersen R, et al. Corticosteroids for treatment of sore throat: systematic review and meta-analysis of randomised trials. *Bmj* 2017;358:j3887. doi: 10.1136/bmj.j3887 [published Online First: 2017/09/22]
26. Vermandere M, Aertgeerts B, Agoritsas T, et al. Antibiotics after incision and drainage for uncomplicated skin abscesses: a clinical practice guideline. *Bmj* 2018;360:k243. doi: 10.1136/bmj.k243 [published Online First: 2018/02/14]

27. Lamontagne F, Rochwerg B, Lytvyn L, et al. Corticosteroid therapy for sepsis: a clinical practice guideline. *Bmj* 2018;362:k3284. doi: 10.1136/bmj.k3284 [published Online First: 2018/08/12]
28. Siemieniuk RAC, Chu DK, Kim LH, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. *Bmj* 2018;363:k4169. doi: 10.1136/bmj.k4169 [published Online First: 2018/10/26]

CHAPTER 2: Introduction to BMJ Rapid Recommendations

This editorial introduces the *BMJ Rapid Recommendation* project. We outline the major limitations of current clinical practice guidelines and describe how we plan to address them. The electronic version is accompanied by a video describing the process to create a *Rapid Recommendation.* A table describes the problems with traditional guidelines that the *Rapid Recommendation* approach addresses.

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Link to accompanying video:
https://youtu.be/KnF0AOqZD3E

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EDITORIALS

Introduction to *BMJ* Rapid Recommendations

New BMJ collaboration accelerates evidence into practice to answer the questions that matter quickly and transparently through trustworthy recommendations

Reed A Siemieniuk *methodologist*[1 2], Thomas Agoritsas *assistant professor*[1 3], Helen Macdonald *acting head of education section*[4], Gordon H Guyatt *distinguished professor*[1 5], Linn Brandt *methodologist*[6], Per O Vandvik *associate professor*[6 7]

[1]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada L8S 4L8; [2]Department of Medicine, University of Toronto, Toronto, Ontario, Canada; [3]Division of General Internal Medicine, and Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland; [4]*The BMJ*, London WC1H 9JP, UK; [5]Department of Medicine, McMaster University, Hamilton, Ontario, Canada L8S 4L8; [6]Institute of Health and Society, Faculty of Medicine, University of Oslo, 0318 Oslo, Norway; [7]Department of Medicine, Innlandet Hospital Trust-division, Gjøvik, Norway

Find a committee. Add evidence, opinion, politics, and money in varying measures, and a murky set of recommendations can emerge. To those on the outside, guideline production may seem like a black box, and, unless it is carefully and transparently managed, loss of trust, patient suffering, waste, and over and under treatment can occur. Clinicians and patients who implement recommendations may feel disenfranchised by the pronouncements of researchers, publishers, and guideline writers. In an era when clinicians and patients aim to discuss and select management options that seem right for them, it is clear that we can do better.[1] An initiative from the MAGIC non-profit research and innovation programme—representing patients, front-line clinicians, researchers, and guideline experts (www.magicproject.org)—has resulted in a collaboration with *The BMJ*. We aim to promptly translate emerging research to user friendly and trustworthy recommendations, evidence summaries, and decision aids.

During the hiatus between new evidence and guideline publication, many patients receive outdated care; it can take years for evidence to filter into guidelines from specialty or government organisations, which face bureaucratic hurdles to updating. Some profit making organisations have capitalised on this gap in the market by providing rapid updates for doctors based on new evidence. But what is gained in speed may be sacrificed in quality if their recommendations are not underpinned by systematic reviews or have a quality process for developing recommendations.

We can all do better, especially when everyone is included and we use the many tools at our disposal. We have the technology and methodology to rapidly incorporate new data into the body of evidence in systematic reviews. We have systems and methodologies to rate and appraise our certainty in the evidence, such as GRADE.[2] The guideline community has described what a trustworthy guideline is.[3] We understand that, to discuss the options, users need the best absolute estimates of benefit and harm, knowledge of the quality of research, an honest offer on the limits of our knowledge, and detail on the resources needed.[2 4] We hope that this project will address a partly characterised spectrum of problems with guidelines and their recommendations, including those mentioned in table 1⇓.

The Rapid Recommendations team from MAGIC, including *The BMJ*, will identify and confirm which studies that might change practice and are of interest to their readers. Researchers will then perform systematic reviews on the benefit and harm of the intervention, baseline risk of important outcomes, and the values and preferences of patients. In parallel a panel including researchers, patients, and doctors will choose the most important outcomes. They will consider the systematic reviews and evaluate the evidence using a GRADE approach, and produce recommendations for practice. The research and recommendations will be submitted to *The BMJ* for peer review and publication (fig 1).

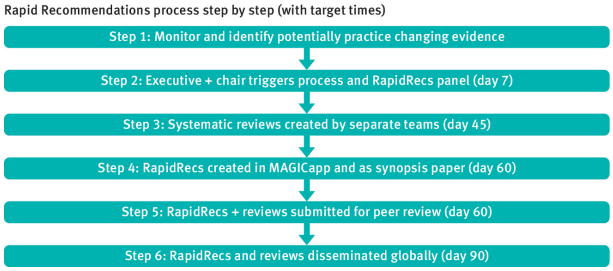

Fig 1 The Rapid Recommendations process step by step with target times

Correspondence to: P O Vandvik per.vandvik@gmail.com

Those who have and will contribute to the project bring diverse experience and anticipate that in working together the sum of our efforts will equal more than our parts. We hope to translate current best evidence into formats that can enhance clinical judgement and discussions with patients.

We hope to demonstrate that state of the art systematic reviews and trustworthy guidelines can be created and published rapidly; that guideline panels need not have worrisome conflicts of interest; that patient, generalist, and allied health professional panellists improve guideline quality; and that recommendations used in guidelines can facilitate shared conversations and decision-making at an individual level. Each guideline panel will consider the expected spectrum in patient values and preferences, the quality of the evidence, the magnitude of benefits and harms, and other key practical issues (such as resources).[5 6]

Published here is the first batch of *BMJ* Rapid Recommendations, together with linked systematic reviews (box 1).[7-10] Readers will find the recommendations, evidence summaries, and consultation decision aids in multilayered digital formats available on MagicApp for use at the point of care. Please read them, try them, and feed back if you find them helpful or if there is anything else that might be helpful. This project has just started and is designed to change as we go.

Competing interests: We have read and understood the BMJ Group policy on declaration of interests and declare that POV, TA, LB, and GHG are founders and board members of the non-profit organisation MAGIC.

1 McCartney M, Treadwell J, Maskrey N, Lehman R. Making evidence based medicine work for individual patients. *BMJ* 2016;353:i2452. doi:10.1136/bmj.i2452 pmid:27185764.
2 Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. doi:10.1136/bmj.39489.470347.AD pmid:18436948.
3 Laine C, Taichman DB, Mulrow C. Trustworthy clinical guidelines. *Ann Intern Med* 2011;154:774-5. doi:10.7326/0003-4819-154-11-201106070-00011 pmid:21646561.
4 Agoritsas T, Heen AF, Brandt L, et al. Decision aids that really promote shared decision making: the pace quickens. *BMJ* 2015;350:g7624. doi:10.1136/bmj.g7624 pmid:25670178.
5 Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ* 2016;353:i2089. doi:10.1136/bmj.i2089 pmid:27365494.
6 Alonso-Coello P, Schünemann HJ, Moberg J, et al. GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ* 2016;353:i2016. doi:10.1136/bmj.i2016 pmid:27353417.
7 Foroutan F, Guyatt GH, O'Brien K, et al. Prognosis after surgical replacement with a bioprosthetic aortic valve in patients with severe symptomatic aortic stenosis: systematic review of observational studies. *BMJ* 2016;354:i5065. doi:10.1136/bmj.i5065.
8 Lytvyn L, Guyatt GH, Manja V, et al. Patient values and preferences on transcatheter or surgical aortic valve replacement therapy for aortic stenosis: a systematic review. *BMJ Open* 2016;6:e014327. doi:10.1136/bmjopen-2016-014327.
9 Siemieniuk RA, Agoritsas T, Manja V, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis. *BMJ* 2016;354:i5130. doi:10.1136/bmj.i5130.
10 Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ* 2016;354:i5085. doi:10.1136/bmj.i5085.

Box 1: Linked articles in this *BMJ* Rapid Recommendations cluster

- Siemieniuk RA, Agoritsas T, Manja V, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis. *BMJ* 2016;354:i5130. doi:10.1136/bmj.i5130
- Foroutan F, Guyatt GH, O'Brien K, et al. Prognosis after surgical replacement with a bioprosthetic aortic valve in patients with severe symptomatic aortic stenosis: systematic review of observational studies. *BMJ* 2016;354:i5065. doi:10.1136/bmj.i5065
- Lytvyn L, Guyatt GH, Manja V, et al. Patient values and preferences on transcatheter or surgical aortic valve replacement therapy for aortic stenosis: a systematic review. *BMJ Open* 2016;6:e014327. doi:10.1136/bmjopen-2016-014327
- Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ* 2016;354:i5085. doi:10.1136/bmj.i5085
  – Summary of the results from the Rapid Recommendation process
- Magic App (www.magicapp.org/public/guideline/aEeKpL)
  – Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

Table

Table 1| **Problems with and solutions for guidelines and recommendations***

Problems with current guidelines	**Improvement offered with *BMJ* Rapid Recommendations**
Guidelines may…	
Speed– …take too long to produce	• We will publish recommendations soon after new potentially practice-changing evidence becomes available • We will publish a short set of recommendations pertinent to the new development rather than an extensive and comprehensive guideline on a topic • We hope that institutional guideline makers will adapt the recommendations them to their system
People– …include an incomplete spectrum of physicians, allied healthcare workers, and patients that ultimately use the recommendations	• We will include relevant end-users including front-line clinicians, allied healthcare workers, and patient representatives as full panel members with the ability to influence the process from the choice of outcomes considered to writing the recommendations • Guidelines will be peer reviewed by a similar spectrum of people, including patients
Interests— …include those with a perceived or actual financial stake in the topic	• No person with financial interests judged by the team as even possibly relevant will participate in the recommendation panel
Interests— …include those with professional and intellectual conflicts which are unreported and unmanaged	• Only a minority with possible intellectual and professional conflicts will be included as panel members • Professional and intellectual conflicts will be published
Data— …be based on unreliable/unsystematic data or without formal quality assessment by outcome	• Each recommendation panel will consider data based on relevant systematic reviews • GRADE evidence summaries from the systematic reviews will support each recommendation
Data— …fail to consider or report the magnitude of benefits and harms	• The best available estimates of absolute risks and benefits will be presented for every outcome
Data— …fail to consider or report on patient-important outcomes or expected patient values and preferences	• Each panel will include patient representatives and will list all considerations important to them at the outset • Panels will systematically consider and report literature on patient values and preferences
Practical considerations— …fail to make practical issues such as medication, routine, or social limitations clear	• All known practical issues will be considered and reported
Usability— …provide too much or poorly formatted information to prove useful to the user	• Clear information for healthcare professionals, researchers, and patients including precisely phrased recommendations, concise evidence summaries, and consultation decision aids in MAGICapp

*This list is not exhaustive but aligns with standards for trustworthy guidelines.[3]

CHAPTER 3: Rapid Recommendations: how to create and disseminate trustworthy responsive clinical practice guidelines

This paper goes into detail about how *Rapid Recommendations* work: it provides a roadmap for others who are interested in creating a similar product. It describes several of the advances in systematic review and guideline methodology that were integral to developing *Rapid Recommendations.*

Publication:
This publication has been commissioned by *The BMJ*. It is currently undergoing critical revisions by *The BMJ* editorial team.

Rapid Recommendations: how to create and disseminate trustworthy responsive clinical practice guidelines

Reed Siemieniuk, Thomas Agoritsas, Helen Macdonald, Gordon Guyatt, Per Vandvik

The problem of outdated guidelines

Of the 3000 to 4000 publications currently indexed in Medline each day, over 100 are randomised trials 2 3. Because most clinicians do not have the skills to critically appraise the primary literature, and none have the time7 8, they rely on clinical practice guidelines to inform their practice20. Current guidelines are typically written by a group of clinical experts who have carefully considered the evidence on a topic. They are massive undertakings that typically take several years to produce21.

Panel member conflicts of interests seriously undermine the trustworthiness of most guidelines. Some argue professional societies should stop producing guidelines, given their inherent conflicts of interest and their failure to address them appropriately22.

Such guidelines are plagued not only by conflict of interest, but also by rapid obsolescence: delays in adapting to new evidence leaves clinicians and patients unable to make well-informed decisions. The guideline community urgently needs to remedy the situation by producing and disseminating recommendations rapidly responsive to practice changing evidence, presented in more user-friendly formats. In doing so, guideline panels cannot sacrifice adherence to widely accepted – though far from always followed 23-25 methodologic standards 26 27. These standards, needed to produce trustworthy content, include effective management of conflict of interest; appropriate panel selection that includes patient involvement; conduct or identification of sound systematic reviews; rating quality of evidence and strength of recommendations; and undergoing peer review.

Enhancing the Evidence Ecosystem

The inefficient flow of new evidence into recommendations originates from a larger problem pervasive throughout the *Evidence Ecosystem (see Figure 1)* of medical science: contributors too often act in silos28. The Making GRADE the Irresistable Choice (MAGIC) group, is working to improve this problem, through various efforts one of which, BMJ Rapid Recommendations, represents the focus of this article29.

Figure 1: Actors and flow of data in the current evidence ecosystem. The objectives of the Rapid Recommendations are focused on bridging and enhancing evidence synthesis and its dissemination to clinicians and patients.

Rapid Recommendations: a new approach

Our work with numerous organisations producing guidelines has highlighted the need for an alternative approach that circumvents the cultural, political, and bureaucratic barriers rife among such organisations. The Rapid Recommendations project is a response to this challenge: a collaborative network of clinicians, methodologists, and patients who respond to potentially practice-changing evidence with evidence syntheses and trustworthy guidance. The Rapid Recommendations project started in 2016 as a partnership between MAGIC and the BMJ30. Here, we provide a road map for others interested in similar approaches, highlight lessons learned, and outline remaining challenges.

Overview

The BMJ Rapid Recommendations process involves continuous monitoring of the literature for potentially practice-changing studies and, when such a study is identified, rapid production and dissemination of new recommendations. We have found efficiencies at each step in the process, while maintaining high quality work. Key components include parallel rather than linear systematic review and guideline creation; strict conflict of interest management; patient partnership; efficient editorial and peer review; and widespread dissemination, including traditional publication formats, interactive infographics, decision aids, and multi-layered electronic publication through MAGIC's electronic platform, the MAGICapp.

Methods

Below, we describe each critical phase of producing a BMJ Rapid Recommendation, highlight lessons learned, and identify remaining challenges. See Appendix 1 for an overview of how BMJ Rapid Recommendations meets trustworthy guideline standards.

Identifying practice changing evidence and initiation of a Rapid Recommendation

In collaboration with McMaster Health Information Research Unit, we designed an online platform for the monitoring potentially practice-changing studies, based on its Premium LiteratUre Service (PLUS)31 32. Trained research staff continually critically appraise tens of thousands of articles each year, identifying methodologically sound studies. A large network of front-line clinicians then identifies studies that are important for their practice.

Every day, a member of our team reviews the studies - approximately 5 per day - and upon identifying a candidate practice-changing study seekd input from content experts, and BMJ journal editors. There are a number of key considerations when deciding whether or not to initiate a Rapid Recommendation (Box A):

1. Is the question sufficiently important (for instance, are large numbers of people/patients affected?

2. Reviewing current recommendations, and expert sense of current practice, could the evidence lead to new recommendations that would change practice?

3. Given logistic considerations and capacity due to competing topics, can the Rapid Recommendation team rapidly produce a new set of compelling, trustworthy recommendations

Box A. *Study characteristics to consider when choosing a Rapid Recommendation topic*

Example: Change in evidence

In June 2018, an RCT was published showing a benefit with antibiotics for patients with uncomplicated skin abscesses[33]. Prior to this, low quality evidence – and recommendations - suggested that antibiotics were not beneficial[34]. The BMJ Rapid Rec systematic review showed that the new study shifted the pooled estimates to favour antibiotics, resulting in a Rapid Rec weak recommendation (the benefit was small in magnitude) in favour of antibiotics[19].

Example: Controversy

In March 2018, two large RCTs with apparently conflicting results addressed the use of corticosteroids for patients with sepsis[35] [36], generating considerable interest and debate. The Rapid Recs team rapidly produced an urgently needed systematic synthesis of the evidence[37] that informed the guideline panel's weak recommendation in favour of steroid use (the mortality benefit was small and remains uncertain) [38].

Example: Anticipation of an impending large study necessitating guideline updating
Through contacts in the worldwide evidence-based community, the Rapid Recs team was aware of the impending publication of a major trial that addressed PSA testing for prostate cancer screening[39]. We anticipated that the results of the 419 582 participant trial would necessitate an update to the guideline, regardless of its results, and so mobilized for rapid production of a new systematic review and guideline that ultimately made a weak recommendation against screening (weak because some men may consider the very small and questionable benefits worthwhile) [40].

Contributors

Creating a Rapid Recommendation requires efficient coordination of many people in a number of roles, each of which are outlined in Appendix 2. All roles and tasks are coordinated by the Rapid Recommendation steering committee (POV, RS, GG, TA, LL, LB), which works closely with the BMJ editors on issues including management of conflict of interest, generic approaches and formats across Rapid Recommendations.

Co-chairs

The Rapid Recommendations steering committee recruits a clinician chair with content expertise and who has experience creating guidelines, whose primary responsibility is to facilitate discussions and decisions among panel members. A second critical role is the methods co-chair: a methodologist highly trained in GRADE and use of the MAGICapp authoring platform is responsible for organizing the process to ensure the guideline meets the predefined methodological standards (Appendix 2). Panel recruitment is primarily the responsibility of the chair and methods co-chair, with the help from the steering committee (Box B).

Box B. Responsibilities of the chair and methods co-chair

Chair's responsibilities:

- Recruit the panel
- Lead discussion on the PICO question and the subgroups? via email or online
- Decide when and how many videoconference calls are necessaryLead the responses to public and private comments on the recommendation

Methods co-chair responsibilities:

- Ensure that the guideline follows the Rapid Recommendation methods, processes and Institute of Medicine standards
- Evaluate and present potential conflicts of interest to the oversight group?
- Oversee the systematic reviews to ensure methodological rigor, appropriate interaction and harmonisation with the guideline panel, including relevance of the evidence provided to inform recommendations

Shared responsibilities:

- Draft the Rapid Recommendation manuscript and MAGICapp content, and coordinate

Panellists

For each panel, we include people representing all major viewpoints on an issue from a medical, social and global perspective (Box C), at the same time achieving gender parity 41.

Box C. Principles of guideline panel composition

All panels include the following people:

- All relevant clinical specialties
    - Focus on primary care when relevant because primary care physicians often bring a broader viewpoint
    - Typically, the chair is a clinician with some experience in the area
- All relevant allied health care specialties
- People with personal experience of having the condition or illness, and/or having cared for someone with the condition or illness
- Methodologists (skills in guideline development, evidence based medicine, and shared

Patient partnership

We empower patient partners to contribute maximally, in part through a patient liaison responsible for recruiting and supporting the patient partners throughout the entire process. The patient liaison utilizes several resources to facilitate the sometimes challenging process of recruiting patient panellists including social media (especially Twitter), Cochrane Task Exchange42, and patient forums such as Patients-Like-Me43.

The patient partner liaison meets with patients to review the process and obtain initial input on the outcomes and practical issues. Patient partners are invited to provide feedback at every point in the process; patient input has proved particularly valuable to inform the panel's judgements on patient values and preferences (Box D). During the panel meetings, patients are typically asked to speak on a topic before other panellists. The sharing of their experiences and appraisal of the evidence, can help make the conversation and ultimate recommendations more patient-centred.

Box D. Examples of critical patient contributions

Strong recommendation against knee arthroscopy

The patient panel members felt that a possible small benefit to function without a reduction in pain would be unimportant to almost all patients1. This was one factor that shifted the recommendation from weak to strong against. Those with lived experience identified key practical issues including concerns with cost and accessibility for both arthroscopy and interventions provided by physiotherapists.

Low intensity pulsed ultrasound (LIPUS) for healing fractures

In light of the absence of any demonstrated benefit 10 and a strong recommendation against LIPUS a patient panellist noted that even discussing LIPUS would take away from already limited time during a physician encounter11. The panel decided to highlight this in the practical advice section, suggesting that clinicians do not discuss LIPUS unless the patient raises the issue.

Transcatheter aortic valve implantation

The patient panellists were alone in initially noting that pain and recovery time are issues of major importance to most people 13. These practical issues were not addressed in the trials 14 or in studies measuring patient values and preferences17, but ultimately made an important impact on the recommendations to offer patients with severe aortic stenosis TAVI rather than open heart surgery.

Minimising conflicts of interest

Conflicts of interest continue to plague major guidelines: panel members, including the chair, have financial conflicts of interest in the majority of major guidelines[44] [45]. Given their inherent conflicts of interest, some argue professional societies should not create guidelines [22]. We do not allow any financial conflicts of interest - defined as having any financial stake in, or having received compensation from, a company that sells any product used to treat the condition or illness (Box E). We consider potential conflicts within the past 3 years, and any anticipated conflicts in the upcoming year[46].

Non-financial conflicts of interest can be more difficult to measure and manage than financial conflicts[47]. To reduce the impact of intellectual conflicts of interest, we minimise the number of people on the panel who have taken a public stance on the matter – either in published academic literature, or any other public venue. Investigators on RCTs are assumed to have an intellectual conflict. When people who have an intellectual conflict are included, we try to balance the stated views with panellists who may have opposing views. Because they may be inclined to over-sell the results of their reviews, we restrict the number of systematic review authors (max 3, check if we have adhered to this).

Professional conflicts of interest occur when one's career may be impacted by the recommendation. For example, a recommendation against a common procedure could result in professional consequences for a healthcare worker who performs the procedure. In many cases, it is necessary to include experts who have a professional conflict. However, we minimise their influence on the vote by including only a small number of people with a professional conflict.

The chair and methods co-chair cannot have any type of conflict of interest.

Each potential panellist and systematic review author completes an online conflicts of interest form (Appendix 3). The form is much more detailed than others, including the standard BMJ form or the International Committee of Medical Journal Editors form[48]. The Rapid Recommendations steering committee and at least two journal editors scrutinise the disclosures; each has veto powers. In addition, we often scrutinize disclosures that potential panellists have made in previous publications.

An appendix to each recommendation presents all conflicts in detail, contextualised to the question at hand. Table 1 shows examples about how we have dealt with conflicts of interest.

Table 1. Examples of conflicts of interest and how we managed them

Topic	**Potential conflict**	**Decision**	**Result**
Dual antiplatelet therapy (aspirin and clopidogrel) for stroke	Research funding from a company that produces carotid stents	Financial conflict – carotid stents are sometimes used for stroke	Excluded
Atraumatic needles for lumbar puncture	A patient who works for a health insurance company	Financial conflict – the guideline could impact spending by the patient's employer.	Excluded
Tenofovir/emtricitabine vs. zidovudine/lamivudine for pregnant women living with HIV	Travel bursary from a company that makes treatments not discussed in the guideline.	Financial conflict – people who received funds from any company that sells HIV treatments were excluded.	Excluded
Transcatheter vs. surgical aortic valve replacement for severe aortic stenosis	Research funding from a company that produces antiplatelet drugs	Financial conflict – antiplatelets are often prescribed to patients after aortic valve implantation.	Excluded
Corticosteroids for sepsis	Principal investigator in the most randomised trial on the topic, with unique expertise to offer	Intellectual conflict – probably predisposed advocate for congruent interpretations.	Included – was one of two panellists with an intellectual conflict
Arthroscopy for degenerative knee disease	Advocate for the "Too Much Medicine" campaign	Intellectual conflict – probably predisposed to advocate for the more conservative approach	Excluded
Transcatheter vs. surgical aortic valve replacement for severe aortic stenosis	Works as an interventional cardiologist who performs transcatheter aortic valve replacement	Professional conflict – probably predisposed to advocate for transcatheter rather than surgical approach	Included - balanced panel with equal representation by cardiac surgeons; most panellists did

			not have a professional conflict

Defining the scope and need for systematic review(s)

The Rapid Recommendation oversight committee and Rapid Recommendation clinical experts tentatively decide the scope of the recommendations and the systematic reviews required to inform the panel[49]. Once convened, the guideline panel also has input. The scope includes not only that of the initiating trial, but also the most important and relevant clinical questions. The panel decides the population and intervention to which the guideline should apply, choices that may result in different recommendations for different populations or interventions.

There are three primary questions that every panel considers in deciding what systematic reviews are needed (Table 2):

1) What are the relative effects of the intervention(s) compared to the comparator on patient-important outcomes? Do we anticipate important subgroup differences?

2) What is the prognosis of patients with the comparator? Are there some subgroups at higher or lower risk? The prognosis (baseline risk of future outcomes) determines the absolute effects of interventions and therefore may have an impact on the recommendations[50].

3) What are the values and preferences of the typical patient and how much do they vary between patients?

Sometimes a trustworthy published systematic review, rather than an individual study, suggests a need to change practice. In such situations the Rapid Recommendations process can occur in response to the systematic review. This has happened on three occasions [51-53].

Table 2. Systematic reviews performed to inform each Rapid Recommendation

Topic	Was a review on relative effects necessary?		Was a review on prognosis necessary?		Was a review on values & preferences necessary?	
	Decision	Rationale	Decision	Rationale	Decision	Rationale
TAVI vs. SAVR13	Yes14	No up to date review available	Yes54	A probable long-term benefit with SAVR was not studied for TAVI (valve stability).	Yes17	Values-sensitive decision between possible valve deterioration and short-term benefits.
LIPUS11	Yes10	No up to date review available	No	No benefit with LIPUS.	No	No benefit with LIPUS.
Knee arthroscopy for degenerative knee disease1	Yes55	No up to date review available	No	No important benefit with arthroscopy.	Yes6	Needed to know MIDs to rule-out an important benefit on patient reported outcomes.
ART for pregnant women with HIV5	Yes16	No up to date review available	No	Credible evidence existed from single large observational studies. Rapid systematic reviews would not have been feasible for all outcomes.	Yes4	Previous guidelines focused on public health perspectives; woman values were critically important for the recommendations.
Corticosteroids for sore throat56	Yes57	No up to date review available	No	RCTs were sufficiently pragmatic that they are probably representative; a scoping review did not identify any more credible observational evidence.	Yes*56	Small benefit closely balanced with burden and potential for adverse effects with treatment
Antibiotics for skin abscesses19	Yes34	No up to date review available	No	RCTs were sufficiently pragmatic that they are probably representative; a scoping review did not identify any more credible observational evidence.	No	A scoping review did not identify any potentially relevant studies. The panel took a cautious approach by assuming that values & preferences vary substantially.
Atraumatic needles for lumbar punctures51	No	A credible systematic review that included all relevant outcomes was recently published58	No	RCTs were sufficiently pragmatic that they are probably representative. There were more than 100 RCTs from diverse populations.	No	No benefit with alternative needles
PFO closure for stroke59	Yes60	No up to date review available	No	A scoping review did not identify any relevant studies; a full review was unlikely to be helpful.	Yes*59	Close trade-off between increased bleeding and stroke reduction for anticoagulation vs. alternatives.
Corticosteroids for sepsis38	Yes37	No up to date review available	No	Several validated scoring systems already exist, are	No	A full systematic review with all related disease states was not feasible

Topic	Was a review on relative effects necessary?		Was a review on prognosis necessary?		Was a review on values & preferences necessary?	
	Decision	Rationale	Decision	Rationale	Decision	Rationale
				widely used, and can be applied to individual patient circumstances.		at the time that the study was performed.
PSA screening for prostate cancer[40]	Yes[61]	No up to date review available	No	The RCTs were pragmatic and widely representative.	Yes[62]	Small and uncertain mortality reduction was closely balanced against harms.
Targets for oxygen therapy for medical inpatients[52]	No	A credible systematic review that included all relevant outcomes was recently published[63]	No	Several validated scoring systems already exist, are widely used, and can be applied to individual patient circumstances. No apparent benefit with higher oxygen targets, so prognosis is less important.	No	No apparent benefit with higher oxygen targets.
Dual antiplatelet therapy for minor stroke and high risk TIA[64]	Yes[65]	No up to date review available	No	A scoping review did not identify any relevant studies to the population of interest; a full review was unlikely to be helpful. The RCTs were thought to be sufficiently pragmatic and representative.	No	A scoping review did not identify any studies in the population of interest. Indirect evidence from a more general systematic review was available[66]
Subacromical decompression surgery[67]	Yes[68 69]	No up to date review available	No	No important benefit with surgery.	Yes[70]	Needed to know MIDs to rule-out an important benefit on patient reported outcomes.
Thyroid hormone therapy for subclinical hypothyroidism[53]	No	A credible systematic review that included all relevant outcomes was recently published[71]	No	All important outcomes favoured not using thyroid hormone therapy	No	All important outcomes favoured not using thyroid hormone therapy
Colorectal cancer screening[72]	Yes**[73 74]	No up to date review available	No	Trustworthy risk estimation tools are readily available	Yes*[72]	Modest benefits closely balanced with modest harms
Gastric acid suppression for bleeding prophylaxis	Yes	No up to date review available	Yes	Need to identify risk factors for bleeding because risk varies substantially between patients	Yes	Modest benefits closely balanced with modest harms

*Published in the online supplemental material with the Rapid Recommendation

**The guideline panel also asked for a microsimulation model because there were not large long-term follow-up studies for some important screening options (e.g., colonoscopy)

Systematic reviews of prognosis do not always provide important additional information: When RCTs are large and pragmatic, the prognoses measured in the comparator arm RCTs

probably approximate those from observational studies[75]. When there is a clear benefit or harm for all important outcomes, reviews of prognosis and values and preferences will be unlikely to change the recommendation (Box E).

Box E. Systematic reviews for patient values & preferences can be essential for trustworthy guidance

In order to make a recommendation, panels must make a judgement about what well informed patients would decide, reflecting the typical patients' values and preferences and their distribution. For patient reported outcomes, this means estimating the minimally important difference (MID), and its distribution[6]. The MIDs were essential to justify a strong recommendation against knee arthroscopy for patients with degenerative knee disease because arthroscopy probably has a very small short-term benefit for some patients. Without the MIDs, the panel would not have been able to confidently say that the statistically significant short-term benefit is small and unimportant for most people [1].

Systematic reviews of values and preferences studies can also help the panel to balance a trade-off between desirable and undesirable consequences. For example, in a Rapid Recommendation on antiretroviral therapies for pregnant women living with HIV, a systematic review of values and preferences found that almost all pregnant women place a very high importance on the ensuring the health of their child, and place less value on simplifying their medication regimen[4]. This knowledge was in large part responsible for a recommendation[16] that differs from other guidelines on the topic[18].

How we conduct the systematic reviews to inform a rapid recommendation

Rapid Recommendations-linked systematic reviews include features that may differ from reviews not associated with guidelines. First, they must explicitly answer the clinical question formulated by the panel (PICO format), which includes reporting all outcomes relevant for decision-making [76]. Second, they should explore whether the effects differ across subgroups. With Rapid Recommendations, each panellist, including the patient partners, identifies all outcomes and subgroups of possible importance. The systematic review teams searches for and ultimately summarizes the best evidence for each outcome and subgroup. We follow GRADE guidance for evidence synthesis [77].

There are a number of efficiencies that we have found in the review process that are unlikely to sacrifice quality (Box G). The overarching principle is a fully harmonised process between the guideline panel and systematic review team(s). The systematic review team(s) start their work in parallel with panel recruitment, but are ultimately guided by the guideline panel – reviews sometimes need to shift focus or redo certain components in order to fulfil the panel's requests.

Box G. Innovations to speed up the systematic review process

- Initially, the journal and guideline leadership agrees on key methods issues (e.gs., analysis method, risk of bias tool, use of GRADE)
- Systematic literature search updated from the most recent and directly relevant systematic review that applied a robust search and screening process
- Register a draft protocol for the systematic review as soon as possible and amend the protocol later to incorporate panel input before registration
- Perform tasks in parallel, with different experts doing each of the following tasks:
    - Search and screening
    - Data extraction and risk of bias assessments for all of the already known studies
    - Preliminary data analyses with known studies that are included
    - Draft of the manuscript introduction and methods
- Key innovations missing in this table and consider structure
- Identify peer reviewers willing to rapidly peer review prior to submission, and send a reminder email a couple of days before submission
- Maintain a network of highly competent researchers who can complete all necessary tasks on short notice
- Machine learning may help in the future[12]

How the recommendations are created

Once the panel is formed, the chair sends an email to the panel requesting structured feedback on the following:

- The scope of the PICO question
- Outcomes, including a rating of importance [49]
- Subgroups, with rationale and hypothesized direction of effect
- The proposed systematic review(s)
- The draft protocol for the systematic review(s)

The panel comes to a consensus on the PICO question, subgroups, and proposed systematic reviews and the systematic review teams then have about 30 to 60 days to finish the first drafts of the reviews.

Guideline perspective and costs

Due to the international audience for our guideline recommendations, we face the challenge of appropriately including cost-effectiveness and other factors relevant when moving from evidence to decisions in health care systems across countries and continents[7,8]. Rapid Recommendations have, to date, taken the individual patient perspective rather than the perspective of a health funder or society. This emphasises autonomy and deemphasises broader considerations such as cost-effectiveness or equity public health concerns (e.g. non-use of vaccines can precipitate disease outbreaks), and non-health related concerns (e.g. environmental issues) (Box H).

Box H. Implications of a person centred-approach

Sometimes, an individual might make a different decision for themselves than those with other perspectives, such as health funders or society as a whole. For example, in the Rapid Recommendation on HIV treatment for pregnant women with HIV, the panel made a recommendation against the standard regimen because of potential serious harm to their child, supported by low certainty evidence [4,5]. However, a public health guideline might still recommend the standard regimen because it is more cost-effective to distribute a single first-line regimen for everyone that they treat[15].

In another example, a panel issued a weak recommendation for antibiotics for patients with uncomplicated skin abscesses primarily because they reduce the risk of recurrence and treatment failure by approximately 10%[19]. In doing so, the panel placed a low value on potentially propagating antimicrobial resistance. A guideline that takes a societal perspective would place a higher value on community rates of antimicrobial resistance and might have reasonably made a recommendation against antibiotics.

Panel meetings

The panels meet by videoconference. Box I, summarizes key elements that occur during the meetings (typically two to four per Rapid Recommendation)

Box I. The chair leads the panel discussions through several key steps:

1. Introductions
2. Review of the Rapid Recommendations process.
3. Review of GRADE, including how to move from evidence to recommendations
4. Review of literature on values and preferences relevant to the recommendations under consideration
5. *Deliberation*: How much importance does the typical patient find various plausible treatment effects, and how much variation is there between patients?
6. Review of the systematic reviews and GRADE evidence profile
7. *Deliberation*: appraise magnitude and certainty for each outcome
8. *Deliberation*: decide on the credibility of possible subgroup effects
9. *Deliberation:* other key considerations of applicability

Peer review and editorial process

The editorial process starts prior to submission. The chair, methods co-chair, Rapid Recommendations steering committee, and journal editors discuss the manuscript and timelines prior to submission. Preliminary editorial input occurs prior to submission.

The journal editors recruit peer reviewers prior to submission and ask them to complete their review within 1-2 weeks. The peer reviewers have access to all of the materials, including the systematic reviews that inform the recommendations. Each manuscript undergoes a standard peer review process, and the authors respond to peer review comments as they would for any other manuscript.

Dissemination

Each Rapid Recommendation publication includes several components to facilitate access, interpretation and application of recommendations and underlying information by health care professionals and their patients (Box J).

Box J. Components of a Rapid Recommendation

- An interactive infographic with enough summary-level information necessary for most people to make a decision
- Multilayered data in MAGICapp, including:
    - Detailed GRADE evidence profile with all outcomes
    - Summary of the panel's judgements regarding benefits and harms, certainty of evidence, patient values and preferences, resources, and other considerations
    - Summary of the rationale for the recommendation
    - Practical information to help implement the recommendation (e.g. drug dosage, adaptation to renal function)
- MAGICapp Decision aids to support shared decision making in clinical encounters [9]
- A concise manuscript with the following components:
    - What you need to know bullet points
    - A box with all of the linked papers
    - Current understanding of the problem
    - Brief guideline methodology
    - Summary of the evidence
    - Patient values and preferences: literature and discussion
    - Practical and other issues
    - Costs and resources
    - Future research
    - A box to list future evidence updates.

Because we anticipate that most users will not read the full text of guideline, we present Rapid Recommendations with a layered approach. The most important information is contained within the infographic at the top of the webpage. This visually appealing interactive graphic contains enough information for most clinicians to implement the recommendation in their practice. Those interested in additional information can read the concise BMJ manuscript or proceed to the full supporting data available in the MAGICapp.

Infographic

The infographic presents, in a visually appealing format, sufficient information to proceed with decision-making. The key components are shown in Figure 1.

Captions for Figure 1.

First layer (all users see):

- Description of the population: who the recommendation does and does not apply to
- A description of the intervention and comparator
- An arrow with the recommendation, with text describing the recommendation

Second layer (after user clicks on a recommendation):

- Outcome timeframe
- Absolute benefits and harms for key selected outcomes
- Quality of evidence
- Link to full evidence profile in MAGICapp
- Link to patient decision aids in MAGICapp
- Key practical issues
- Boxes for other consideration, such as values and preferences, resources,

Third layer (after user clicks on an outcome):

- Lay interpretation of the outcome, with certainty and effect size
- GRADE domains

Link to the whole guideline and supporting data in the MAGICapp.

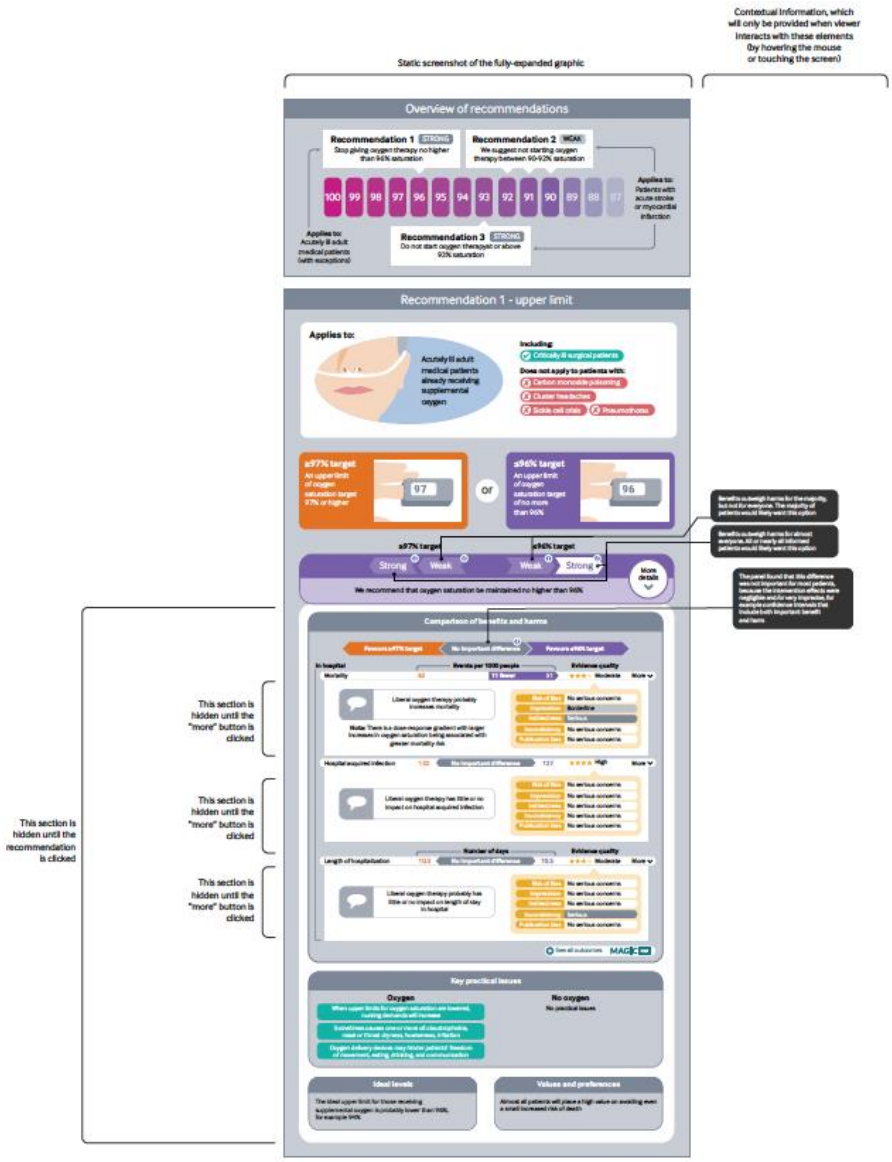

Figure 1. *Rapid Recommendations* infographic

MAGICapp and decision aids

Each Rapid Recommendation is simultaneously created and published online through MAGICapp[79]. MAGICapp is formatted for all devices including smart phones and can be embedded into electronic medical records, making it accessible at the point of care. MAGICapp content is structured in a layered format in which users control access so they see only the information they are most interested in.

Decision aids are designed to support shared decision making between patients and clinicians. We have also used a multi-layered and interactive approach tested developed through iterative user-cantered design in real clinical encounters. [9]. The decision aids are freely available on the MAGICapp and accessible through the main infographic.

Post-publication

Each Rapid Recommendation comes with a rapid response forum for online debate[80]. The panel chair monitors and responds promptly to comments for at least six months after publication.

Lessons Learned

We hope that others can adopt the Rapid Recommendations' approach to clinical practice guidelines. Table 3 presents lessons we have learned in the process, and associated challenges, that others may find helpful.

Table 3. Lessons learned and ongoing challenges for creating rapid recommendations

Steps	Lessons learned	Challenges
Literature monitoring	• Use systematic and informal literature monitoring • Anticipate major new studies and start prior to publication	• The literature filtering process can take days • Requires daily attention (about 15-30 minutes)
Deciding to pursue a recommendation	• Initiate the RapidRecs process as soon as possible • Include range of stakeholders early, including clinical experts and policy makers • Consider complexity of the evidence and likely recommendation, and internal resources	• Anticipating all of the nuances of potential challenges before publication may not be possible
Coordination	• Separate teams conduct the systematic review(s) and guideline simultaneously • Review and guideline leaders communicate regularly	• Systematic review and guideline teams sometimes have different priorities or interpretations of the evidence that require resolution through discussion
Systematic reviews	• Build on the search and literature screening of a recently published review • Have different teams perform tasks simultaneously: ○ Write protocol/introduction/methods ○ Search, study screening ○ Data extraction/risk of bias assessments of studies known to be included ○ Preliminary statistical analyses • Work in parallel with guideline team • Search for recent unpublished and/or anticipated trials	• Recruiting a competent and motivated team ready to put aside other commitments to complete a rapid recommendation • The guideline panel's requests often require several iterations of revisions that would not otherwise occur • The guideline panel sometimes has a different conclusions than the review team • Publication bias is exacerbated when reviews are initiated in response to positive trials
Guideline creation	• Set all meeting dates early • Discuss key issues over email when possible • Agree on focused PICO question(s) and patient values & preferences before discussing evidence on intervention effects • Follow a structured process • Conduct multiple smaller videoconferences to ensure everyone can participate on a short timeline	• Scheduling meetings on short notice with an international panel is resource demanding • Agreeing on the clinical question up front can be a challenge • Adequately obtaining public input is a challenge on short notice

Steps	Lessons learned	Challenges
	• A guideline steering group of three to five people is often useful • Editors provide input prior to initial submission • Produce and refine generic templates of the publication, infographics and other figures prior to submission	
Peer review and interaction with journal	• Preliminary editorial input prior to submission • Identify peer reviewers prior to submission • Identify more peer reviewers than necessary • Have a quick deadline (e.g., 1-2 weeks) • Plan to discuss at an editorial meeting shortly after peer reviews are returned • Invite editor(s) from sister journals to the manuscript meeting to consider publishing the paper in the event that the review manuscript is rejected from the primary target journal • Schedule post peer review copy editing in advance	• Coordinating with other journals when systematic reviews are not published by the same journal can be difficult • Journal editors involved in the RapidRec initiative may have an intellectual conflict; we seek impartial independent editorial input is sought for key decisions
Publication	• Publish online first as soon as copy editing is complete	• Editing for all formats (i.e., computer, mobile, PDF, and print) can take considerable effort and sometimes requires publishing the online version before print and other versions

Unresolved limitations and warnings

First, we are unsure how clinicians will use individual, or a limited number of recommendations rather than complete guidelines. Clinicians may prefer to have a single resource on a topic, in which they can find all relevant recommendations. Traditional publishing practices make it difficult to add individual recommendations to larger documents – a new publication must be released, which can have negative implications for journal impact factor and other metrics. Electronic publishing platforms such as MAGICapp may help by allowing individual recommendations to be added seamlessly into a larger guideline.

Second, although we have identified several efficiencies, invariably trustworthy recommendations require a substantial resource investment, especially when they are rapid.

Third, public consultation prior to publication is difficult when publication is on such a tight timeline. So far, we have avoided public consultations although we do partner with patients throughout the process. Moreover, the BMJ peer-review process systematically involves independent patient partners. Publishing pre-prints could allow for reasonable public consultations to occur, even if they are expedited.

Fourth, a responsive approach to guideline creation will exacerbate publication bias because trials with positive results are published sooner than trials with negative results[81]. There was evidence that this might have happened in our Rapid Recommendation for TAVI. A trial[82] that

did not show a short-term mortality benefit was completed before but published after our systematic review. Authors of responsive recommendations need to pay particular attention to unpublished trials[83]; additional trials in this case confirmed the short-term mortality benefit.

Conclusions

Rapid Recommendations demonstrate the feasibility of producing and disseminating trustworthy clinical practice guidelines in response to new evidence in a very short timeframe. This responsive approach to guideline creation is new and demonstrates that it is possible, while maintaining standards of trustworthiness, to substantially reduce the time it takes for evidence to reach the point of care,

Appendix 1. How Rapid Recommendations meet each of the Institutes of Medicines standards for a trustworthy guideline

1. Establishing transparency **"The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible"***
● This method is available and published as a supplementary file as well as in MAGICapp where all recommendations and underlying content is available. ● We ask the peer-reviewers to judge whether the guidance is trustworthy and will respond to concerns raised.
2. Managing conflicts of interest **"Prior to selection of the guideline development group, individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity....",**
● Interests of each panel member are declared prior to involvement and published with the rapid recommendations ● No one with any potential financial interests in the past three years, or forthcoming 12 months will participate - as judged by the panel chair and *The BMJ* ● No more than two panel members have declared an intellectual conflict of interest. Such conflicts include having taken a position on the issue for example by a written an editorial, commentary, or conflicts related to performing a primary research study or written a prior systematic review on the topic. ● The Chair must have methods expertise, a clinical background and no financial or intellectual interests. ● Funders and pharmaceutical companies have no role in these recommendations.
3. Guideline Development Group Composition **"The guideline development group should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG"**
● *The RapidRecs* group will aim to include representation from most or every major

geographic region in the world, with specific efforts made to achieve gender-balance. ● We will facilitate patient and public involvement by including patient experience, via patient-representatives and systematic reviews addressing values and preferences to guide outcome choices and relative weights of each outcome, where available ● Patient-representatives will be given priority during panel meetings and will have an explicit role in vetting the panel's judgements of values and preferences.
4. Clinical Practice Guideline–Systematic Review Intersection **"CPG developers should use systematic reviews that meet standards set by the IOM. Guideline development group and systematic review team should interact regarding the scope, approach, and output of both processes".**
● Each rapid recommendation will be based on one or more high-quality SRs either developed and published in parallel with our *BMJ* Rapid Recommendations or produced by other authors and available at the time of making the recommendaiton. ● The recommendation panel and SR teams will interact, with up to three members participating in both teams to facilitate communication and continuity in the process
5. Establishing Evidence Foundations for and Rating Strength of Recommendations **"For each recommendation: explain underlying reasoning, including a clear description of potential benefits and harms, a summary of relevant available evidence and description of the quality., explain the part played by values, opinion, theory, and clinical experience in deriving the recommendation, "provide rating of strength of recommendations"**
● The GRADE approach will provide the framework for establishing evidence foundations and rating strength of recommendations.84 For each recommendation systematic and transparent assessments are made across the following key factors: ○ Absolute benefit and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE Summary of Findings tables)77

  - Quality of the evidence
  - Values and preferences of patients
  - Resources and other considerations (e.g. feasibility, applicability, equity)
- Each outcome will - if data are available through systematic reviews - include an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in Summary of Findings tables. If such data are not available narrative summaries will be provided.
- A summary of the underlying reasoning and all additional information (e.g. key factors, practical advice, references) will be available online in an interactive format at www.magicapp.org. This summary will include descriptions of how theory (e.g. patophysiology) and clinical experience played into the evidence assessment and recommendation development.
- Recommendations will be rated either weak or strong, as defined by GRADE.
- If the panel members disagree regarding evidence assessment or strength of recommendations, we will follow a structured consensus process customized to the GRADE system and report any final differences in opinion, with their rationale, in the online supplement and online at www.magicapp.org.

6. Articulation of recommendations

"Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed, and so that compliance with the recommendation(s) can be evaluated"

- Each recommendation will appear at the top of the guideline infographic, published in *The BMJ*, and will be available in standardised formats in MAGICapp, articulated to be actionable based on best current evidence on presentation formats of guidelines.
- There will be a statement included in each summary article in *The BMJ* and in the MAGICapp that these are recommendations to provide clinicians with guidance. They do not form a mandate of action and should be contextualised in the healthcare system a clinician's works in, and or with an individual patient.

7. External review

"External reviewers should comprise a full spectrum of relevant stakeholders....,

authorship should be kept confidential....., all reviewer comments should be considered....a rationale for modifying or not should be recorded in writing.... a draft of the recommendation should be made available to general public for comment.."
● At least two external peer-reviewers and one patient reviewer will review the article for *The BMJ* and provide open peer review. Each will have access to all the information in the package. They will be asked for general feedback as well as to make an overall judgement on whether they view the guidelines as trustworthy ● A *BMJ* series adviser with methodological and/or statistical expertise will review the *BMJ* Rapid Recommendations publication and the systematic reviews. ● The *Rapidrecs* panel will be asked to read and respond to the peer review comments and make amendments where they judge reasonable ● *The BMJ* and *RapidRecs* steering committee may, on a case-by-case basis, choose to invite key organizations, agencies, or patient/public representatives to provide and submit public peer-review. ● There will be post-publication public review process through which people can provide comments and feedback through MAGICapp (or through *The BMJ*). The Chair will, on behalf of panel authors, aim to respond to each publicly-available peer-review within 30 days, for a period of six months after publication.
8. Updating **"The date for publication, systematic review and proposed date for future review should be documented, the literature should be monitored regularly and the recommendation should be updated when warranted by new evidence"**
• The *Rapidrecs* panel will, through monitoring of new research evidence for published *BMJ* Rapid Recommendations, aim to provide updates of the recommendations in situations in which the evidence suggests a change in practice. These updates will be initially performed in MAGICapp and submitted to *The BMJ* for consideration of publication of a new Rapid Recommendation.

References:

1. Siemieniuk RAC, Harris IA, Agoritsas T, et al. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *BMJ (Clinical research ed)* 2017;357:j1982. doi: 10.1136/bmj.j1982 [published Online First: 2017/05/12]

2. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? *PLoS medicine* 2010;7(9):e1000326. doi: 10.1371/journal.pmed.1000326 [published Online First: 2010/09/30]
3. U.S. National Library of Medicine. Citations Added to MEDLINE® by Fiscal Year: National Institutes of Health; 2018 [updated 10 September 2018. Available from: https://www.nlm.nih.gov/bsd/stats/cit_added.html accessed 2 January 2019 2019.
4. Lytvyn L, Siemieniuk RA, Dilmitis S, et al. Values and preferences of women living with HIV who are pregnant, postpartum or considering pregnancy on choice of antiretroviral therapy during pregnancy. *BMJ open* 2017;7(9):e019023. doi: 10.1136/bmjopen-2017-019023 [published Online First: 2017/09/13]
5. Siemieniuk RAC, Lytvyn L, Mah Ming J, et al. Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline. *BMJ (Clinical research ed)* 2017;358:j3961. doi: 10.1136/bmj.j3961 [published Online First: 2017/09/13]
6. Devji T, Guyatt GH, Lytvyn L, et al. Application of minimal important differences in degenerative knee disease outcomes: a systematic review and case study to inform BMJ Rapid Recommendations. *BMJ open* 2017;7(5):e015587. doi: 10.1136/bmjopen-2016-015587 [published Online First: 2017/05/13]
7. Macdonald H. Should clinicians spend more time thinking about guidelines than evidence? Should clinicians spend more time thinking about guidelines than evidence? The BMJ Opinion: BMJ, 2018.
8. Guyatt GH, Meade MO, Jaeschke RZ, et al. Practitioners of evidence based care. Not all clinicians need to appraise evidence from scratch but all need some skills. *BMJ (Clinical research ed)* 2000;320(7240):954-5. doi: 10.1136/bmj.320.7240.954 [published Online First: 2001/02/07]
9. Agoritsas T, Heen AF, Brandt L, et al. Decision aids that really promote shared decision making: the pace quickens. *BMJ (Clinical research ed)* 2015;350:g7624. doi: 10.1136/bmj.g7624 [published Online First: 2015/02/12]
10. Schandelmaier S, Kaushal A, Lytvyn L, et al. Low intensity pulsed ultrasound for bone healing: systematic review of randomized controlled trials. *BMJ (Clinical research ed)* 2017;356:j656. doi: 10.1136/bmj.j656 [published Online First: 2017/03/30]
11. Poolman RW, Agoritsas T, Siemieniuk RA, et al. Low intensity pulsed ultrasound (LIPUS) for bone healing: a clinical practice guideline. *BMJ (Clinical research ed)* 2017;356:j576. doi: 10.1136/bmj.j576 [published Online First: 2017/02/24]
12. Thomas J, Noel-Storr A, Marshall I, et al. Living systematic reviews: 2. Combining human and machine effort. *Journal of clinical epidemiology* 2017;91:31-37. doi: 10.1016/j.jclinepi.2017.08.011 [published Online First: 2017/09/16]
13. Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ (Clinical research ed)* 2016;354:i5085. doi: 10.1136/bmj.i5085 [published Online First: 2016/09/30]
14. Siemieniuk RA, Agoritsas T, Manja V, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis. *BMJ (Clinical research ed)* 2016;354:i5130. doi: 10.1136/bmj.i5130 [published Online First: 2016/09/30]

15. Welbourn A. WHO and the rights of women living with HIV. theBMJ Opinion: BMJ, 2017.
16. Siemieniuk RA, Foroutan F, Mirza R, et al. Antiretroviral therapy for pregnant women living with HIV or hepatitis B: a systematic review and meta-analysis. *BMJ open* 2017;7(9):e019022. doi: 10.1136/bmjopen-2017-019022 [published Online First: 2017/09/13]
17. Lytvyn L, Guyatt GH, Manja V, et al. Patient values and preferences on transcatheter or surgical aortic valve replacement therapy for aortic stenosis: a systematic review. *BMJ open* 2016;6(9):e014327. doi: 10.1136/bmjopen-2016-014327 [published Online First: 2016/10/01]
18. Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2018 Recommendations of the International Antiviral Society-USA Panel. *Jama* 2018;320(4):379-96. doi: 10.1001/jama.2018.8431 [published Online First: 2018/07/26]
19. Vermandere M, Aertgeerts B, Agoritsas T, et al. Antibiotics after incision and drainage for uncomplicated skin abscesses: a clinical practice guideline. *BMJ (Clinical research ed)* 2018;360:k243. doi: 10.1136/bmj.k243 [published Online First: 2018/02/14]
20. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *Lancet (London, England)* 1993;342(8883):1317-22. [published Online First: 1993/11/27]
21. Shekelle PG, Ortiz E, Rhodes S, et al. Validity of the Agency for Healthcare Research and Quality clinical practice guidelines: how quickly do guidelines become outdated? *Jama* 2001;286(12):1461-7. [published Online First: 2001/09/27]
22. Ioannidis JPA. Professional Societies Should Abstain From Authorship of Guidelines and Disease Definition Statements. *Circ Cardiovasc Qual Outcomes* 2018;11(10):e004889. doi: 10.1161/circoutcomes.118.004889 [published Online First: 2018/10/26]
23. Alonso-Coello P, Irfan A, Sola I, et al. The quality of clinical practice guidelines over the last two decades: a systematic review of guideline appraisal studies. *Quality & safety in health care* 2010;19(6):e58. doi: 10.1136/qshc.2010.042077 [published Online First: 2010/12/04]
24. Kung J, Miller RR, Mackowiak PA. Failure of clinical practice guidelines to meet institute of medicine standards: Two more decades of little, if any, progress. *Archives of internal medicine* 2012;172(21):1628-33. doi: 10.1001/2013.jamainternmed.56 [published Online First: 2012/10/24]
25. Armstrong MJ, Bloom JA. Patient involvement in guidelines is poor five years after institute of medicine standards: review of guideline methodologies. *Research involvement and engagement* 2017;3:19. doi: 10.1186/s40900-017-0070-2 [published Online First: 2017/10/25]
26. Steinberg E, Greenfield S, Wolman DM, et al. Clinical practice guidelines we can trust: National Academies Press 2011.
27. Qaseem A, Forland F, Macbeth F, et al. Guidelines International Network: toward international standards for clinical practice guidelines. *Annals of internal medicine* 2012;156(7):525-31. doi: 10.7326/0003-4819-156-7-201204030-00009 [published Online First: 2012/04/05]
28. Brandt L, Agoritsas T, Guyatt G, et al. A Trustworthy, Efficient and Integrated Evidence Ecosystem, to Increase Value and Reduce Waste in Health Care. (In preparation)

29. MAGIC group. Creating trustworthy guidelines, evidence summaries and decision aids that we can all use and share 2018 [Available from: http://magicproject.org/ accessed 2 January 2019 2019.
30. Siemieniuk RA, Agoritsas T, Macdonald H, et al. Introduction to BMJ Rapid Recommendations. *BMJ (Clinical research ed)* 2016;354:i5191. doi: 10.1136/bmj.i5191 [published Online First: 2016/09/30]
31. McMaster Premium Literature Service (PLUS): an evidence-based medicine information service delivered on the Web. AMIA annual symposium proceedings; 2005. American Medical Informatics Association.
32. Haynes RB, Cotoi C, Holland J, et al. Second-order peer review of the medical literature for clinical practitioners. *Jama* 2006;295(15):1801-8. doi: 10.1001/jama.295.15.1801 [published Online First: 2006/04/20]
33. Daum RS, Miller LG, Immergluck L, et al. A Placebo-Controlled Trial of Antibiotics for Smaller Skin Abscesses. *The New England journal of medicine* 2017;376(26):2545-55. doi: 10.1056/NEJMoa1607033 [published Online First: 2017/06/29]
34. Wang W, Chen W, Liu Y, et al. Antibiotics for uncomplicated skin abscesses: systematic review and network meta-analysis. *BMJ open* 2018;8(2):e020991. doi: 10.1136/bmjopen-2017-020991 [published Online First: 2018/02/14]
35. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *The New England journal of medicine* 2018;378(9):809-18. doi: 10.1056/NEJMoa1705716 [published Online First: 2018/03/01]
36. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *The New England journal of medicine* 2018;378(9):797-808. doi: 10.1056/NEJMoa1705835 [published Online First: 2018/01/20]
37. Rochwerg B, Oczkowski SJ, Siemieniuk RAC, et al. Corticosteroids in Sepsis: An Updated Systematic Review and Meta-Analysis. *Critical care medicine* 2018;46(9):1411-20. doi: 10.1097/ccm.0000000000003262 [published Online First: 2018/07/07]
38. Lamontagne F, Rochwerg B, Lytvyn L, et al. Corticosteroid therapy for sepsis: a clinical practice guideline. *BMJ (Clinical research ed)* 2018;362:k3284. doi: 10.1136/bmj.k3284 [published Online First: 2018/08/12]
39. Martin RM, Donovan JL, Turner EL, et al. Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial. *Jama* 2018;319(9):883-95. doi: 10.1001/jama.2018.0154 [published Online First: 2018/03/07]
40. Tikkinen KAO, Dahm P, Lytvyn L, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a clinical practice guideline. *BMJ (Clinical research ed)* 2018;362:k3581. doi: 10.1136/bmj.k3581 [published Online First: 2018/09/07]
41. Merman E, Pincus D, Bell C, et al. Differences in clinical practice guideline authorship by gender. *Lancet (London, England)* 2018;392(10158):1626-28. doi: 10.1016/s0140-6736(18)32268-2 [published Online First: 2018/11/30]
42. Cochrane Collaboration. Cochrane TaskExchange: Cochrane; [Available from: https://taskexchange.cochrane.org/ accessed 3 January 2019 2019.
43. PatientsLikeMe. patientslikeme 2019 [Available from: https://www.patientslikeme.com/ accessed 3 January 2019 2019.

44. Khan R, Scaffidi MA, Rumman A, et al. Prevalence of Financial Conflicts of Interest Among Authors of Clinical Guidelines Related to High-Revenue Medications. *JAMA internal medicine* 2018;178(12):1712-15. doi: 10.1001/jamainternmed.2018.5106 [published Online First: 2018/11/02]
45. Norris SL, Holmer HK, Ogden LA, et al. Conflict of interest in clinical practice guideline development: a systematic review. *PloS one* 2011;6(10):e25153. doi: 10.1371/journal.pone.0025153 [published Online First: 2011/11/01]
46. Chew M, Brizzell C, Abbasi K, et al. Medical journals and industry ties. *BMJ (Clinical research ed)* 2014;349:g7197. doi: 10.1136/bmj.g7197 [published Online First: 2014/11/30]
47. Guyatt G, Akl EA, Hirsh J, et al. The vexing problem of guidelines and conflict of interest: a potential solution. *Annals of internal medicine* 2010;152(11):738-41. doi: 10.7326/0003-4819-152-11-201006010-00254 [published Online First: 2010/05/19]
48. Drazen JM, de Leeuw PW, Laine C, et al. Towards more uniform conflict disclosures: the updated ICMJE conflict of interest reporting form. *BMJ (Clinical research ed)* 2010;340:c3239. doi: 10.1136/bmj.c3239 [published Online First: 2010/07/02]
49. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of clinical epidemiology* 2011;64(4):395-400. doi: 10.1016/j.jclinepi.2010.09.012 [published Online First: 2011/01/05]
50. Spencer FA, Iorio A, You J, et al. Uncertainties in baseline risk estimates and confidence in treatment effects. *BMJ (Clinical research ed)* 2012;345:e7401. doi: 10.1136/bmj.e7401 [published Online First: 2012/11/16]
51. Rochwerg B, Almenawer SA, Siemieniuk RAC, et al. Atraumatic (pencil-point) versus conventional needles for lumbar puncture: a clinical practice guideline. *BMJ (Clinical research ed)* 2018;361:k1920. doi: 10.1136/bmj.k1920 [published Online First: 2018/05/24]
52. Siemieniuk RAC, Chu DK, Kim LH, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. *BMJ (Clinical research ed)* 2018;363:k4169. doi: 10.1136/bmj.k4169 [published Online First: 2018/10/26]
53. Bekkering GE, Agoritsas T, Lytvyn L, et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. *BMJ (Clinical research ed)* 2019;365:l2006. doi: 10.1136/bmj.l2006 [published Online First: 2019/05/16]
54. Foroutan F, Guyatt GH, O'Brien K, et al. Prognosis after surgical replacement with a bioprosthetic aortic valve in patients with severe symptomatic aortic stenosis: systematic review of observational studies. *BMJ (Clinical research ed)* 2016;354:i5065. doi: 10.1136/bmj.i5065 [published Online First: 2016/09/30]
55. Brignardello-Petersen R, Guyatt GH, Buchbinder R, et al. Knee arthroscopy versus conservative management in patients with degenerative knee disease: a systematic review. *BMJ open* 2017;7(5):e016114. doi: 10.1136/bmjopen-2017-016114 [published Online First: 2017/05/13]
56. Aertgeerts B, Agoritsas T, Siemieniuk RAC, et al. Corticosteroids for sore throat: a clinical practice guideline. *BMJ (Clinical research ed)* 2017;358:j4090. doi: 10.1136/bmj.j4090 [published Online First: 2017/09/22]
57. Sadeghirad B, Siemieniuk RAC, Brignardello-Petersen R, et al. Corticosteroids for treatment of sore throat: systematic review and meta-analysis of

randomised trials. *BMJ (Clinical research ed)* 2017;358:j3887. doi: 10.1136/bmj.j3887 [published Online First: 2017/09/22]
58. Nath S, Koziarz A, Badhiwala JH, et al. Atraumatic versus conventional lumbar puncture needles: a systematic review and meta-analysis. *Lancet (London, England)* 2018;391(10126):1197-204. doi: 10.1016/s0140-6736(17)32451-0 [published Online First: 2017/12/11]
59. Kuijpers T, Spencer FA, Siemieniuk RAC, et al. Patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy alone for management of cryptogenic stroke? A clinical practice guideline. *BMJ (Clinical research ed)* 2018;362:k2515. doi: 10.1136/bmj.k2515 [published Online First: 2018/07/27]
60. Mir H, Siemieniuk RAC, Ge LC, et al. Patent foramen ovale closure, antiplatelet therapy or anticoagulation in patients with patent foramen ovale and cryptogenic stroke: a systematic review and network meta-analysis incorporating complementary external evidence. *BMJ open* 2018;8(7):e023761. doi: 10.1136/bmjopen-2018-023761 [published Online First: 2018/07/28]
61. Ilic D, Djulbegovic M, Jung JH, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. *BMJ (Clinical research ed)* 2018;362:k3519. doi: 10.1136/bmj.k3519 [published Online First: 2018/09/07]
62. Vernooij RWM, Lytvyn L, Pardo-Hernandez H, et al. Values and preferences of men for undergoing prostate-specific antigen screening for prostate cancer: a systematic review. *BMJ open* 2018;8(9):e025470. doi: 10.1136/bmjopen-2018-025470 [published Online First: 2018/09/07]
63. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet (London, England)* 2018;391(10131):1693-705. doi: 10.1016/s0140-6736(18)30479-3 [published Online First: 2018/05/05]
64. Prasad K, Siemieniuk R, Hao Q, et al. Dual antiplatelet therapy with aspirin and clopidogrel for acute high risk transient ischaemic attack and minor ischaemic stroke: a clinical practice guideline. *BMJ (Clinical research ed)* 2018;363:k5130. doi: 10.1136/bmj.k5130 [published Online First: 2018/12/20]
65. Hao Q, Tampi M, O'Donnell M, et al. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. *BMJ (Clinical research ed)* 2018;363:k5108. doi: 10.1136/bmj.k5108 [published Online First: 2018/12/20]
66. MacLean S, Mulla S, Akl EA, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 Suppl):e1S-e23S. doi: 10.1378/chest.11-2290 [published Online First: 2012/02/15]
67. Vandvik PO, Lahdeoja T, Ardern C, et al. Subacromial decompression surgery for adults with shoulder pain: a clinical practice guideline. *BMJ (Clinical research ed)* 2019;364:l294. doi: 10.1136/bmj.l294 [published Online First: 2019/02/08]
68. Karjalainen TV, Jain NB, Page CM, et al. Subacromial decompression surgery for rotator cuff disease. *The Cochrane database of systematic reviews*

2019;1:Cd005619. doi: 10.1002/14651858.CD005619.pub3 [published Online First: 2019/02/02]
69. Lahdeoja T, Karjalainen T, Jokihaara J, et al. Subacromial decompression surgery for adults with shoulder pain: a systematic review with meta-analysis. *Br J Sports Med* 2019 doi: 10.1136/bjsports-2018-100486 [published Online First: 2019/01/17]
70. Hao Q, Devji T, Zeraatkar D, et al. Minimal important differences for improvement in shoulder condition patient-reported outcomes: a systematic review to inform a BMJ Rapid Recommendation. *BMJ open* 2019;9(2):e028777. doi: 10.1136/bmjopen-2018-028777 [published Online First: 2019/02/23]
71. Feller M, Snel M, Moutzouri E, et al. Association of Thyroid Hormone Therapy With Quality of Life and Thyroid-Related Symptoms in Patients With Subclinical Hypothyroidism: A Systematic Review and Meta-analysis. *Jama* 2018;320(13):1349-59. doi: 10.1001/jama.2018.13770 [published Online First: 2018/10/05]
72. Helsingen LM, Vandvik PO, Jodal HC, et al. Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a clinical practice guideline. *BMJ (Clinical research ed)* 2019;367:l5515. doi: 10.1136/bmj.l5515 [published Online First: 2019/10/04]
73. Buskermolen M, Cenin DR, Helsingen LM, et al. Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a microsimulation modelling study. *BMJ (Clinical research ed)* 2019;367:l5383. doi: 10.1136/bmj.l5383 [published Online First: 2019/10/04]
74. Jodal HC, Helsingen LM, Anderson JC, et al. Colorectal cancer screening with faecal testing, sigmoidoscopy or colonoscopy: a systematic review and network meta-analysis. *BMJ open* 2019;9(10):e032773. doi: 10.1136/bmjopen-2019-032773 [published Online First: 2019/10/04]
75. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ (Clinical research ed)* 2015;350:h870. doi: 10.1136/bmj.h870 [published Online First: 2015/03/18]
76. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of clinical epidemiology* 2011;64(4):383-94. doi: 10.1016/j.jclinepi.2010.04.026 [published Online First: 2011/01/05]
77. Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. *Journal of clinical epidemiology* 2013;66(2):158-72. doi: 10.1016/j.jclinepi.2012.01.012 [published Online First: 2012/05/23]
78. Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ (Clinical research ed)* 2016;353:i2089. doi: 10.1136/bmj.i2089 [published Online First: 2016/07/02]
79. Brandt L, Vandvik PO, Alonso-Coello P, et al. Multilayered and digitally structured presentation formats of trustworthy recommendations: a combined survey and randomised trial. *BMJ open* 2017;7(2):e011569. doi: 10.1136/bmjopen-2016-011569 [published Online First: 2017/02/12]

80. Crossan L, Delamothe T. Letters to the editor: the new order. Please respond to articles using website, email, or disk-but not paper. *BMJ (Clinical research ed)* 1998;316(7142):1406-10. [published Online First: 1998/06/02]
81. Hopewell S, Loudon K, Clarke MJ, et al. Publication bias in clinical trials due to statistical significance or direction of trial results. *The Cochrane database of systematic reviews* 2009(1):Mr000006. doi: 10.1002/14651858.MR000006.pub3 [published Online First: 2009/01/23]
82. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. *The New England journal of medicine* 2017;376(14):1321-31. doi: 10.1056/NEJMoa1700456 [published Online First: 2017/03/18]
83. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *Journal of clinical epidemiology* 2011;64(12):1277-82. doi: 10.1016/j.jclinepi.2011.01.011 [published Online First: 2011/08/02]
84. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical research ed)* 2008;336(7650):924-6. doi: 10.1136/bmj.39489.470347.AD [published Online First: 2008/04/26]

Appendix 2. Roles and responsibilities of the Rapid Recommendations contributors

Tasks	Responsibilities								
						Guideline panel			
	Oversight group		Systematic review team(s)						
Role:	RapidRecs steering committee	BMJ Editorial oversight committee	Other systematic review team members	Systematic review lead(s)	Methods co-chair	Clinical chair	Patient liaison	Other panellists	BMJ Graphics Designer
Identify candidate topic									
Agree on topic									
Recruit co-chairs, and SR leads									
Approve co-chairs, and SR leads									
Recruit panel and SR leads									
Recruit SR teams									
Summarize all conflicts of interest									
Approve panel and SR teams									
Schedule panel meetings									
Start SR process on draft PICO									
Educate & empower patient partners									
Finalise PICOs and subgroups									
Complete draft SRs in ~30 days									
Create evidence profile in MAGICapp									
Finalise recommendations									
Draft (or delegate) RapidRec*									
Finalize pre-submission RapidRec									
Co-create infographics									
Identify peer reviewers									
Submit manuscripts to journal									
Expedite usual journal process									
Draft responses to peer reviews									
Agree on final submissions									
Publish papers simultaneously									
Monitor & respond to comments									

*Including manuscript, and MAGICapp content

Note that the tasks are roughly ordered from the first tasks at the top to the last at the bottom. However, to maximise efficiency, several tasks should be ongoing simultaneously.

CHAPTER 4: Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis: a systematic review

The paper presents a rapid systematic review informing the first *Rapid Recommendation.* This paper demonstrated the feasibility of creating and publishing a trustworthy systematic review in just a few months; the first draft of the review was available to the guideline panel within one month.

Advances:
We were one of the first to use Kaplan-Meier curves to reconstruct time-based individual patient data for a detailed picture to estimate the time-changing nature of some outcomes. We were the first to successfully use GRADE to evaluate the quality of the evidence from such an exercise. In this study, the risk of death was higher with surgery, but the increased risk was limited to the first few months after surgery. This cautioned the panel to make a weak rather than strong recommendation, because it gave the panel a clue that the mortality benefit with transcatheter aortic valve insertion might not last long term. The method has since been used more widely in meta-analysis, including by subsequent *Rapid Recommendations*.

Citation:
Siemieniuk RA, Agoritsas T, Manja V, Devji T, Chang Y, Bala MM, Thabane L, Guyatt GH. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis. *BMJ*. 2016 Sep 28;354:i5130. doi: 10.1136/bmj.i5130.

Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis

Reed A Siemieniuk,[1,2] Thomas Agoritsas,[1,3] Veena Manja,[1,4,5] Tahira Devji,[1] Yaping Chang,[1] Malgorzata M Bala,[6] Lehana Thabane,[1] Gordon H Guyatt[1]

[1]Department of Clinical Epidemiology and Biostatistics, McMaster University, 1280 Main St West, Hamilton, ON, Canada L8S 4L8

[2]Department of Medicine, University of Toronto, Toronto, ON, Canada

[3]Division General Internal Medicine, and Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland

[4]Department of Internal Medicine, State University of New York at Buffalo, Buffalo, NY,USA

[5]VA WNY Health Care System at Buffalo, Department of Veterans Affairs, Buffalo, NY, USA

[6]Department of Hygiene and Dietetics, Jagiellonian University Medical College, Kraków, Poland

Correspondence to: R Siemieniuk
reed.siemieniuk@medportal.ca

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ABSTRACT

OBJECTIVE

To examine the effect of transcatheter aortic valve implantation (TAVI) versus surgical replacement of an aortic valve (SAVR) in patients with severe aortic stenosis at low and intermediate risk of perioperative death.

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

Medline, Embase, and Cochrane CENTRAL.

STUDY SELECTION

Randomized trials of TAVI compared with SAVR in patients with a mean perioperative risk of death <8%.

REVIEW METHODS

Two reviewers independently extracted data and assessed risk of bias for outcomes important to patients that were selected a priori by a parallel guideline committee, including patient advisors. We used the GRADE system was used to quantify absolute effects and quality of evidence.

RESULTS

4 trials with 3179 patients and a median follow-up of two years were included. Compared with SAVR, transfemoral TAVI was associated with reduced mortality (risk difference per 1000 patients: –30, 95% confidence interval –49 to –8, moderate certainty), stroke (–20, –37 to 1, moderate certainty), life threatening bleeding (–252, –293 to –190, high certainty), atrial fibrillation (–178, –150 to –203, moderate certainty), and acute kidney injury (–53, –39 to –62, high certainty) but increased short term aortic valve reintervention (7, 1 to 21, moderate certainty), permanent pacemaker insertion (134, 16 to 382, moderate certainty), and moderate or severe symptoms of heart failure (18, 5 to 34, moderate certainty). Compared with SAVR, transapical TAVI was associated higher mortality (57, –16 to 153, moderate certainty, P=0.015 for interaction between transfemoral versus transapical TAVI) and stroke (45, –2 to 125, moderate certainty, interaction P=0.012). No study reported long term follow-up, which is particularly important for structural valve deterioration.

CONCLUSIONS

Many patients, particularly those who have a shorter life expectancy or place a lower value on the risk of long term valve degeneration, are likely to perceive net benefit with transfemoral TAVI versus SAVR. SAVR, however, performs better than transapical TAVI, which is of interest to patients who are not candidates for transfemoral TAVI.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42016042879.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Surgical aortic valve replacement (SAVR) is more invasive than transcatheter aortic valve replacement (TAVI)

TAVI is preferred over SAVR for patients at high or extreme surgical risk

WHAT THIS STUDY ADDS

Success with TAVI relative to SAVR depends on the approach: transfemoral TAVI probably reduces risk of death and stroke while transapical TAVI can increase these risks

TAVI results in a 6% increased risk of symptoms of heart failure and 1% increase in valve reinterventions at two years

Long term outcomes remain uncertain

Introduction

Severe symptomatic aortic stenosis is common and, without aortic valve replacement, results in a life expectancy of less than three years.[1] Each year in the United States, about 75 000 patients undergo surgical aortic valve replacements (SAVR).[2] Because aortic stenosis increases with age, this number will increase with the evolving population demographic.[3]

Transcatheter aortic valve implantation (TAVI) is an increasingly popular alternative to SAVR, at least in part because it does not require thoracotomy.[4] Current practice guidelines recommend either TAVI or SAVR in patients at high surgical risk, defined as a Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) score of 8% or less, but recommend SAVR over TAVI for lower risk patients.[5 6] Despite this recommendation, half of the TAVI centers in Europe perform TAVI in intermediate risk patients (STS-PROM 4-8%) and 10% of centers do so in low risk patients (risk score <4%).[7]

The PARTNER 2A trial compared TAVI with SAVR in intermediate risk patients (risk score 4-8% or <4% with coexisting conditions that are not represented in the STS-PROM model).[8] The authors claimed non-inferiority for TAVI versus SAVR for the primary composite endpoint of death from any cause or disabling stroke at two years. Two recent meta-analyses that included patients from PARTNER 2A suggested that compared with SAVR, TAVI was associated with reduced odds of major bleeding, acute kidney injury, and new onset atrial fibrillation and with increased risks of pacemaker implantation, vascular complications, and aortic regurgitation.[9 10] The reviews did not, however, address the durability of valves and need for

aortic reintervention after TAVI.[9 10] Moreover, the reviews failed to formally rate either the quality of the evidence or the credibility of subgroup analyses (leaving the credibility of findings uncertain) or provide absolute risks, crucial for trading off the desirable and undesirable aspects of TAVI versus SAVR.

The limitations of the prior review prompted us to perform an updated systematic review and meta-analysis of randomized controlled trials of TAVI compared with SAVR for patients at low and intermediate surgical risk. We conducted this systematic review to inform recommendations[11] for the first in a new series in *The BMJ* of trustworthy recommendations published in response to potentially practice changing evidence,[12] so called Rapid Recommendations. Our review complements a co-published meta-analysis of observational data on baseline risk to inform absolute effects[13] and a systematic review on patients' values and preferences to inform the relative importance of outcomes (box 1).[14]

Methods

Protocol

The registered study protocol is available on PROSPERO (CRD42016042879).[15]

Information sources

A search from a previous systematic review that we judged as comprehensive included articles up to 15 July 2012.[16] We complemented that review with a search of Medline, Medline in-process, Embase, and Cochrane CENTRAL from 1 January 2012 to 12 May 2016 using a combination of keywords and MeSH terms for "aortic stenosis" AND "valve replacement", using the sensitive search filters for therapeutic interventions developed by the Health Information Research Unit at McMaster University (appendix 1).[17 18] There were no restrictions on language or publication type. We also searched all references from included studies and studies citing the included studies on Google Scholar.

Study selection

We included randomized controlled trials comparing TAVI and SAVR in patients with severe aortic stenosis and a mean risk score of 8% or less. All titles and abstracts were screened in duplicate with the Covidence online service (Alfred Health, Melbourne, Australia). If either reviewer judged that the study could meet the inclusion criteria, we assessed eligibility in duplicate using the full text.

Data collection process

Two reviewers independently abstracted data and resolved conflicts by discussion. When possible, we analyzed patients in groups to which they were randomized and from the as treated population when intention to treat data were not available.

Summary measures and patient involvement

The outcomes chosen in this research paper were influenced by two people with experience of living with aortic stenosis. It was part of a wider project and is published in the Rapid Recommendation series exploring TAVI versus SAVR for people with severe aortic stenosis.[11] The two patients worked with the panel to list the outcomes that were important to them; they identified several outcomes that other panel members had identified and also uniquely highlighted pain and recovery time as critical to decision making. We were not able to find direct evidence for those outcomes in the randomized controlled trials. All outcomes are consistent with the Valve Academic Research Consortium (VARC)-2 standardized endpoint definitions.[19]

Risk of bias and quality of evidence

We assessed risk of bias in duplicate with a modified Cochrane tool;[20] reviewers resolved conflicts through consensus. With respect to missing data, we judged individual trials at high risk of bias if data from more than 10% of patients were unavailable.

We rated the certainty in the evidence informing absolute effects using the GRADE approach.[21 22] All authors, in consultation with the parallel Rapid Recommendations guidelines panel,[11] participated in and came to consensus regarding certainty of estimates ratings. The GRADE risk of bias assessment included plausible worst case sensitivity analyses addressing missing follow-up data.[23]

Synthesis of results

For dichotomous outcomes we conducted a random effects meta-analysis using both Hartung-Knapp-Sidik-Jonkman (HKSJ) 95% confidence intervals and DerSimonian and Laird confidence intervals of relative risks and chose between the two for the primary report based on plausibility of results.[24] We intended to pool continuous outcomes with mean differences with a similar statistical approach. We present the DerSimonian and Laird confidence intervals for all dichotomous and continuous outcomes because the other confidence intervals were implausibly wide in 15 of the 70 (21.4%) analyses (95% confidence interval of the relative effect >50 or <0.02) and implausibly narrow in two.

For symptoms of heart failure, we used ordinal regression to estimate an odds ratio across the New York Heart Association (NYHA) scores for each study at

Box 1: Linked articles in this *BMJ* Rapid Recommendations cluster

- Foroutan F, Guyatt GH, O'Brien K, et al. Prognosis after surgical replacement with a bioprosthetic aortic valve in patients with severe symptomatic aortic stenosis: systematic review of observational studies. *BMJ* 2016;354:i5065. doi:10.1136/bmj.i5065
- Lytvyn L, Guyatt GH, Manja V, et al. Patient values and preferences on transcatheter or surgical aortic valve replacement therapy for aortic stenosis: a systematic review. *BMJ Open* 2016;6:e014327. doi:10.1136/bmjopen-2016-014327
- Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ* 2016;354:i5085. doi:10.1136/bmj.i5085
  - summary of the results from the Rapid Recommendation process
- Magic App (www.magicapp.org)
  - expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

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the longest follow-up. We then pooled the odds ratios with random effects, weighted by inverse variance. We assumed and tested the proportional odds across NYHA classes for each individual study, using likelihood ratio tests. In this analysis, odds ratios can be interpreted as the odds of having a 1 point increase in NYHA class.

When available, we digitized Kaplan-Meier curves and extracted patient level data on time to event;[25] we took this approach for mortality. We checked the proportional hazards assumption and then fitted a Cox regression model with the study as a random effects (shared frailty) variable and report hazard ratios with confidence intervals. Sensitivity analyses were performed with random effects pooling of the hazard ratios reported in individual studies and by pooling dichotomous data at the prespecified timepoints of one month and one year.

We explored effect modification for four variables: transfemoral versus transapical approach, balloon expandable versus self expanding valve, higher perioperative risk (mean risk score ≥6%) versus lower (<6%), and high versus low risk of bias for each risk of bias criterion. We expected that trials would have outcomes more favorable to TAVI than SAVR if they used a transfemoral approach, balloon expandable valves, and enrolled patients with higher perioperative risk. Subgroup analyses were performed only if there were at least two randomized controlled trials in each subgroup or a trial's report permitted a comparison within the trial (for example, the trial reported results separately for patients with lower versus higher risk). We compared the summary estimates from each subgroup with binary, continuous, or ordinal data with a fixed effect comparison between subgroups, except when a within study subgroup was reported. In those situations, we performed two level mixed effects regression with random effects at the study level. For subgroup analyses of time to event data with extracted patient level and within trial subgroup data available, we used a shared frailty Cox model with random effects at the study level. All primary analyses were performed with STATA v13 (StataCorp, College Station, TX).

To calculate absolute effect estimates, we applied the relative effects from this review to the best estimates of baseline risk. Baseline risk estimates were derived from a systematic review of observational studies of SAVR conducted in parallel with this review for mortality and length of hospital stay.[13] We used the baseline risk from the SAVR arms of the randomized controlled trials for the other outcomes.

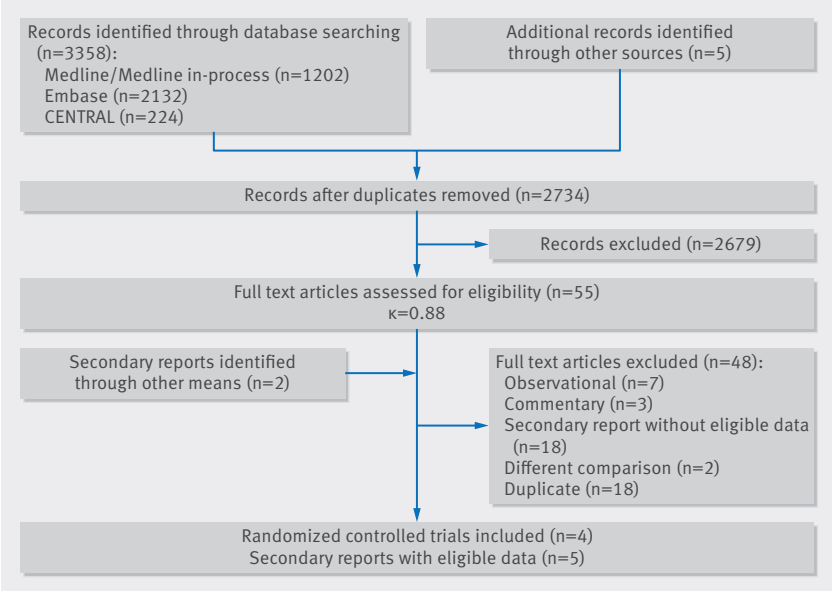

Fig 1 | **PRISMA flow diagram of studies included in review of transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk**

Results

We screened 2734 unique citations, of which 55 were judged potentially eligible during screening of titles and abstracts and four were deemed eligible on full text review (fig 1). The four randomized controlled trials, all published after 2012, included 3179 patients: two trials took place in North America[8 26] and two in Europe.[27 28] We included additional data published in five secondary reports.[29-33] Most patients were men (54%) and most were aged over 80 (table 1; appendix 2 provides additional study characteristics). One study included patients with a mean risk score of 7.4% but required patients with scores <8% to have additional comorbidites not included in the STS-PROM calculator.[26]

Two studies used a percutaneous retrograde approach (transfemoral),[26 28] one study used a transapical approach,[27] and one study used both but stratified randomization based on the heart team's preferred approach (direct aortic approach was grouped with the transapical approach).[8] Across all studies, 94.4% (n=1222) of the patients who underwent percutaneous retrograde TAVI had transfemoral access and 5.6% (n=72) had trans-subclavian access; 77.1% (n=209) of the patients who underwent non-percutaneous TAVI had transapical access and 29% (n=62) had the direct aortic approach.

Assessment of risk of bias

All four trials were at low risk of bias for allocation concealment; none blinded patients, healthcare practitioners, or data collectors, and only one attempted to blind outcome assessors[8] (appendix 3). One study blinded data analysts; this study, however, had a greater degree of missing data than other studies.[26] The TAVI valve industry funded three studies.[8 26 28] All outcomes favoring TAVI, or transfemoral TAVI, over SAVR were robust to worst plausible sensitivity analyses.

Table 2 summarizes findings for all outcomes. Age stratified interactive summary of findings tables are available online at https://www.magicapp.org/public/guideline/aEeKpL. Appendix 4 reports abstracted outcome data by study arm.

Outcomes favoring transfemoral but not transapical TAVI over SAVR

Mortality

At the longest follow-up (median two years), 319 of the 1578 (20.2%) patients undergoing TAVI and 340 of 1550

Table 1 | Characteristics of studies included in review of transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis

Trial	No randomized	Longest follow-up (months)	TAVI valve	No of women (%)	Mean (SD) age (years)	Mean (SD) risk score*	No (%) of patients					
							Low risk (score <4%)	NYHA class III or IV	Diabetes	Atrial fibrillation	Kidney disease	COPD
STACCATO	72	3	Edwards SAPIEN balloon expanding	49 (70.0)	81.0 (4.0)	3.3 (1.4)	NR	34 (48.6)	4 (5.7)	NR	NR	2 (2.9)
US Pivotal	795	36	Medtronic CoreValve self expanding	372 (46.8)	83.4 (6.7)	7.4 (3.1)	75 (9.4)	686 (86.3)	308 (38.7)	351 (44.3)	100 (12.7)	88 (11.1)
NOTION	280	24	Medtronic CoreValve self expanding	131 (46.8)	79.1 (4.8)	3.0 (1.6)	~230 (81.8)	131 (46.8)	54 (19.3)	74 (26.7)	3 (1.1)	33 (11.8)
PARTNER 2A	2032	24	Edwards SAPIEN XT balloon expanding	924 (45.5)	81.6 (6.7)	5.8 (2.0)	~136 (6.7)	1558 (76.7)	730 (35.9)	671 (33.0)	104 (5.1)	627 (30.9)

NR=not reported; NYHA=New York Heart Association; COPD=chronic obstructive pulmonary disease.
*STS-PROM (Society of Thoracic Surgeons predicted risk of mortality) risk score.

(21.9%) patients randomized to SAVR died (hazard ratio 0.86, 95% confidence interval 0.74 to 1.01; I^2=37.6%). The one month mortality was 3.9% for TAVI and 4.0% for SAVR, despite an average predicted risk score of 5.9%.

There was a significant interaction between transfemoral TAVI and transapical TAVI (P=0.015; appendix 5). Mortality was lower with transfemoral TAVI than with SAVR (hazard ratio 0.79, 95% confidence interval 0.66 to 0.94; I^2=0%, 30 fewer per 1000 patients, moderate certainty; fig 2 and table 2). For transapical TAVI, the point estimate suggested harm relative to SAVR, but the confidence interval overlapped no effect (1.34, 0.91 to 1.97, I^2=0%, 57 more per 1000 patients, moderate certainty; fig 3 and table 2).

Stroke

The hazard for stroke was lower with TAVI but the confidence interval overlapped no effect (hazard ratio 0.81, 95% confidence interval 0.63 to 1.01). There was an interaction by approach favoring percutaneous retrograde TAVI over transapical TAVI (P=0.012; fig 4, appendix 5). The relative risk of stroke compared with SAVR was 0.80 (0.63 to 1.01; I^2=0%, 20 fewer per 1000 patients, moderate certainty; table 2) for transfemoral TAVI and 1.67 (0.97 to 2.87; I^2=0%, 45 more per 1000 patients, moderate certainty; table 2) for transapical TAVI.

Acute kidney injury

Acute kidney injury was less common with TAVI (relative risk 0.48, 95% confidence interval 0.27 to 0.84; I^2=50%). Heterogeneity was explained by the TAVI approach (interaction P<0.001; fig 5 and appendix 5). The risk of acute kidney injury for transfemoral TAVI compared with SAVR was 0.38 (0.27 to 0.53; I^2=0%, 53 fewer per 1000 patients, high certainty; table 2) and for transapical TAVI was 1.54 (0.77 to 3.07; I^2=0%, 23 more per 1000 patients, low certainty; table 2).

Outcomes favoring TAVI

Bleeding

The risk of life threatening or disabling bleeding was reduced with TAVI (relative risk 0.39, 95% confidence interval 0.35 to 0.45; I^2=31%). Bleeding was reduced with both transfemoral TAVI (0.39, 0.29 to 0.54; I^2=71%, 252 fewer per 1000 patients, high certainty; table 2) and transapical TAVI (0.53, 0.42 to 0.67; I^2=0%, 194 fewer per 1000 patients, high certainty; table 2), but significantly more so with transfemoral TAVI (P=0.037 for interaction) (fig 6 and appendix 5).

Atrial fibrillation

New onset atrial fibrillation (which includes transient perioperative atrial fibrillation) was less common in patients randomized to TAVI (three studies, relative risk 0.43, 95% confidence interval 0.35 to 0.52; I^2=38%, 178 fewer per 1000 patients, high certainty (table 2 and fig B in appendix 6).

Recovery time

Three trials reported length of index admission to hospital: patients in the TAVI group in the two larger

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Table 2 | GRADE summary of findings for outcomes in review of transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis

Outcome (timeframe*)	Study results (95% CI) and measurements	Absolute effect estimates (per 1000)†		Difference (95% CI)	Certainty in effect estimates (quality of evidence)	Summary
		SAVR	TAVI			
Transfemoral TAVI						
Mortality‡ (2 years)	HR 0.79 (0.66 to 0.94). Based on data from 2576 patients in 3 studies; follow up 2 years	152	122	–30 (–49 to –8)	Moderate (serious imprecision)	Probably reduces risk
Stroke (2 years)	RR 0.80 (0.63 to 1.01). Based on data from 2576 patients in 3 studies; follow up 2 years	99	79	–20 (–37 to 1)	Moderate (serious imprecision)	Probably reduces risk
Acute kidney injury (2 years)	RR 0.38 (0.27 to 0.54). Based on data from 2576 patients in 3 studies; follow-up 2 years	85	32	–53 (–62 to –39)	High	Reduces risk
Life threatening or disabling bleeding (2 years)	RR 0.39 (0.29 to 0.54). Based on data from 2576 patients in 3 studies; follow-up 2 years	413	161	–252 (–293 to –190)	High	Reduces risk
Transapical TAVI						
Mortality‡ (2 years)	HR 1.34 (0.91 to 1.97). Based on data from 552 patients in 2 studies; follow up 2 years	196	253	57 (–16 to 153 more)	Moderate (borderline inconsistency and serious imprecision: I^2=45%, wide CI)	Might increase risk
Stroke (2 years)	RR 1.67 (0.97 to 2.87). Based on data from 552 patients in 2 studies; follow up 2 years	67	112	45 (–2 to 125)	Moderate (serious imprecision: wide CI)	Probably increases risk
Acute kidney injury (2 years)	RR 1.54 (0.77 to 3.07). Based on data from 552 patients in 2 studies; follow up 2 years	43	66	23 (–10 to 89)	Low (serious imprecision and inconsistency)	Might increase risk
Life threatening or disabling bleeding (2 years)	RR 0.53 (0.42 to 0.67). Based on data from 552 patients in 2 studies; follow up 2 years	413	219	–194 (–240 to –136)	High	Reduces risk
TAVI *v* SAVR (outcomes consistent for both TAVI approaches)						
Atrial fibrillation (2 years)	RR 0.43 (0.35 to 0.52). Based on data from 3058 patients in 3 studies; follow-up 2 years	312	134	–178 (–203 to –150)	High	Reduces risk of new onset
Heart failure symptoms (NYHA ≥II) (2 years)	OR 1.29 (1.08 to 1.55). Based on data from 2146 patients in 4 studies; follow-up 2 years	330	389	59 (17 to 103)	High	Increases risk
Moderate/severe heart failure symptoms (NYHA ≥III) (2 years)	OR 1.29 (1.08 to 1.55). Based on data from 2146 patients in 4 studies; follow-up 2 years	69	87	18 (5 to 34)	Moderate (serious imprecision)	Increases risk
Aortic valve reintervention (2 years)	RR 3.25 (1.29 to 8.14). Based on data from 3058 patients in 3 studies; follow-up 2 years	3	10	7 (1 to 21)	Moderate (serious imprecision: wide CI. Rated down for indirectness because follow-up period not long enough)	Probably increases risk
Permanent pacemaker insertion (2 years)	RR 2.46 (1.17 to 5.15). Based on data from 3128 patients in 4 studies; follow-up 2 years	92	226	134 (16 to 382)	High (I^2=88% but not rated down because all studies suggested benefit)	Increases risk
Myocardial infarction (2 years)	RR 0.87 (0.59 to 1.29). Based on data from 3128 patients in 4 studies; follow-up 2 years	36	31	–5 (–15 to 10)	Moderate (serious risk of bias: inadequate blinding of outcome assessors)	Might have little or no impact
Health related quality of life (2 years)	Measured by: difference from baseline in KCCQ score. Minimal important difference 5 points. Scale: 0-100 (high better). Based on data from 797 patients in 1 study (US Pivotal); follow-up 2 years	Mean 18.7 points	Mean 22.2 points	3.5 (–1.9 to 8.9)	Low (serious risk of bias and serious imprecision)	Might have little or no impact
Length of index admission§	Measured by scale (lower better). Based on data from 2032 patients in 1 study	Median 12.0 days	Median 8.0 days	–4.0 (–5 to –3)	High	Reduces length of stay

HR=hazard ratio, RR=relative risk, OR=odds ratio, NYHA=New York Heart Association, KCCQ=Kansas City Cardiomyopathy Questionnaire.
*Median follow-up
†Unless otherwise specified.
‡Age adjusted baseline risk of death for ages 75-85, calculated from baseline risk of death with SAVR in a linked meta-analysis of observational studies.[13]
§Calculated from baseline risk of death with SAVR in linked meta-analysis of observational studies.[13]

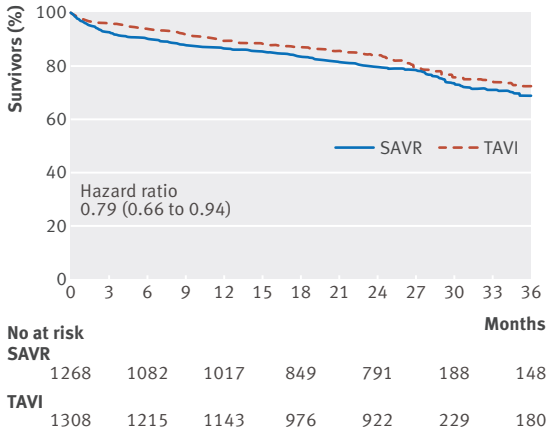

Fig 2 | **Kaplan-Meier survival curve for transfemoral transcatheter aortic valve implantation (TAVI) versus surgical aortic valve replacement (SAVR) for severe aortic stenosis. NOTION and PARTNER 2A provided data to 24 months, and US Pivotal provided data to 36 months**

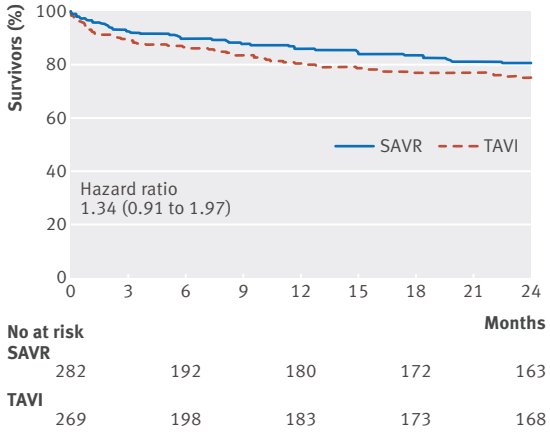

Fig 3 | **Kaplan-Meier survival curve for transapical transcatheter aortic valve implantation (TAVI) versus surgical aortic valve replacement (SAVR) for severe aortic stenosis. STACCATO provided data to 3 months, and PARTNER 2A provided data to 24 months**

studies (n=2308) were in hospital for about three and four fewer days than the SAVR group (both about 33% shorter and P≤0.001).[8 28] We could not pool data because one randomized controlled trial did not report standard deviations.[8] There was no significant difference in the smallest STACCATO trial, but numbers were not reported.[27]

Pain

No studies reported on pain after the intervention.

Outcomes favoring SAVR

Symptoms of heart failure

The TAVI group had higher odds of having 1 point worse symptoms of heart failure on the NYHA scale than the SAVR group (odds ratio 1.29, 95% confidence interval 1.08 to 1.55 (ordinal regression); I^2=0%; fig C in appendix 6). For every 1000 patients, 59 (17 to 103) more patients experienced any symptoms of heart failure, of which 18 (5 to 34) were NYHA class III or IV (moderate certainty; table 2). The proportional odds assumption was not violated for any study.

Aortic valve reintervention

Aortic valve reinterventions occurred more often in the TAVI group at a median of two years (relative risk 3.25, 95% confidence interval 1.29 to 8.14; I^2=0%, 7 more per 1000 patients, moderate certainty; table 2 and fig D in appendix 6).

Insertion of permanent pacemaker

Permanent pacemaker insertion was more common with TAVI than SAVR (relative risk 2.45, 95% confidence interval 1.17 to 5.14; I^2=88%, 134 more per 1000 patients, moderate certainty; table 2 and fig 7).

Moderate or severe aortic valve regurgitation

Aortic valve regurgitation of at least moderate severity was more common in the TAVI group than in the SAVR group (three randomized controlled trials, relative risk 12.22, 95% confidence interval 5.17 to 28.88; I^2=0%, 80 more per 1000 patients, high certainty; fig E in appendix 6).

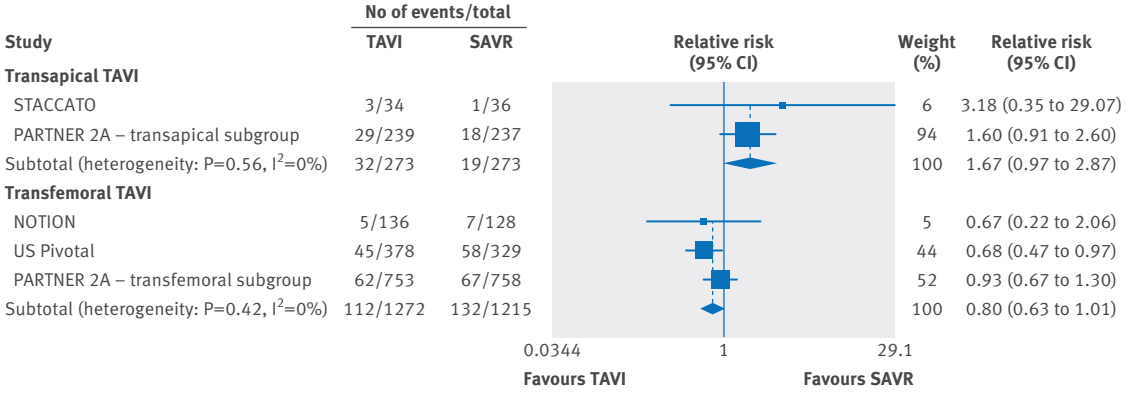

Fig 4 | **Forest plot for relative risk of stroke at longest follow-up for transcatheter aortic valve implantation (TAVI) compared with surgical aortic valve replacement (SAVR) for severe aortic stenosis, by valve approach. P=0.012 for interaction**

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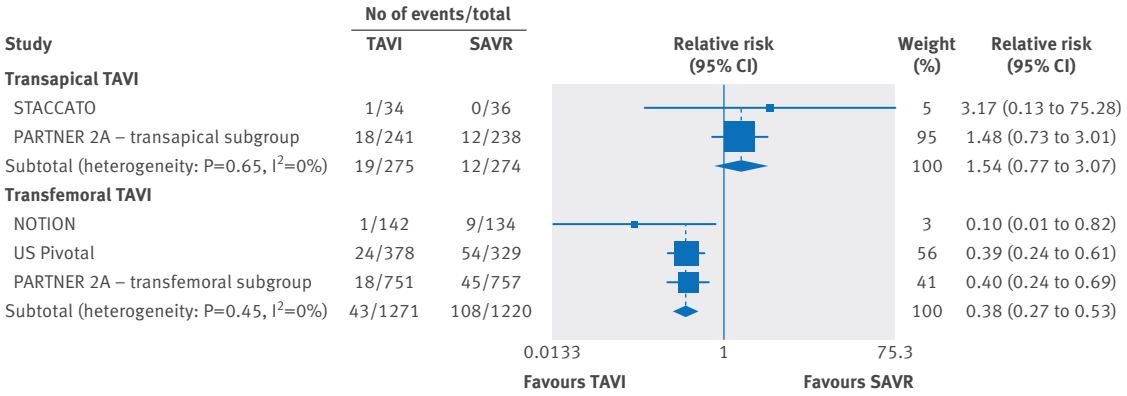

Fig 5 | **Forest plot for relative risk of acute kidney injury at longest follow-up for transcatheter aortic valve implantation (TAVI) compared with surgical aortic valve replacement (SAVR) for severe aortic stenosis, by valve approach. P<0.001 for interaction**

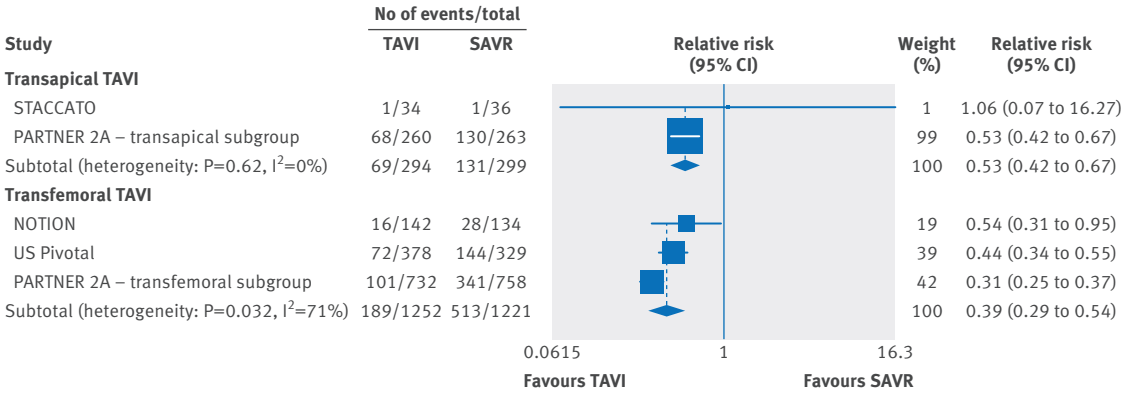

Fig 6 | **Forest plot for relative risk of life threatening or disabling bleeding at longest follow-up for transcatheter aortic valve implantation (TAVI) compared with surgical aortic valve replacement (SAVR) for severe aortic stenosis, by valve approach. P=0.037 for interaction**

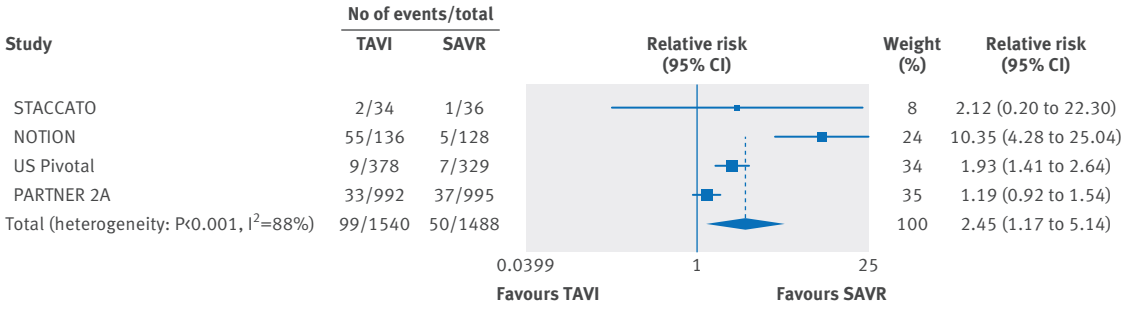

Fig 7 | **Forest plot for permanent pacemaker insertion at longest follow-up for transcatheter aortic valve implantation (TAVI) compared with surgical aortic valve replacement (SAVR) for severe aortic stenosis**

Outcomes similar between groups

Myocardial infarction

There was no detectable difference in myocardial infarction between TAVI and SAVR (relative risk 0.87, 95% confidence interval 0.58 to 1.29; I^2=0%, 5 fewer per 1000 patients, moderate certainty; table 2 and fig F in appendix 6).

Health related quality of life (HRQoL)

Only the US Pivotal[26] and STACCATO[27] trials reported HRQoL. The PARTNER 2A study protocol included HRQoL, but the primary publication did not include these data.[8] The US Pivotal trial found an improvement between groups that was important to patients in overall HRQoL at one month in the TAVI group, but there was no difference with SAVR at six months and up to two years.[29 30] The STACCATO trial found no differences between groups in HRQoL at three months.[27]

Sensitivity and other subgroup analyses

The STACCATO trial was stopped early and was the only study to exclusively use a transapical approach.[27]

Sensitivity analyses without STACCATO did not change statistical or clinical interpretation for any outcome.

As the included studies otherwise had similar risks of bias, subgroup analyses by risk of bias were not possible. Results at one year were similar to those at longest follow-up (appendix 7). There were no credible subgroup differences between balloon expandable and self expanding valves or between trials enrolling patients at higher or lower perioperative risk (appendix 5).

Discussion

This review shows that in patients with severe aortic stenosis, for several outcomes, transfemoral TAVI results in better outcomes relative to SAVR than the transapical approach relative to SAVR; this was true for mortality, stroke, acute kidney injury, and bleeding. These subgroup effects are highly credible. They are among a small number of a priori hypotheses with a prespecified direction, including a comparison within studies,[8] chance is an unlikely explanation, and the effect is consistent across these related outcomes.[34]

Mortality was reduced with transfemoral TAVI compared with SAVR by about 3%, stroke by 2%, acute kidney injury by 5%, bleeding by 24%, new onset atrial fibrillation by 18%, and duration of index admission by three days. These benefits, however, come with associated harms. TAVI was associated with an increased risk of experiencing symptoms of heart failure by about 6% (2% of which were moderate or severe), permanent pacemaker insertion by about 15%, and aortic valve reintervention over the short term by about 1%.

The picture is quite different with transapical TAVI, which, though it probably shares benefits of less bleeding, less atrial fibrillation, and shorter hospital stay, increased the risk of stroke compared with SAVR by about 5% and could also increase mortality.

Strength and limitations

Strengths of this review include a comprehensive search for evidence; duplicate assessment of eligibility, risk of bias, and data abstraction; and assessments of risk of bias that included addressing loss to follow-up across studies (and found results robust to loss to follow-up).[23] The review included rigorous assessment of the quality of evidence (and found the quality for many critical outcomes high and others moderate) and of the credibility of subgroup analyses (with crucial differences between transfemoral and transapical TAVR approaches). We have presented absolute and relative risks, which are crucial for making decisions between TAVI and SAVR.

Limitations include a modest total number of patients (3179) and questionable generalization of results to low risk patients (most patients were at intermediate rather than low surgical risk). The randomized controlled trials used bioprosthetic valves, typically used in older patients, in all SAVRs.[5 6] Our results therefore apply only to patients who have already chosen to use a bioprosthetic valve instead of a mechanical valve. No trial reported recovery time—beyond length of hospital stay—or pain after the intervention, two outcomes that our patient representatives identified as important. The incidence of chronic pain after sternotomy is about 28% and 13% for any and moderate pain at one year, respectively, suggesting that chronic pain might be less common in TAVI.[35] An unadjusted observational study that included both TAVI and SAVR patients, however, showed no difference in pain scores at three months.[36] We are not able to ascertain how much of the increased risk of atrial fibrillation with SAVR represents transient postoperative atrial fibrillation—less important for patients than persistent atrial fibrillation. Further, we did not find a subgroup effect by type of TAVI valve on pacemaker insertion and thus present a single estimate of effect. We note, however, that there is evidence external to this review that self expanding valves impart a higher risk of need for pacemaker insertion than balloon expanding valves.[37] Technology for TAVI[38 39] and SAVR[40] is continually changing, potentially further increasing the attractiveness of the TAVI option.

The most important limitation is that the relatively short duration of follow-up leaves uncertainty about one critical outcome: the need for reintervention over the longer term, a major concern with TAVI valves. We did find that TAVI is associated with a higher risk of aortic valve reintervention, although we were not able to determine whether this was because of paravalvular regurgitation or structural valve degeneration, and the absolute risk was low. The younger the patient, the greater the extent to which the uncertainty regarding the long term durability of TAVI valves is likely to influence the decision between TAVI and SAVR.

Our findings are consistent with those from recently published meta-analyses for many outcomes,[9 10] but we have also provided absolute as well as relative risks and a formal rating of the quality of the evidence and documented the credibility of the crucial outcome differences between transfemoral and transapical TAVI approaches. Further, we quantified several new findings, including an increased risk of aortic valve reintervention, an increased risk of symptoms of heart failure with TAVI, and an increased risk of life threatening or disabling bleeding (rather than major bleeding, which is less important to patients) with SAVR.

In conclusion, we have clarified the trade-offs between TAVI and SAVR and identified issues of residual uncertainty. For patients with lower life expectancy (such as those aged over 85), in whom longer term valve deterioration is likely to be less of an issue, the benefits of transfemoral TAVI versus SAVR on mortality, stroke, life threatening or disabling bleeding, and a less invasive procedure are compelling. Younger patients (such as those aged 65-85), who are less concerned about the limited evidence regarding valve deterioration and the necessity for a second procedure, might (or might not) also find these mortality and morbidity benefits compelling. Even younger patients (such as those aged under 65), for whom valve longevity could be extremely important, are more likely to choose SAVR over TAVI or even to choose a mechanical over a bioprosthetic valve. Finally, patients in whom a transfemoral TAVI approach

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is not feasible are unlikely to view the transapical approach, which is associated with a higher rate of stroke and a possibly higher mortality rate than SAVR, as an attractive option.

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Contributors: Frederick Spencer, Per Vandvik, RAS, TA, and GHG conceived the study idea. RAS performed the literature search and data analysis. RAS, TA, VM, and GHG interpreted the data analysis. RAS and VM wrote the first draft of the manuscript. TA, VM, TD, YC, and MMB acquired the data and judged risk of bias in the studies. TD extracted patient level survival data from Kaplan-Meier curves. LT provided statistical advice. TA, VM, TD, YC, MMB, and GHG critically revised the manuscript. RAS had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. RAS is guarantor.

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Ethical approval: Not required.

Data sharing: Abstracted trial level and patient level survival data, as well as STATA code will be made publicly available on publication.

Transparency declaration: The lead author (RAS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

1 Turina J, Hess O, Sepulcri F, Krayenbuehl HP. Spontaneous course of aortic valve disease. *Eur Heart J* 1987;8:471-83.
2 HCUPnet. Healthcare Cost and Utilization Project Rockville, MD Agency for Healthcare Research and Quality. [Available from: http://hcupnet.ahrq.gov/.
3 Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368:1005-11. doi:10.1016/S0140-6736(06)69208-8.
4 Holmes DR Jr, Nishimura RA, Grover FL, et al. STS/ACC TVT Registry. Annual Outcomes With Transcatheter Valve Therapy: From the STS/ACC TVT Registry. *J Am Coll Cardiol* 2015;66:2813-23. doi:10.1016/j.jacc.2015.10.021.
5 Vahanian A, Alfieri O, Andreotti F, et al. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012;33:2451-96. doi:10.1093/eurheartj/ehs109.
6 Nishimura RA, Otto CM, Bonow RO, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2438-88. doi:10.1016/j.jacc.2014.02.537.
7 Petronio AS, Capranzano P, Barbato E, et al. Current status of transcatheter valve therapy in Europe: results from an EAPCI survey. *EuroIntervention* 2016;12:890-5. doi:10.4244/EIJY16M06_01.
8 Leon MB, Smith CR, Mack MJ, et al. PARTNER 2 Investigators. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med* 2016;374:1609-20. doi:10.1056/NEJMoa1514616.
9 Gargiulo G, Sannino A, Capodanno D, et al. Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement: A Systematic Review and Meta-analysis. *Ann Intern Med* 2016;165:334-44. doi:10.7326/M16-0060.
10 Siontis GC, Praz F, Pilgrim T, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. *Eur Heart J* 2016;ehw225. doi:10.1093/eurheartj/ehw225.
11 Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ* 2016;354:i5085.
12 Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:i5191.
13 Foroutan F, Guyatt GH, O'Brien K, et al. Prognosis after surgical replacement with a biprosthetic aortic valve in patients with severe symptomatic aortic stenosis: systematic review of observational studies. *BMJ* 2016;354:i5065.
14 Lytvyn L, Guyett GH, Manja V, et al. Patient values and preferences on transcatheter or surgical aortic valve replacement therapy for aortic stenosis: a systematic review. *BMJ Open* 2016;6:e0147327.
15 Siemieniuk RA, Agoritsas T, Manja V, et al. PROTOCOL: Transcatheter versus surgical aortic valve replacement in low and intermediate risk patients with severe aortic stenosis: a systematic review and meta-analysis. PROSPERO, 2016 http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016042879.
16 Cao C, Ang SC, Indraratna P, et al. Systematic review and meta-analysis of transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis. *Ann Cardiothorac Surg* 2013;2:10-23.
17 Health Information Research Unit. Search Filters for MEDLINE in Ovid Syntax and the PubMed translation 2016 http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx.
18 Health Information Research Unit. Search Strategies for EMBASE in Ovid Syntax 2016 http://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx.
19 Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J* 2012;33:2403-18. doi:10.1093/eurheartj/ehs255.
20 Busse JWG. G. Modification of Cochrane tool to assess risk of bias in randomized trials 2013 https://distillercer.com/wp-content/uploads/2014/02/Tool-to-Assess-Risk-of-Bias-in-Randomized-Controlled-Trials.docx.
21 Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. doi:10.1136/bmj.39489.470347.AD.
22 Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008;336:995-8. doi:10.1136/bmj.39490.551019.BE.
23 Akl EA, Johnston BC, Alonso-Coello P, et al. Addressing dichotomous data for participants excluded from trial analysis: a guide for systematic reviewers. *PLoS One* 2013;8:e57132. doi:10.1371/journal.pone.0057132.
24 Siemieniuk R, Vandvik P, Alonso-Coello P, et al. Hartung-Knapp-Sidik-Jonkman confidence intervals can be bizarrely narrow when heterogeneity is very low. Cochrane Colloquium. Seoul, Korea, 2016.
25 Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;12:9. doi:10.1186/1471-2288-12-9.
26 Adams DH, Popma JJ, Reardon MJ, et al. U.S. CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;370:1790-8. doi:10.1056/NEJMoa1400590.
27 Nielsen HH, Klaaborg KE, Nissen H, et al. A prospective, randomised trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve replacement in operable elderly patients with aortic stenosis: the STACCATO trial. *EuroIntervention* 2012;8:383-9. doi: 10.4244/EIJV8I3A58
28 Thyregod HG, Steinbrüchel DA, Ihlemann N, et al. Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis: 1-Year Results From the All-Comers NOTION Randomized Clinical Trial. *J Am Coll Cardiol* 2015;65:2184-94. doi:10.1016/j.jacc.2015.03.014.
29 Arnold SV, Reynolds MR, Wang K, et al. CoreValve US Pivotal Trial Investigators. Health Status After Transcatheter or Surgical Aortic Valve Replacement in Patients With Severe Aortic Stenosis at Increased Surgical Risk: Results From the CoreValve US Pivotal Trial. *JACC Cardiovasc Interv* 2015;8:1207-17. doi:10.1016/j.jcin.2015.04.018.
30 Chatterjee S, Kumbhani DJ, Sardar P, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: an updated review of literature. *Curr Cardiol Rep* 2014;16:473. doi:10.1007/s11886-014-0473-8.
31 Deeb GM, Reardon MJ, Chetcuti S, et al. CoreValve US Clinical Investigators. 3-Year Outcomes in High-Risk Patients Who Underwent Surgical or Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol* 2016;67:2565-74. doi:10.1016/j.jacc.2016.03.506.
32 Reardon MJ, Adams DH, Kleiman NS, et al. 2-Year Outcomes in Patients Undergoing Surgical or Self-Expanding Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol* 2015;66:113-21. doi:10.1016/j.jacc.2015.05.017.

33 Søndergaard L, Steinbrüchel DA, Ihlemann N, et al. Two-Year Outcomes in Patients With Severe Aortic Valve Stenosis Randomized to Transcatheter Versus Surgical Aortic Valve Replacement: The All-Comers Nordic Aortic Valve Intervention Randomized Clinical Trial. *Circ Cardiovasc Interv* 2016;9:e003665. doi:10.1161/CIRCINTERVENTIONS.115.003665.
34 Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010;340:c117. doi:10.1136/bmj.c117.
35 Meyerson J, Thelin S, Gordh T, Karlsten R. The incidence of chronic post-sternotomy pain after cardiac surgery--a prospective study. *Acta Anaesthesiol Scand* 2001;45:940-4. doi:10.1034/j.1399-6576.2001.450804.x.
36 Kocaaslan C, Ketenci B, Yılmaz M, et al. Comparison of Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement to Improve Quality of Life in Patients >70 Years of Age with Severe Aortic Stenosis. *Braz J Cardiovasc Surg* 2016;31:1-6.
37 Abdel-Wahab M, Neumann FJ, Mehilli J, et al. CHOICE Investigators. 1-Year Outcomes After Transcatheter Aortic Valve Replacement With Balloon-Expandable Versus Self-Expandable Valves: Results From the CHOICE Randomized Clinical Trial. *J Am Coll Cardiol* 2015;66:791-800. doi:10.1016/j.jacc.2015.06.026.
38 Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. *Eur Heart J* 2016;37:2252-62. doi:10.1093/eurheartj/ehw112.
39 Manoharan G, Walton AS, Brecker SJ, et al. Treatment of Symptomatic Severe Aortic Stenosis With a Novel Resheathable Supra-Annular Self-Expanding Transcatheter Aortic Valve System. *JACC Cardiovasc Interv* 2015;8:1359-67. doi:10.1016/j.jcin.2015.05.015.
40 Borger MA, Moustafine V, Conradi L, et al. A randomized multicenter trial of minimally invasive rapid deployment versus conventional full sternotomy aortic valve replacement. *Ann Thorac Surg* 2015;99:17-25. doi:10.1016/j.athoracsur.2014.09.022.

Appendix 1: Search strategy
Appendix 2: Additional study characteristics
Appendix 3: Risk of bias of included studies
Appendix 4: Abstracted event numbers and patients evaluated at longest follow-up
Appendix 5: Subgroup and sensitivity analyses
Appendix 6: Supplementary forest plots A-E
Appendix 7: Sensitivity analyses of outcomes at prespecified timepoints

Appendix 1: Search strategy [posted as supplied by authors]

Cochrane CENTRAL:
(Aortic stenosis OR aorta stenosis OR Aortic Valve Stenoses OR aortic valve stenosis) AND (aortic valve implantation OR heart valve implantation OR TAVR OR TAVI OR transcatheter OR transfemoral OR transapical OR transaxillary OR SAVR OR heart valve replacement OR surgical aortic valve replacement OR surgical AVR OR SAVR)
In: Title, abstract, keywords
Limits: Publication Year from 2012, in Trials (Word variations have been searched)

Ovid Medline (May week 1 2016) and Medline in-process (May 12 2016):
1. Aortic Stenosis.mp. or exp Aortic Valve Stenosis/
2. (aortic valve implantation or TAVR or transcatheter or transfemoral or transapical or transaxillary or SAVR or heart valve replacement or surgical aortic valve replacement or surgical AVR or SAVR or TAVI or aortic valve replacement or transvascular).af.
3. clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs.
4. 1 and 2 and 3
5. limit 4 to yr="2012 -Current"
6. limit 5 to humans

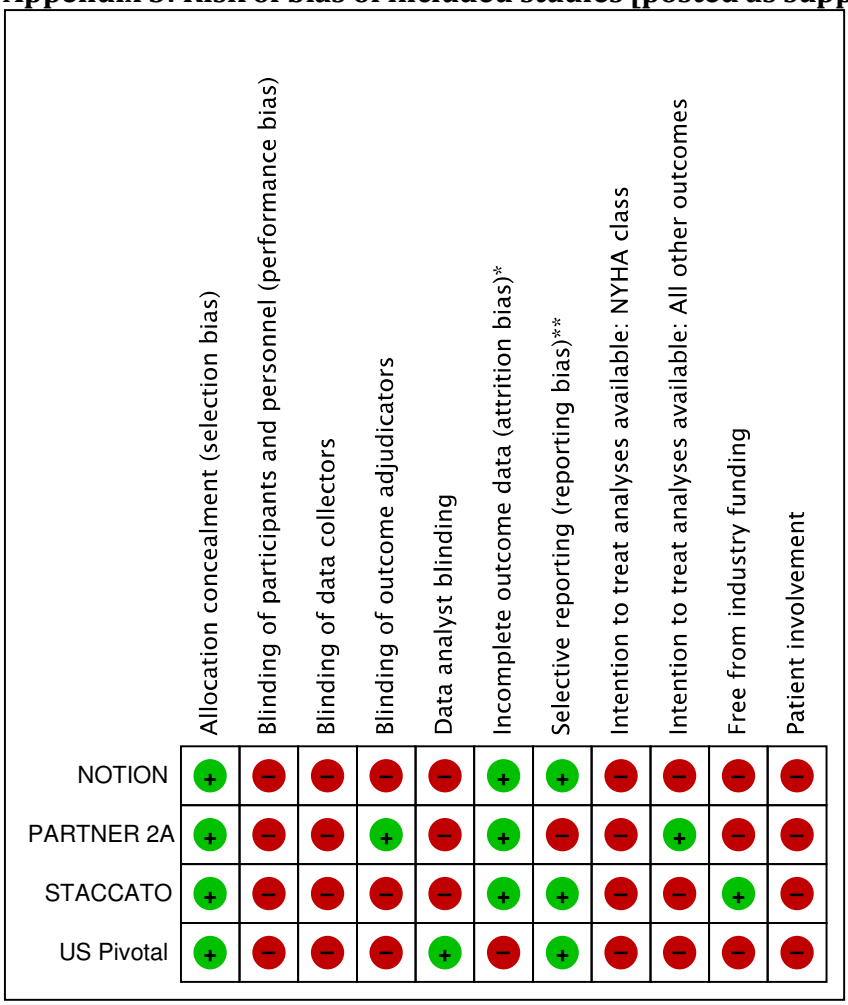
Ovid EMBASE (2016 Week 19):
1. aortic stenosis.mp. or exp aorta stenosis/
2. (aortic valve implantation or heart valve implantation or TAVR or TAVI or transcatheter or transfemoral or transapical or transaxillary or SAVR or heart valve replacement or surgical aortic valve replacement or surgical AVR or SAVR or aortic valve replacement or transvascular).af.
3. random:.tw. or placebo:.mp. or double-blind:.tw.
4. 1 and 2 and 3
5. limit 4 to yr="2012 -Current"
6. limit 5 to human

Appendix 2 Additional study characteristics [posted as supplied by author]

Study	Number of centres	Study design	TAVI n randomized n treated	SAVR n randomized n treated	TAVI approach (n % transfemoral) (n % transsubclavian) (n % transapical) (n % transaortic)	n CAD (%)	n prior CABG (%)	n prior PCI (%)	n PVD (%)	n prior pacemaker (%)
STACCATO	2	RCT	36 34	36 34	0 0 70 (100) 0	NR	NR	NR	5 (7.1)	NR
US Pivotal	45	RCT	394 390	401 357	323 (82.8) 67 (17.2)* 0 0	603 (75.8)	238 (29.9)	285 (35.8)	332 (42.1)	175 (22.0)*
NOTION	3	RCT	145 139	135 135	137 (96.5) 5 (3.5) 0 0	14 (5.0)**	NR	23 (8.2)	15 (5.4)	11 (3.9)
PARTNER 2A	57	RCT	1011 994	1021 944	775 (76.7) 0 174 (17.2) 62 (6.1)	1379 (67.9)	500 (24.6)	556 (27.4)	618 (30.4)	241 (11.9)

TAVI, transcatheter aortic valve insertion; CAD, coronary artery disease; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCT, randomized controlled trial; NR, not reported;
*Pacemaker or implantable cardiodefibrillator
**Prior myocardial infarction

Appendix 3: Risk of bias of included studies [posted as supplied by author]



Risk of bias judgments for individual studies
NYHA, New York Heart Association
*>10% of patients missing
**The PARTNER 2A trial did not report health-related quality of life in their initial publication, despite it being a prespecified outcome

Appendix 4: Abstracted event numbers and patients evaluated at longest follow-up [posted as supplied by author]

	STACCATO		US Pivotal		NOTION		PARTNER 2A All		PARTNER 2A Transfemoral subgroup		PARTNER 2A Transapical subgroup	
	TAVI events/n	SAVR events/n	TAVI events/n	SAVR events/n	TAVI events/n	SAVR events/n	TAVI events/n	SAVR events/n	TAVI events/n	SAVR events/n	TAVI events/n	SAVR events/n
Mortality	4/34	0/36	126/381	160/359	11/142	10/134	166/992	170/1021	108/775	124/775	58/236	46/246
Stroke	3/34	1/36	45/378	58/329	5/136	7/128	91/992	85/995	62/753	67/758	29/239	18/237
Bleeding*	1/34	1/36	72/378	144/329	16/142	28/134	169/992	471/1021	101/732	341/758	68/260	130/263
Major vascular complications	5/34	1/36	27/378	7/329	8/142	2/134	86/992	55/995	69/775	34/775	17/236	21/246
Atrial fibrillation	--	--	71/386	121/337	30/142	79/134	110/992	273/995	55/775	211/775	55/236	62/246
Acute kidney injury	1/34	0/36	24/378	54/329	1/142	9/134	36/992	57/995	18/751	45/757	18/241	12/238
Aortic valve reintervention	--	--	9/378	1/329	0/136	0/128	13/992	5/995	9/775	5/775	4/236	0/246
Myocardial infarction	--	--	9/378	7/329	7/136	8/128	33/992	37/995	21/775	29/775	12/236	8/246
Permanent pacemaker insertion	2/34	1/36	102/378	46/329	55/136	5/128	114/992	96/995	85/775	77/775	29/236	19/246
NYHA class ≥3	4/30	4/36	13/146	15/195	4/123	4/114	74/737	45/649	--	--	--	--
Aortic regurgitation**	--	--	13/190	0/139	19/123	1/112	49/600	4/514	--	--	--	--

*Life threatening or disabling bleeding.
**Moderate or severe aortic regurgitation

Appendix 5: Subgroup and sensitivity analyses [posted as supplied by author]

Subgroup	Studies	I^2	Relative effect (95% CI)*	Interaction P
Mortality				
Transfemoral	3	0.0**	HR: 0.79 (0.66 to 0.94)	0.015
Transapical***	2	0.0**	HR: 1.34 (0.91 to 1.97)	
Balloon expandable	2	22.4**	HR: 0.93 (0.75 to 1.15)	0.35
Self-expanding	2	0.0**	HR: 0.79 (0.62 to 1.00)	
Lower risk***	2	43.3**	HR: 0.95 (0.37 to 2.29)	0.85
Higher risk	2	27.4**	HR: 0.86 (0.73 to 1.01)	
Without STACCATO	3	0.0**	HR: 0.85 (0.73 to 1.00)	
Stroke				
Transfemoral	3	0.0	0.80 (0.63 to 1.01)	0.012
Transapical	2	0.0	1.67 (0.97 to 2.87)	
Balloon expandable	2	0.0	1.09 (0.83 to 1.45)	0.033
Self-expanding	2	0.0	0.68 (0.48 to 0.95)	
Lower risk	2	33.9	1.08 (0.27 to 4.40)	0.77
Higher risk	2	74.7	0.86 (0.55 to 1.36)	
Without STACCATO	3	52.4	0.85 (0.58 to 1.23)	
Acute kidney injury				
Transfemoral	3	0.0	0.38 (0.27 to 0.54)	<0.001
Transapical	2	0.0	1.54 (0.77 to 3.07)	
Balloon expandable	2	0.0	0.65 (0.43 to 0.98)	0.169
Self-expanding	2	34.1	0.30 (0.11 to 0.84)	
Lower risk	1	68.3	0.46 (0.02 to 12.80)	0.96
Higher risk	2	59.8	0.50 (0.31 to 0.81)	
Without STACCATO	3	57.9	0.45 (0.26 to 0.79)	
Life-threatening or disabling bleeding				
Transfemoral	3	70.9	0.39 (0.29 to 0.54)	0.037
Transapical	2	0.0	0.53 (0.42 to 0.67)	
Balloon expandable	2	0.0	0.37 (0.32 to 0.43)	0.125
Self-expanding	2	0.0	0.45 (0.36 to 0.56)	
Lower risk	2	0.0	0.55 (0.32 to 0.97)	0.23
Higher risk	2	21.5	0.39 (0.34 to 0.45)	
Without STACCATO	3	20.7	0.40 (0.34 to 0.47)	
Heart failure symptoms				
Transfemoral	3			--
Transapical	1			
Balloon expandable	2	0.0	OR: 1.36 (1.10 to 1.68)	0.41
Self-expanding	2	0.0	OR: 1.15 (0.83 to 1.60)	
Lower risk	2	0.0	OR: 1.24 (0.75 to 2.05)	0.86
Higher risk	2	0.0	OR: 1.30 (1.08 to 1.57)	
Without STACCATO	3	0.0	OR: 1.29 (1.08 to 1.55)	
Permanent pacemaker insertion				
Transfemoral	3	92.2	2.45 (1.06 to 5.78)	0.64
Transapical	2	0.0	1.62 (0.95 to 2.76)	
Balloon expandable	2	0.0	1.20 (0.93 to 1.55)	>0.99
Self-expanding	2	92.5	4.23 (0.77 to 23.62)	
Lower risk	2	35.5	6.88 (1.75 to 27.05)	0.039
Higher risk	2	81.5	1.50 (0.94 to 2.41)	
Without STACCATO	3	91.8	2.50 (1.13 to 5.52)	

HR, hazard ratio; OR, odds ratio

*Relative risk unless otherwise specified. All relative effects are presented as transcatheter aortic valve insertion (TAVI) versus surgical aortic valve replacement (SAVR).

**I^2 is reported from pooling of study-level data

***Estimate from a fixed-effects stratified Cox regression model because the random effects (shared frailty) model was too complex for the data.

Subgroup analyses were not possible for atrial fibrillation, permanent pacemaker insertion, aortic valve reintervention, myocardial infarction, or moderate/severe aortic regurgitation because there were not at least 2 in each study.

Appendix 6: Supplementary forest plots [posted as supplied by author]

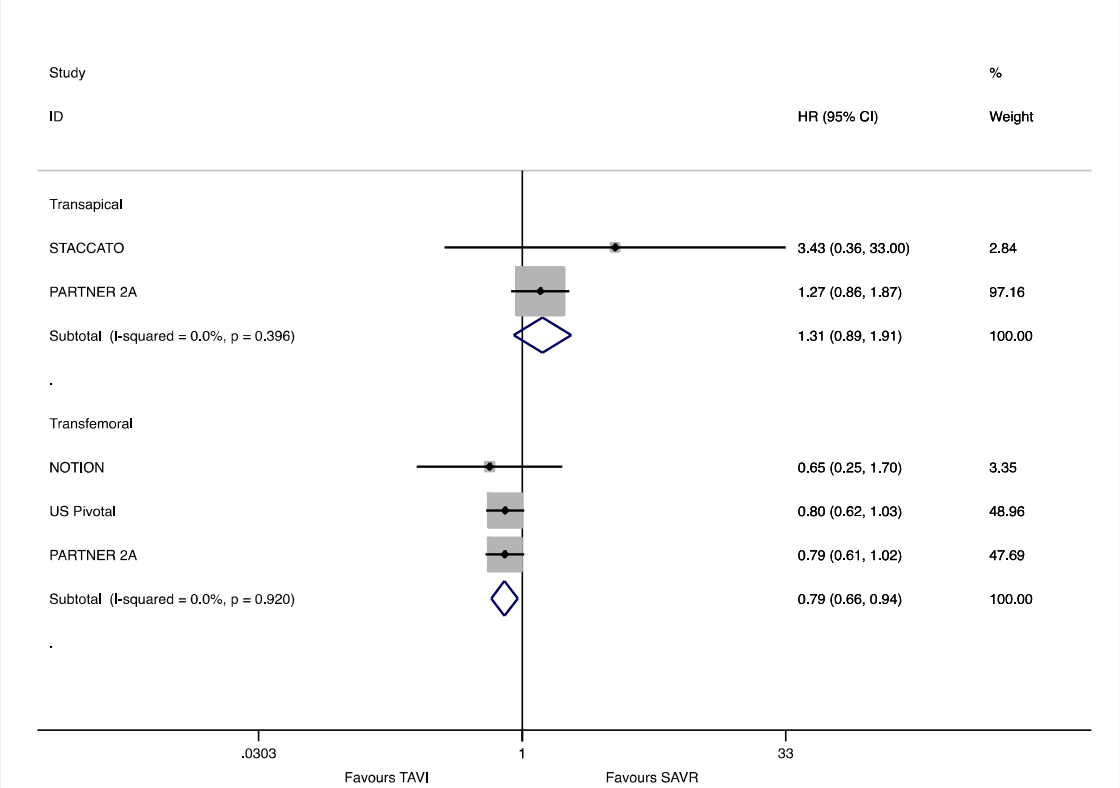


Figure A. Sensitivity analysis: forest plot of the reported hazard ratios for mortality.

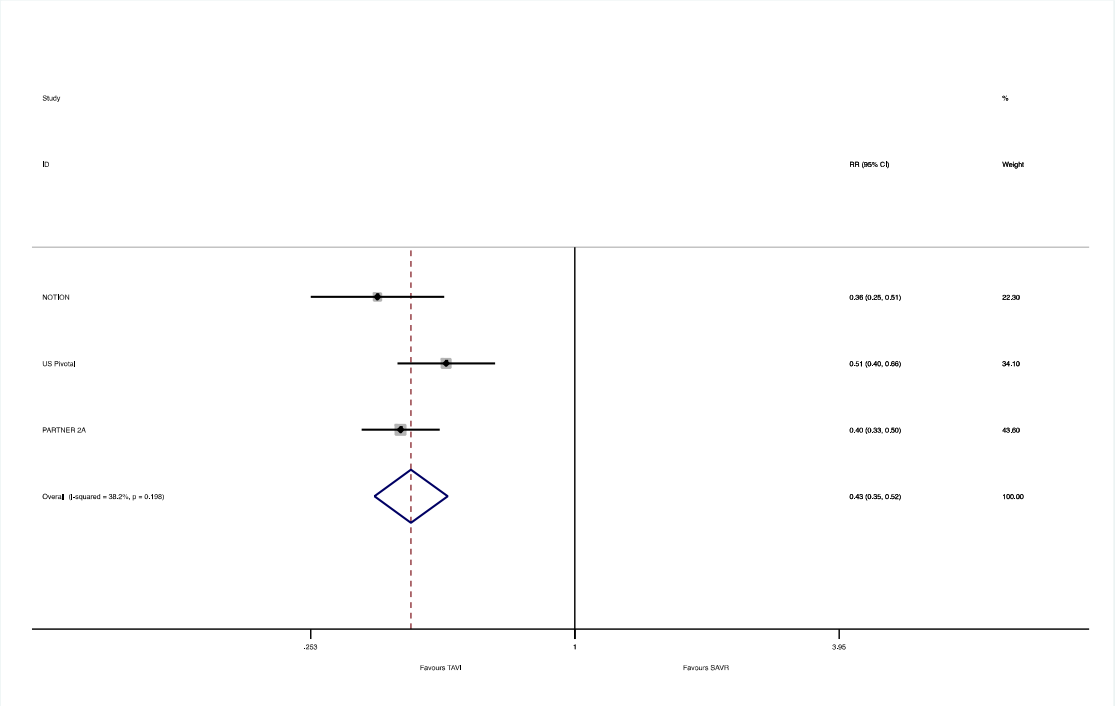


Figure B. Forest plot of relative risk for new onset atrial fibrillation at the longest follow-up for transcatheter aortic valve implantation (TAVI) compared to surgical aortic valve replacement (SAVR) for severe aortic stenosis.

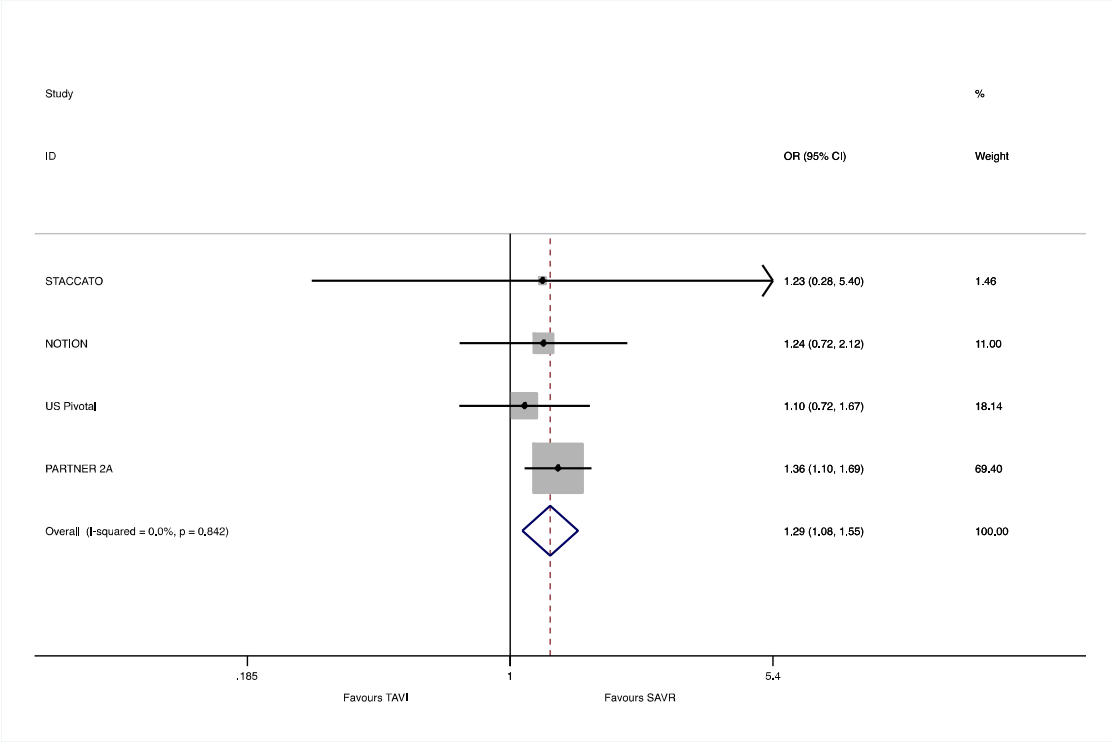


Figure C. Forest plot for odds of having 1-point worse heart failure symptoms on the New York Heart Association (NYHA) scale at the longest follow-up. The proportional odds model was used.

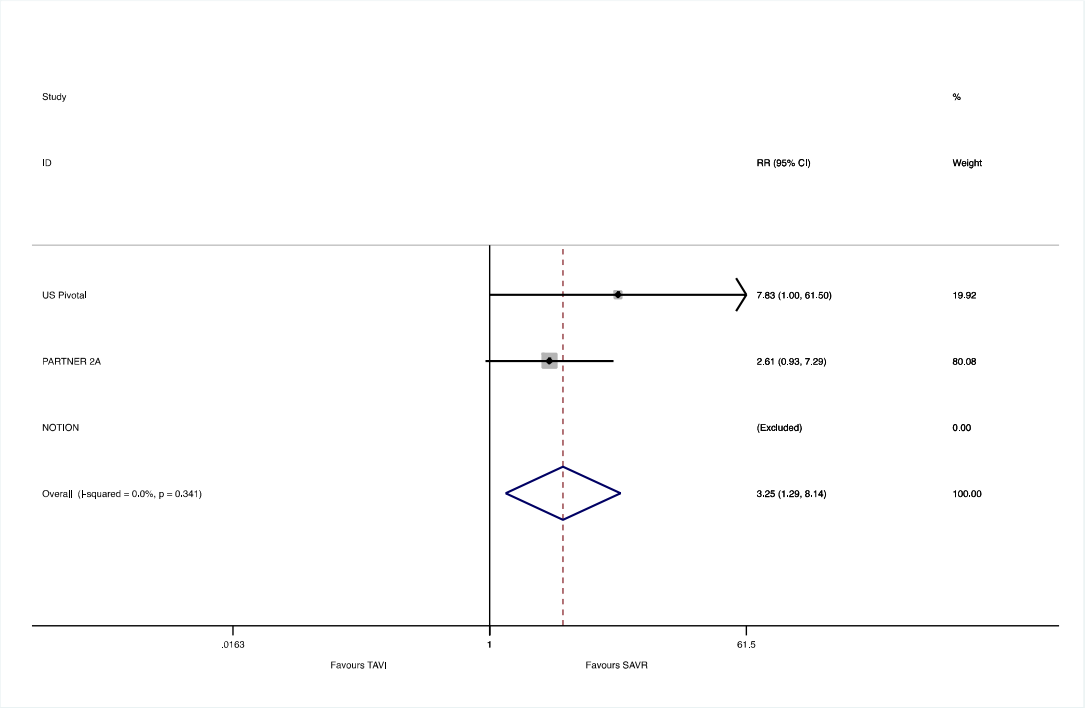


Figure D. Forest plot for relative risk of aortic valve reintervention at the longest follow-up for transcatheter aortic valve implantation (TAVI) compared to surgical aortic valve replacement (SAVR) for severe aortic stenosis. The NOTION trial was excluded because there were no reinterventions in either arm.

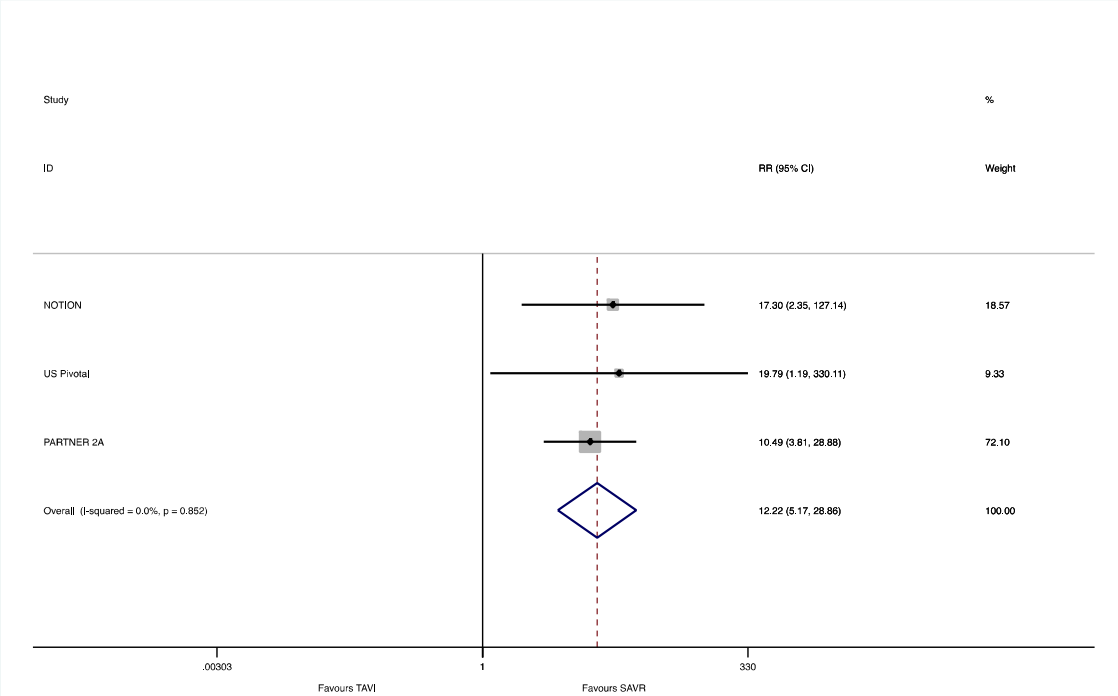


Figure E. Forest plot for relative risk of moderate-to-severe aortic regurgitation at the longest follow-up for transcatheter aortic valve implantation (TAVI) compared to surgical aortic valve replacement (SAVR) for severe aortic stenosis.

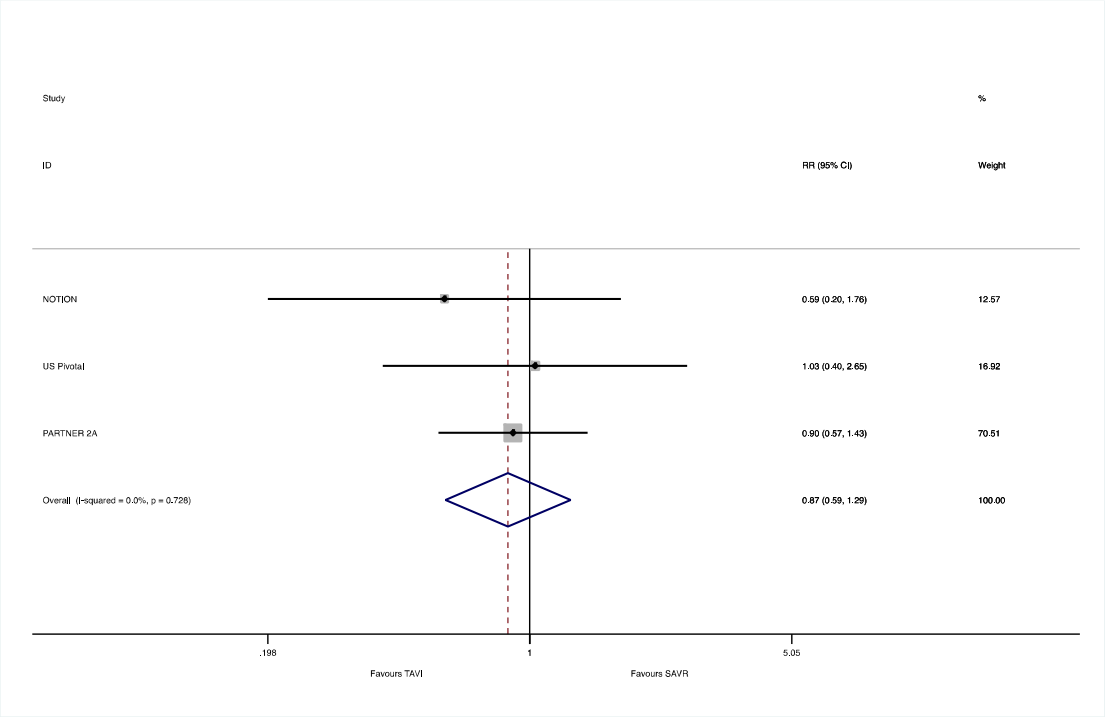


Figure E. Forest plot for relative risk of myocardial infarction at the longest follow-up for transcatheter aortic valve implantation (TAVI) compared to surgical aortic valve replacement (SAVR) for severe aortic stenosis.

Appendix 7. Sensitivity analyses of outcomes at prespecified timepoints [posted as supplied by author]

Outcome	Follow-up time	Studies	Relative effect (95% CI)*	I^2
Mortality	1 year	3	0.94 (0.76 to 1.12)	0.0
	1 month	4	0.95 (0.67 to 1.34)	0.0
Stroke	1 year	3	0.88 (0.69 to 1.13)	0.0
	1 month	4	0.88 (0.65 to 1.19)	0.0
Acute kidney injury	1 year	3	0.52 (0.30 to 0.88)	64.2
	1 month	4	0.39 (0.26 to 0.60)	9.8
Life-threatening bleeding	1 year	2	0.37 (0.29 to 0.48)	64.4
	1 month	4	0.36 (0.23 to 0.56)	77.1
Atrial fibrillation	1 year	3	0.40 (0.34 to 0.47)	17.6
	1 month	3	0.35 (0.29 to 0.41)	0.0
Heart failure symptoms**	1 year	3	OR: 1.25 (0.90 to 1.74)	62.9
	1 month	2	OR: 0.66 (0.55 to 0.78)	19.4
Myocardial infarction	1 year	3	0.84 (0.54 to 1.31)	0.0
	1 month	3	0.62 (0.35 to 1.10)	0.0
Aortic valve reintervention	1 year	3	3.68 (1.06 to 12.74)	10.7
	1 month	3	7.65 (0.96 to 61.16)	0.0
PPM insertion	1 year	3	2.71 (1.11 to 6.64)	91.7
	1 month	4	3.10 (1.21 to 7.95)	87.0
Moderate/severe aortic regurgitation	1 year	3	3.00 (0.64 to 14.12)	86.9
	1 month	3	2.84 (0.55 to 14.72)	92.2

CI, confidence interval; OR, odds ratio; PPM, permanent pacemaker
The median longest follow-up time was 2 years
*Relative risk unless otherwise specified
**Odds of having a 1-point worse New York Heart Association heart failure symptom score class. OR>1 favours surgical aortic valve replacement.

CHAPTER 5: Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline

This is a *Rapid Recommendation* on the use of arthroscopy for degenerative knee disease. We made a strong recommendation against the use of arthroscopy.

Advances:
We incorporated data on subjective patient-reported outcomes using a linked meta-analysis on minimally important differences (MIDs). Making a strong recommendation implies that almost all informed patients would choose the same course of action, and that the evidence is unlikely to substantially change. Arthroscopy reduces pain and improves function in the short term, but the effects do not last. Based on the review of MIDs, the guideline panel unanimously agreed that almost no one would choose to go through the pain and recovery period for such a small short-term benefit. This approach to incorporating MIDs has since been successfully adopted by others, including subsequent *Rapid Recommendations*.

Citations:
Siemieniuk RAC, Harris IA, Agoritsas T, Poolman RW, Brignardello-Petersen R, Van de Velde S, Buchbinder R, Englund M, Lytvyn L, Quinlan C, Helsingen L, Knutsen G, Olsen NR, Macdonald H, Hailey L, Wilson HM, Lydiatt A, Kristiansen A. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *BMJ*. 2017 May 10;357:j1982. doi: 10.1136/bmj.j1982.

Siemieniuk RAC, Harris IA, Agoritsas T, Poolman RW, Brignardello-Petersen R, Van de Velde S, Buchbinder R, Englund M, Lytvyn L, Quinlan C, Helsingen L, Knutsen G, Olsen NR, Macdonald H, Hailey L, Wilson HM, Lydiatt A, Kristiansen A. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *Br J Sports Med*. 2018 Mar;52(5):313. doi: 10.1136/bjsports-2017-j1982rep

RAPID RECOMMENDATIONS

Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline

Reed A C Siemieniuk,[1 2] Ian A Harris,[3 4] Thomas Agoritsas,[1 5] Rudolf W Poolman,[6] Romina Brignardello-Petersen,[1 7] Stijn Van de Velde,[8] Rachelle Buchbinder,[9 10] Martin Englund,[11] Lyubov Lytvyn,[12] Casey Quinlan,[13] Lise Helsingen,[14] Gunnar Knutsen,[15] Nina Rydland Olsen,[16] Helen Macdonald,[17] Louise Hailey,[18] Hazel M Wilson,[19] Anne Lydiatt,[20] Annette Kristiansen[21 22]

Full author details can be found at the end of the article

Correspondence to: R Siemieniuk
reed.siemieniuk@medportal.ca

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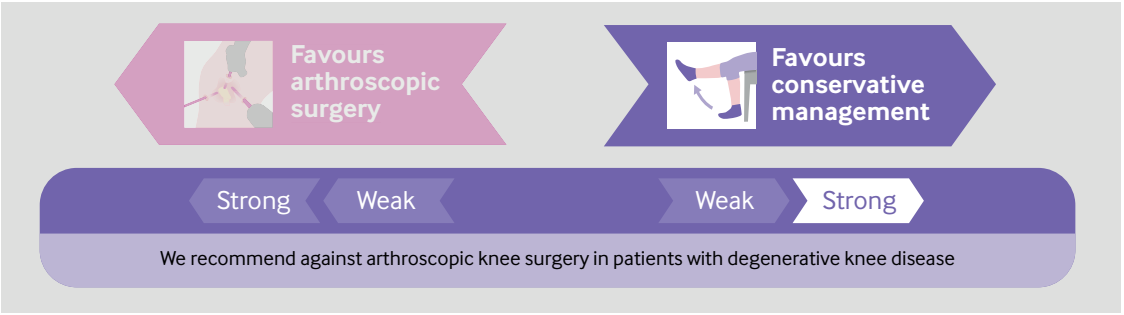
doi: 10.1136/bmj.j1982

This BMJ Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. BMJ Rapid Recommendations represent a collaborative effort between the MAGIC group (www.magicproject.org) and The BMJ. A summary is offered here and the full version including decision aids is on the MAGICapp (www.magicapp.org), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualisation of our recommendations to local contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact The BMJ for permission to reuse content in this article.



What is the role of arthroscopic surgery in degenerative knee disease? An expert panel produced these recommendations based on a linked systematic review triggered by a randomised trial published in The BMJ in June 2016, which found that, among patients with a degenerative medial meniscus tear, knee arthroscopy was no better than exercise therapy. The panel make a strong recommendation against arthroscopy for degenerative knee disease. Box 1 shows all of the articles and evidence linked in this Rapid Recommendation package. The infographic provides an overview of the absolute benefits and harms of arthroscopy in standard GRADE format. Table 2 below shows any evidence that has emerged since the publication of this article.

Current practice

Approximately 25% of people older than 50 years experience knee pain from degenerative knee disease (box 2).[2 3] Management options include watchful waiting, weight loss if overweight, a variety of interventions led by physical therapists, exercise, oral or topical pain medications such as non-steroidal anti-inflammatory drugs, intra-articular corticosteroid and other injections, arthroscopic knee surgery, and knee replacement or osteotomy. The preferred combination or sequence of these options is not clear and probably varies between patients.

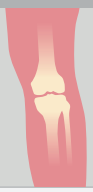
Knee replacement is the only definitive therapy, but it is reserved for patients with severe disease after non-operative management has been unsuccessful.[4 5] Some believe that arthroscopic debridement, including wash-out of intra-articular debris, with or without arthroscopic partial meniscectomy to remove damaged meniscus, may improve pain and function.

Current guidelines generally discourage arthroscopy for patients with clear radiographic evidence of osteoarthritis alone, but several support or do not make clear statements regarding arthroscopic surgery in other common groups of patients (table 1).

WHAT YOU NEED TO KNOW

- We make a strong recommendation against the use of arthroscopy in nearly all patients with degenerative knee disease, based on linked systematic reviews; further research is unlikely to alter this recommendation
- This recommendation applies to patients with or without imaging evidence of osteoarthritis, mechanical symptoms, or sudden symptom onset
- Healthcare administrators and funders may use the number of arthroscopies performed in patients with degenerative knee disease as an indicator of quality care.
- Knee arthroscopy is the most common orthopaedic procedure in countries with available data
- This Rapid Recommendation package was triggered by a randomised controlled trial published in *The BMJ* in June 2016 which found that, among patients with a degenerative medial meniscus tear, knee arthroscopy was no better than exercise therapy

Population

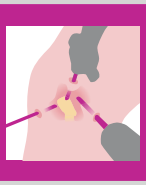


People with degenerative knee disease

Including people with or without:

- Radiographic evidence of osteoarthritis
- Mild to severe osteoarthritis
- Mechanical symptoms
- Acute onset knee pain
- Meniscal tears

Choice of intervention



Arthroscopic surgery

Arthroscopic surgery with or without partial meniscectomy or debridement

or

Conservative management

Any conservative management strategy (exercise therapy, injections, drugs)

Recommendations

Favours arthroscopic surgery		Favours conservative management	
Strong	Weak	Weak	**Strong**

We recommend against arthroscopic knee surgery in patients with degenerative knee disease

Comparison of benefits and harms

Favours arthroscopic surgery | No important difference | Favours conservative management

	Mean score (0–100, high better)			Evidence quality
Long term benefits (1–2 years)				
Pain	21.9	No important difference	18.8	★★★★ High
Function	13.3	No important difference	10.1	★★★☆ Moderate
Short term benefits (<3 months)	Mean score (0–100, high better)			
Pain	20.4	**5.38 higher**	15.0	★★★★ High
Function	14.2	**4.94 higher**	9.3	★★★☆ Moderate
Short term harms (<3 months)	Events per 1000 people			
Venous thromboembolism	5	**5 fewer**	0	★★☆☆ Low
Infection	2	**2 fewer**	0	★★☆☆ Low

Key practical issues

Arthroscopic surgery	Conservative management
Performed by a surgeon, in an operating theatre	May be performed in hospital or the community
Recovery typically between 2 to 6 weeks	No recovery time
At least 1–2 weeks off work, depending on speed of recovery and physical demands of job	Time off work may be required for appointments, such as physiotherapy and injections

Interpreting the outcomes

The panel agreed "Minimally important difference" scores for pain and function, which represent what most patients would consider a worthwhile change:

Pain 12 | Function 8

Preferences and values

The panel believes that almost everyone would prefer to avoid the pain and inconvenience of the recovery period after arthroscopy, since it offers only a small chance of a small benefit

Resourcing

Arthroscopy is not cost-effective from a societal perspective

Box 1 | Linked articles in this *BMJ* Rapid Recommendations cluster

- Siemieniuk RAC, Harris IA, Agoritsas T, et al. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *BMJ* 2017;257:j1982. doi:10.1136/bmj.j1982
  Summary of the results from the Rapid Recommendation process
- Brignardello-Peterson R, Guyatt GH, Schandelmaier S, et al. Knee arthroscopy versus conservative management in patients with degenerative knee disease: a systematic review. *BMJ Open* 2017;7:e016114. doi:10.1136/bmjopen-2017-016114
  Review of all available randomised trials that assessed the benefits of knee arthroscopy compared with non-operative care and observational studies that assessed risks
- Devji T, Guyatt GH, Lytvyn L, et al. Application of minimal important differences in degenerative knee disease outcomes: a systematic review and case study to inform BMJ Rapid Recommendations. *BMJ Open* 2017;7:e015587. doi:10.1136/bmjopen-2016-015587
  Review addressing what level of individual change on a given scale is important to patients (minimally important difference). The study informed sensitivity analyses for the review on net benefit, informed discussions on patient values and preferences, and was key to interpreting the magnitude of effect sizes and the strength of the recommendation
- MAGICapp (www.magicapp.org)
  Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

Box 2 | What is degenerative knee disease?

- Degenerative knee disease is an inclusive term, which many consider synonymous with osteoarthritis. We use the term degenerative knee disease to explicitly include patients with knee pain, particularly if they are >35 years old, with or without:
  - Imaging evidence of osteoarthritis
  - Meniscus tears
  - Locking, clicking, or other mechanical symptoms except persistent objective locked knee
  - Acute or subacute onset of symptoms
- Most people with degenerative arthritis have at least one of these characteristics.[1] The term degenerative knee disease does not include patients having recent debut of their symptoms after a major knee trauma with acute onset of joint swelling (such as haemarthrosis)

Arthroscopic knee surgery for degenerative knee disease is the most common orthopaedic procedure in countries with available data[14] and on a global scale is performed more than two million times each year (fig 1).[15-18] Arthroscopic procedures for degenerative knee disease cost more than $3bn per year in the US alone.[19] A high prevalence of features advocated to respond positively to arthroscopic surgery (such as meniscal tears, mechanical symptoms, and sudden symptom onset) as well as financial incentives may explain why arthroscopic knee surgery continues to be so common despite recommendations against its use for osteoarthritis. Further, patients may be frustrated with their symptoms, having tried several less invasive management strategies by the time that they see the surgeon, and in many cases this may come with an expectation for surgical management. Moreover, many patients experience important and marked improvements after arthroscopy, which may be erroneously attributed to the effects of the procedure itself instead of the natural course of the disease, co-interventions, or placebo effects.

Table 1 | Support from current guidance for arthroscopic surgery in patients with subgroups of degenerative knee disease

	Lavage or debridement			Partial meniscectomy for meniscal tears	
	Patients with radiographic osteoarthritis	Patients without radiographic osteoarthritis	Patients with mechanical symptoms	Patients with evidence of osteoarthritis	Patients without evidence of osteoarthritis
AAOS[6]	Against	Supportive	Supportive	Supportive	Supportive
NICE[7 8]	Against	Against	For	No comment	No comment
ESSKSA[9]	Against	For	For	Against	For
BOA[10]*	Against	For	For	No comment	For
AOA[11]*	Against	No comment	No comment	Against	For
OARSI[12 13]	Against	No comment	No comment	Supportive	No comment

AAOS=American Academy of Orthopaedic Surgeons; NICE=National Institute of Health and Care Excellence; ESSKSA=European Society for Sports Traumatology, Knee Surgery and Arthroscopy; BOA=British Orthopaedic Association; AOA=Australian Orthopaedic Association; OARSI=Osteoarthritis Research Society International.
For=Explicit statement that arthroscopy should be performed in some patients.
Against=Explicit statement that arthroscopy should not be performed in some patients.
Supportive=Seemingly supportive of arthroscopy in some contexts.
*Official statement, not guidelines

The evidence

The panel requested two systematic reviews to inform the recommendation.[20 21]

The systematic review on the net benefit of knee arthroscopy compared with non-operative care pools data from 13 randomised trials for benefit outcomes (1668 patients) and an additional 12 observational studies for complications (>1.8 million patients).[21] Figure 2 gives an overview of the patients included, the study funding, and patient involvement in the design of the studies.

Panel members identified three outcomes—pain, function, and quality of life—as the most important for patients with degenerative knee disease who are considering surgery. Although the included studies reported these patient-important outcomes, it is difficult to know whether changes recorded on an instrument measuring subjective symptoms are important to those with symptoms—for example, a change of three points might have completely different meanings in two different pain scales.

Therefore, a second team performed a linked systematic review addressing what level of individual change on a given scale is important to patients,[20] a characteristic called the minimally important difference (MID).[22] The study identified a range of credible MIDs for each key outcome; this range of MID estimates informed sensitivity analyses for the review on net benefit, informed discussions on the patient values and preferences, and was key to interpreting the magnitude of effect sizes as well as the strength of the recommendation.[20]

Understanding the recommendations

The infographic provides an overview of the benefits and harms of arthroscopy in standard GRADE format.

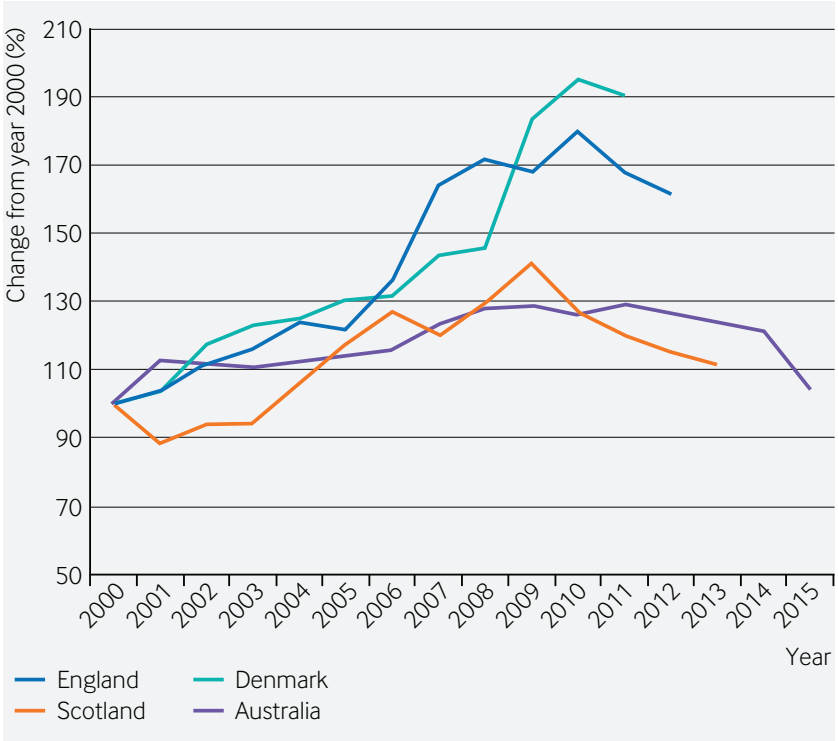


Fig 1 | Population adjusted trends in frequency of knee arthroscopy; percent. Arthroscopic knee surgery remains common despite accumulating evidence suggesting little benefit

Estimates of baseline risk for effects comes from the control arms of the trials; for complications, comparator risk was assumed to be nil.

The panel is confident that arthroscopic knee surgery does not, on average, result in an improvement in long term pain or function. Most patients will experience an important improvement in pain and function without arthroscopy. However, in <15% of participants, arthroscopic surgery resulted in a small or very small improvement in pain or function at three months after surgery—this benefit was not sustained at one year. In addition to the burden of undergoing knee arthroscopy (see practical issues below), there are rare but important harms, although the precision in these estimates is uncertain (low quality of evidence).

It is unlikely that new information will change interpretation of the key outcomes of pain, knee function, and quality of life (as implied by high to moderate quality of evidence).

The panel is confident that the randomised controlled trials included adequate representation from groups commonly cited to derive benefit from arthroscopic knee surgery for degenerative knee disease—notably those with meniscal tears, no or minimal radiographic evidence of osteoarthritis, and those with sudden but non-traumatic symptom onset. Thus the recommendation applies to all or almost all patients with degenerative knee disease. Further, the evidence applies to patients with any severity of mechanical symptoms, with the only possible exception being those who are objectively unable to fully extend their knee (that is, a true locked knee). We did not consider young patients with sports related injuries or patients with major trauma in any age.

Trials that enrolled a majority of patients without radiographic osteoarthritis showed similar effect sizes to trials enrolling patients with radiographic evidence of osteoarthritis. Most of these trials exclusively included patients

HOW THE RECOMMENDATION WAS CREATED

A randomised controlled trial published in *The BMJ* in June 2016 found that, among patients with a degenerative medial meniscus tear, knee arthroscopy was no better than exercise therapy.[32] This study adds to the body of evidence suggesting that the benefits of arthroscopy may not outweigh the burden and risks.[33 34] The *RapidRecs* executive felt that the study, when considered in context of the full body of evidence, might change practice.[35]

Our international panel including orthopaedic surgeons, a rheumatologist, physiotherapists, a general practitioner, general internists, epidemiologists, methodologists, and people with lived experience of degenerative knee disease (including those who had undergone and those who had not undergone arthroscopy) met to discuss the evidence. No person had financial conflicts of interest; intellectual and professional conflicts were minimised and managed (see appendix 1 on bmj.com).

The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation[35 36] and used the GRADE approach to critically appraise the evidence and create recommendations (appendix 2).[37] The panel considered the balance of benefits, harms, and burdens of the procedure, the quality of evidence for each outcome, typical and expected variations in patient values and preferences, and acceptability. Recommendations can be strong or weak, for or against a course of action.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Three people with lived experience of osteoarthritis, one of whom had arthroscopic knee surgery, were full panel members. These panel members identified important outcomes and led the discussion on values and preferences. Pain was weighed as higher importance for most patients: for example, the patient panel members felt that a possible small benefit to function without a reduction in pain would be unimportant to almost all patients. Those with lived experience identified key practical issues including concerns with cost and accessibility for both arthroscopy and interventions provided by physiotherapists. The members participated in the teleconferences and email discussions and met all authorship criteria.

EDUCATION INTO PRACTICE

- Project: how many arthroscopic procedures are scheduled in your organisation for degenerative knee disease?
- Based on the information you have read in this article or in this package of Rapid Recommendation articles, is there anything which you might alter your practice?
- To what extent might you use information in this article to alter the conversations you have with patients with degenerative knee disease, or those considering arthroscopic surgery?

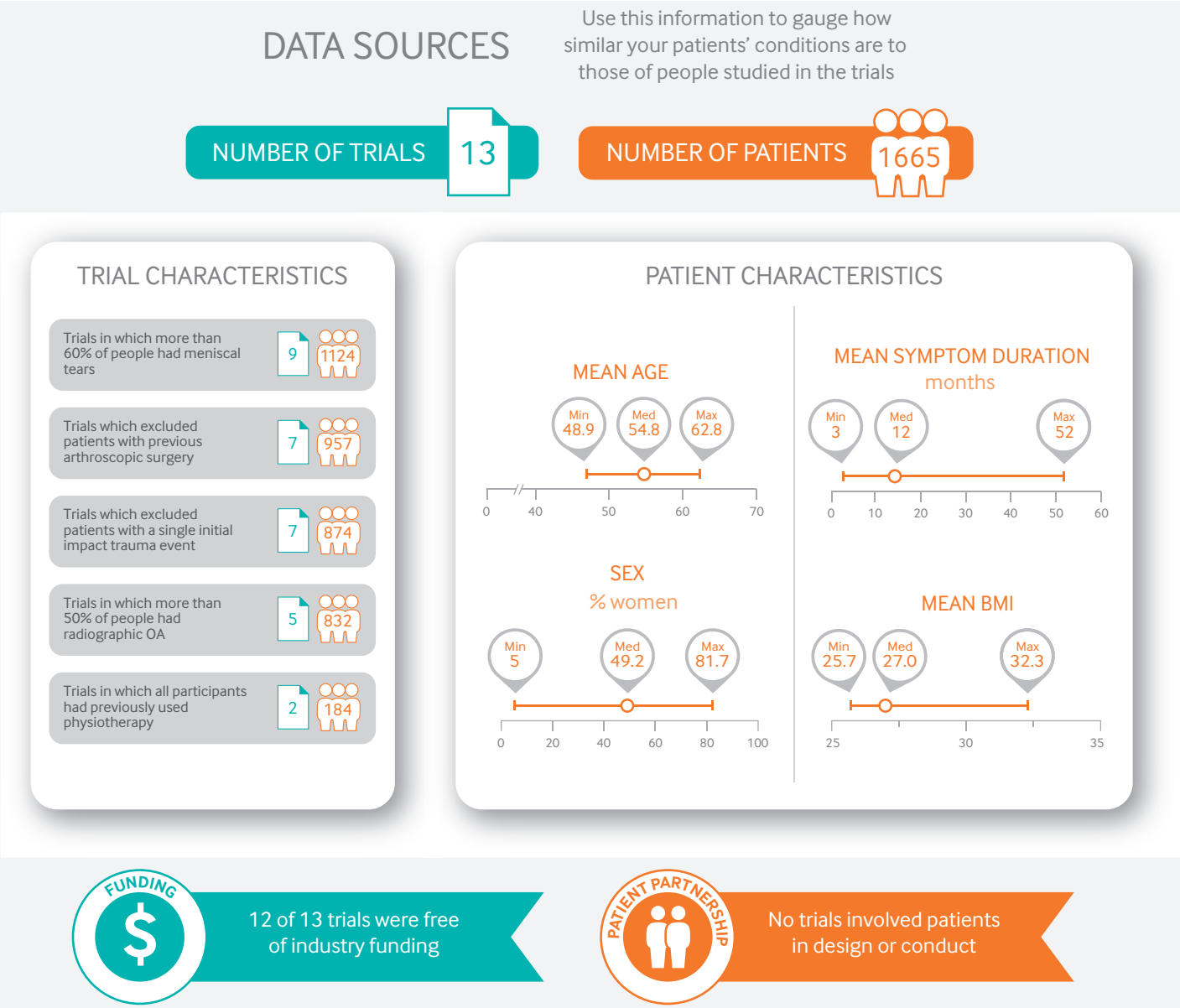


Fig 2| Characteristics of patients and trials included in systematic review of arthroscopic knee surgery

with meniscus tears. Meniscus tears are common, usually incidental findings, and unlikely to be the cause of knee pain, aching, or stiffness.[1] Mechanical symptoms were also a prominent feature for most trial participants, and many had sudden or subacute onset of symptoms.[23-26] Given that there is evidence of harm and no evidence of important lasting benefit in any subgroup, the panel believes that the burden of proof rests with those who suggest benefit for any other particular subgroup before arthroscopic surgery is routinely performed in any subgroup of patients.

Practical issues

It takes between two and six weeks to recover from arthroscopy, during which time patients may experience pain, swelling, and limited function.[27 28] Most patients cannot bear full weight on the leg (that is, they may need crutches) in the first week after surgery, and driving or physical activity is limited during the recovery period.[27] Figure 3 outlines the key practical issues for those considering arthroscopic knee surgery versus non-surgical management for degenerative knee disease.

Degenerative knee disease is a chronic condition in which symptoms fluctuate. On average, pain tends to improve over time after seeing a physician for pain,[21 29] and delaying knee replacement is encouraged when possible.[4]

Values and preferences

Our strong recommendation against arthroscopy reflects a low value on a modest probability (<15%) of small or very small improvement in short term pain and function that does not persist to one year, and a higher value on avoiding the burden, postoperative limitations, and rare serious adverse effects associated with knee arthroscopy. The panel, including the patient participants, felt that

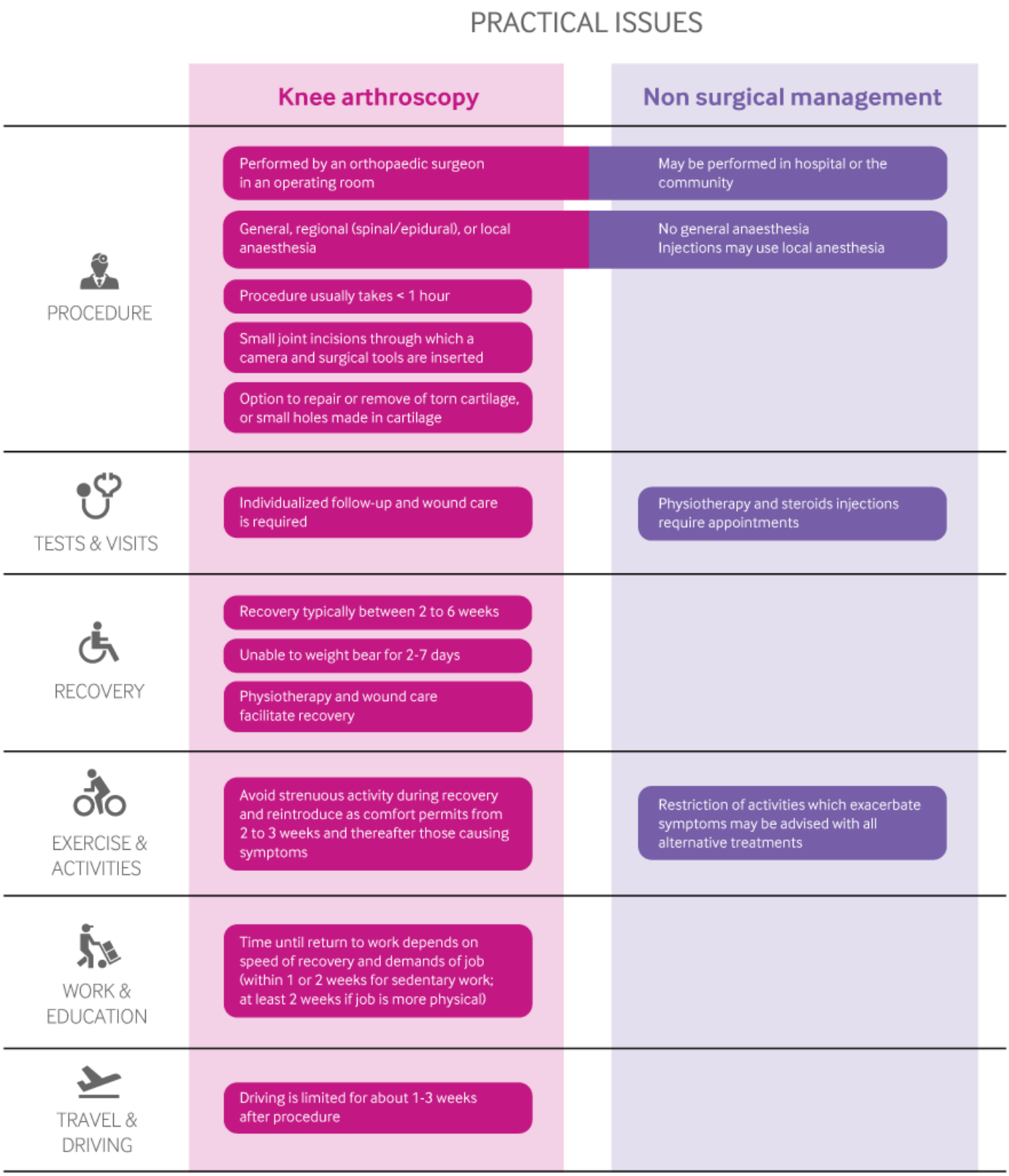


Fig 3| Practical issues about use of arthroscopic knee surgery versus non-surgical management for degenerative knee disease

Table 2 | New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article				

almost all patients would share these values. The recommendation is not applicable to patients who do not share these values (that is, those who place a high value on a small, uncertain, and transient reduction in pain and function, and a low value on avoiding the burden and postoperative limitation associated with arthroscopy).

Costs and resources

The panel focused on the patient perspective rather than that of society when formulating the recommendation. However, implementation of this recommendation will almost certainly result in considerable cost savings for health funders. A rigorous economic analysis found that knee arthroscopy for degenerative knee disease is not close to cost effective by traditional standards, even in extreme scenarios that assume a benefit with arthroscopy.[30] The panel made a strong recommendation against arthroscopy, which applies to almost all patients with degenerative knee disease, implying that non-use of knee arthroscopy can be used as a performance measure or tied to health funding.[31]

Future research

Key research questions to inform decision makers and future guidelines are:

- Randomised trials—Does arthroscopic knee surgery benefit patients who are objectively unable to fully extend their knee or who have persistent, severe, and frequent mechanical symptoms?
- Implementation studies—What are the most effective ways to reduce the overuse of arthroscopic surgery for degenerative knee disease?

Updates to this article

Table 2 shows evidence which has emerged since the publication of this article. As new evidence is published, a group will assess the new evidence and make a judgment on to what extent it is expected to alter the recommendation.

We thank Alison Hoens for critical review of the recommendation and manuscript. We also thank Tahira Devji for expertly leading the systematic review of minimally important differences.

Funding: This guideline was not funded.

Competing interests: All authors have completed the *BMJ* Rapid Recommendations interests disclosure form, and a detailed, contextualised description of all disclosures is reported in appendix 1. As with all *BMJ* Rapid Recommendations, the executive team and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions.

Transparency: R Siemieniuk affirms that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

1 Englund M, Guermazi A, Gale D, et al. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. *N Engl J Med* 2008;359:1108-15. doi:10.1056/NEJMoa0800777 pmid:18784100.
2 Nguyen US, Zhang Y, Zhu Y, Niu J, Zhang B, Felson DT. Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. *Ann Intern Med* 2011;155:725-32. doi:10.7326/0003-4819-155-11-201112060-00004 pmid:22147711.
3 Turkiewicz A, Gerhardsson de Verdier M, Engström G, et al. Prevalence of knee pain and knee OA in southern Sweden and the proportion that seeks medical care. *Rheumatology (Oxford)* 2015;54:827-35. doi:10.1093/rheumatology/keu409 pmid:25313145.
4 McGrory B, Weber K, Lynott JA, et al. American Academy of Orthopaedic Surgeons. The American Academy of Orthopaedic Surgeons evidence-based clinical practice guideline on surgical management of osteoarthritis of the knee. *J Bone Joint Surg Am* 2016;98:688-92. doi:10.2106/JBJS.15.01311 pmid:27098328.
5 Skou ST, Roos EM, Laursen MB, et al. A randomized, controlled trial of total knee replacement. *N Engl J Med* 2015;373:1597-606. doi:10.1056/NEJMoa1505467 pmid:26488691.
6 Jevsevar DS. Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. *J Am Acad Orthop Surg* 2013;21:571-6.pmid:23996988.
7 National Institute for Health and Clinical Excellence. Arthroscopic knee washout, with or without debridement, for the treatment of osteoarthritis (Interventional procedures guidance IPG230). 2007. www.nice.org.uk/guidance/ipg230.
8 National Institute for Health and Clinical Excellence. Osteoarthritis: care and management (clinical guideline CG177). 2014. www.nice.org.uk/guidance/cg177.
9 Beaufils P, Roland B. ESSKA Meniscus Consensus Project. Degenerative meniscus lesions. European Society for Sports Traumatology, Knee Surgery and Arthroscopy, 2016. http://c.ymcdn.com/sites/www.esska.org/resource/resmgr/Docs/2016-meniscus-consensus-proj.pdf.
10 British Orthopaedic Association, British Association for Surgery of the Knee. BOA/BASK response to media reports regarding knee arthroscopy. 2015. www.boa.ac.uk/latest-news/boabask-response-to-media-reports-regarding-knee-arthroscopy/.
11 Australian Knee Society on Arthroscopic Surgery of the Knee. Position statement from the Australian Knee Society on Arthroscopic Surgery of the Knee, including reference to the presence of osteoarthritis or degenerative joint disease. 2016. www.kneesociety.org.au/resources/aks-arthroscopy-position-statement.pdf.
12 Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008;16:137-62. doi:10.1016/j.joca.2007.12.013 pmid:18279766.
13 Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage* 2010;18:476-99. doi:10.1016/j.joca.2010.01.013 pmid:20170770.
14 Cullen KA, Hall MJ, Golosinskiy A. Ambulatory surgery in the United States, 2006. *Natl Health Stat Report* 2009;(11):1-25.pmid:19294964.
15 Adelani MA, Harris AH, Bowe TR, Giori NJ. Arthroscopy for knee osteoarthritis has not decreased after a clinical trial. *Clin Orthop Relat Res* 2016;474:489-94. doi:10.1007/s11999-015-4514-4 pmid:26290345.
16 Bohensky MA, Sundararajan V, Andrianopoulos N, et al. Trends in elective knee arthroscopies in a population-based cohort, 2000-2009. *Med J Aust* 2012;197:399-403. doi:10.5694/mja11.11645 pmid:23025737.
17 Hamilton DF, Howie CR. Knee arthroscopy: influence of systems for delivering healthcare on procedure rates. *BMJ* 2015;351:h4720. doi:10.1136/bmj.h4720 pmid:26405226.
18 Thorlund JB, Hare KB, Lohmander LS. Large increase in arthroscopic meniscus surgery in the middle-aged and older population in Denmark from 2000 to 2011. *Acta Orthop* 2014;85:287-92. doi:10.3109/17453674.2014.919558 pmid:24800623.
19 Järvinen TL, Guyatt GH. Arthroscopic surgery for knee pain. *BMJ* 2016;354:i3934. doi:10.1136/bmj.i3934 pmid:27439983.
20 Devji T, Guyatt GH, Lytvyn L, et al. Application of minimal important differences in degenerative knee disease outcomes: a systematic review and case study to inform BMJ Rapid Recommendations. *BMJ Open* 2017;7:e015587. doi:10.1136/bmjopen-2016-015587.
21 Brignardello-Peterson R, Guyatt GH, Schandelmaier S, et al. Knee arthroscopy versus conservative management in patients with degenerative knee disease: a systematic review. *BMJ Open* 2017;7:e016114. doi:10.1136/bmjopen-2017-016114.
22 Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. *BMJ* 1998;316:690-3. doi:10.1136/bmj.316.7132.690 pmid:9522799.
23 Gauffin H, Tagesson S, Meunier A, Magnusson H, Kvist J. Knee arthroscopic surgery is beneficial to middle-aged patients with meniscal symptoms: a prospective, randomised, single-blinded study. *Osteoarthritis Cartilage* 2014;22:1808-16. doi:10.1016/j.joca.2014.07.017 pmid:25086401.
24 Kirkley A, Birmingham TB, Litchfield RB, et al. A randomized trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2008;359:1097-107. doi:10.1056/NEJMoa0708333 pmid:18784099.
25 Sihvonen R, Englund M, Turkiewicz A, Järvinen TL. Finnish Degenerative Meniscal Lesion Study Group. Mechanical symptoms and arthroscopic partial meniscectomy in patients with degenerative meniscus tear: a secondary analysis of a randomized trial. *Ann Intern Med* 2016;164:449-55. doi:10.7326/M15-0899 pmid:26856620.
26 Sihvonen R, Paavola M, Malmivaara A, et al. Finnish Degenerative Meniscal Lesion Study (FIDELITY) Group. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. *N Engl J Med* 2013;369:2515-24. doi:10.1056/NEJMoa1305189 pmid:24369076.

27 Lubowitz JH, Ayala M, Appleby D. Return to activity after knee arthroscopy. *Arthroscopy* 2008;24:58-61.e4. doi:10.1016/j.arthro.2007.07.026 pmid:18182203.
28 Pihl K, Roos EM, Nissen N, JøRgensen U, Schjerning J, Thorlund JB. Over-optimistic patient expectations of recovery and leisure activities after arthroscopic meniscus surgery. *Acta Orthop* 2016;87:615-21. doi:10.1080/17453674.2016.1228411 pmid:27622598.
29 de Rooij M, van der Leeden M, Heymans MW, et al. Prognosis of pain and physical functioning in patients with knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* 2016;68:481-92. doi:10.1002/acr.22693 pmid:26316234.
30 Marsh JD, Birmingham TB, Giffin JR, et al. Cost-effectiveness analysis of arthroscopic surgery compared with non-operative management for osteoarthritis of the knee. *BMJ Open* 2016;6:e009949. doi:10.1136/bmjopen-2015-009949 pmid:26758265.
31 Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;66:726-35. doi:10.1016/j.jclinepi.2013.02.003 pmid:23570745.
32 Kise NJ, Risberg MA, Stensrud S, Ranstam J, Engebretsen L, Roos EM. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up. *BMJ* 2016;354:i3740. doi:10.1136/bmj.i3740 pmid:27440192.
33 Khan M, Evaniew N, Bedi A, Ayeni OR, Bhandari M. Arthroscopic surgery for degenerative tears of the meniscus: a systematic review and meta-analysis. *CMAJ* 2014;186:1057-64. doi:10.1503/cmaj.140433 pmid:25157057.
34 Thorlund JB, Juhl CB, Roos EM, Lohmander LS. Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. *BMJ* 2015;350:h2747. doi:10.1136/bmj.h2747 pmid:26080045.
35 Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:i5191. doi:10.1136/bmj.i5191 pmid:27680768.
36 Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ* 2016;354:i5085. doi:10.1136/bmj.i5085 pmid:27680583.
37 Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. doi:10.1136/bmj.39489.470347.AD pmid:18436948.

Web extras on bmj.com

Appendix 1: Full list of authors' declarations of interests

Appendix 2: Methodology for development of *BMJ* Rapid Recommendations

Appendix 3: All electronic multilayered information available on the MAGICapp'

[1]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada L8S 4L8
[2]Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[3]South Western Sydney Clinical School, UNSW, Australia
[4]Whitlam Orthopaedic Research Centre, Ingham Institute for Applied Medical Research, Liverpool, NSW 2170, Australia
[5]Division General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, CH-1211, Geneva, Switzerland
[6]Department of Orthopaedic Surgery, Joint Research, OLVG, 1090 HM Amsterdam, The Netherlands
[7]Faculty of Dentistry, Universidad de Chile, Independencia, Santiago, Chile
[8]Norwegian Institute of Public Health, Nydalen, N-0403 Oslo, Norway
[9]Department of Epidemiology and Preventive Medicine, School of Public Health & Preventive Medicine, Monash University, Melbourne, Vic 3004, Australia
[10]Monash Department of Clinical Epidemiology, Cabrini Institute; Suite 41 Cabrini Medical Centre, Malvern Vic, 3144, Australia
[11]Clinical Epidemiology Unit, Orthopaedics, Department of Clinical Sciences Lund Faculty of Medicine, Lund University, SE-221 85 Lund, Sweden
[12]Oslo University Hospital, Blindern 0317 Oslo, Norway
[13]Richmond, Virginia, USA
[14]Clinical Effectiveness Research Group, Institute of Health and Society, University of Oslo, Blindern 0317 Oslo, Norway
[15]University Hospital North Norway, 9038 Tromso, Norway
[16]Department of Occupational Therapy, Physiotherapy and Radiography, Faculty of Health and Social sciences, Bergen University College, 5020 Bergen, Norway
[17]BMJ Editorial, BMA House, London WC1H 9JR, UK
[18]Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Foundation Trust, Oxford OX3 7HE, UK
[19]London, Ontario, Canada
[20]Ingersoll, Ontario, Canada N5C 3N1
[21]Department of Health and Science, University of Oslo, Oslo, Norway
[22]Department of Medicine, Hospital Innlandet Trust, Gjøvik, Norway

Appendix 1: Conflicts of Interest

Pre-screening

All panel members were pre-screened for conflicts of interest prior to the guideline process that resulted in the BMJ Rapid Recommendations. The RapidRecs Executive team from the non-profit organisation MAGIC (www.magicproject.org) performed the prescreening with support from BMJ editors. No financial conflicts of interest were allowed (specifically, no financial ties to the arthroscopy industry or any other intervention for degenerative knee disease) and intellectual and professional conflicts of interest were managed appropriately (see appendix 2: Methods for BMJ Rapid Recommendations). We could not find an appropriate orthopaedic content expert to chair the panel, despite seriously considering approximately ten otherwise highly qualified individuals, so we chose to use a

Financial disclosures

No guideline panel members have any financial conflicts of interest to disclose in any way related to this clinical question. Some panel members have received funding from industry: Dr. Poolman is the primary investigator in hip fracture trials funded by LIMA and LINK, who do not have any products related to degenerative knee disease. Dr. Buchbinder has sat on panel discussions and given talks at symposiums funded by Roche Australia and BMS Rheumatology; neither company has any products used in degenerative knee disease.

Professional disclosures:

Drs. Harris, Poolman, and Knutsen perform arthroscopic surgery. Drs. Van De Velde (physiotherapist), Buchbinder (rheumatologist), Hailey (physiotherapist), and Olsen (physiotherapist) manage patients with degenerative knee disease non-operatively.

Intellectual disclosures:

Dr. Harris is a board member of the Australian Orthopaedic Association, which has taken a position on the matter; he has made some statements generally discouraging widespread use of arthroscopy. Dr. Poolman is the primary investigator of an ongoing randomised trial examining arthroscopy versus physical therapy for degenerative meniscal tears. Dr. Buchbinder is a board member on the Australian Rheumatology Association, is the chair of the Knee Osteoarthritis Clinical Care Standard Topic Working Group for the Australian Commission on Quality and Safety in Health Care, and the Joint Coordinating Editor, Cochrane Musculoskeletal group, and has made statements generally discouraging routine use of arthroscopy for osteoarthritis. Dr. Englund is a board member for the Osteoarthritis Research Society International (OARSI); he has previously made statements discouraging arthroscopy for osteoarthritis. Dr. Englund and Ms. Wilson are members of the European Society for Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA) guideline panel on arthroscopy for knee meniscus disease, which made statements generally more supportive of arthroscopy than the current guideline. Dr. Siemieniuk, Agoritsas, Lytvyn, and Kristiansen are members of the GRADE Working Group.

BACKGROUND

From MAGIC to WikiRecs and the BMJ Rapid Recommendations project

Systematic reviews and clinical practice guidelines are key vehicles for translating research knowledge into practice. However, organisations creating systematic reviews and guidelines often struggle to deliver timely and trustworthy recommendations in response to potentially practice-changing evidence.

Making GRADE the Irresistible Choice (MAGIC) is a non-profit research and innovation programme (www.magicproject.org). It was created to address key issues with authoring, publication, and updating of clinical practice guidelines. Through our online authoring and publication platform (http://www.magicapp.org), clinicians can access digital multilayered evidence summaries, recommendations, and consultation decision aids.(1) Although an increasing number of guideline organisations are using electronic authoring platforms like MAGICApp, challenges that go beyond dissemination remain. There is a need for overarching solutions to close the loop from evidence production, through synthesis, dissemination and implementation, ultimately resulting in documented improved care, increased value and reduced waste of healthcare resources.

MAGIC launched the WikiRecs (Rapid Recommendations and Evidence summaries Composed as Synopses) project to circumvent traditional organisational barriers of guideline development. Through an international multidisciplinary network of stakeholders, we aim to synthesise and disseminate evidence summaries and recommendations through MAGICapp within 90 days of publication of potentially practice changing evidence. The MAGIC organisation has also partnered with top medical journals to increase the reach of the recommendations.

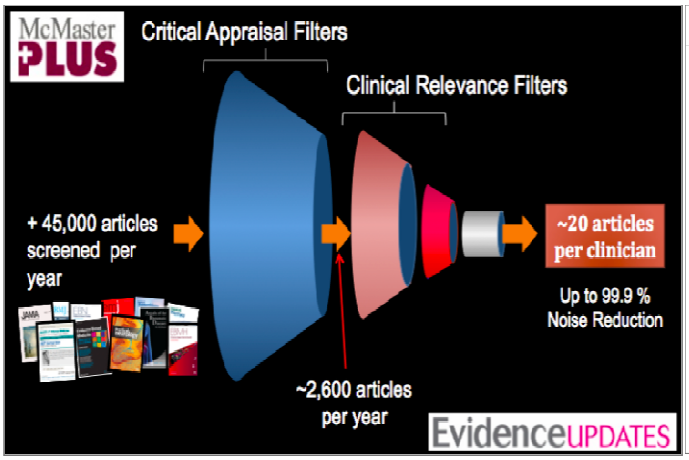
In the BMJ Rapid Recommendations project (also known as BMJ RapidRecs), the MAGIC WikiRecs group has partnered with The British Medical Journal (BMJ) to publish rapid recommendations as a synopsis paper in the BMJ, along with one or more systematic reviews linked to the recommendations.(2) The BMJ Rapid Recommendation package includes parallel publication of a multilayered electronic publication in MAGICapp, a synopsis and infographic published in The BMJ, and the systematic reviews that informed the recommendation in BMJ group Journals (BMJ, BMJ Open, and/or others). Here we outline the process and methods applied to translate evidence into evidence summaries, recommendations, and consultation decision aids for clinical practice.

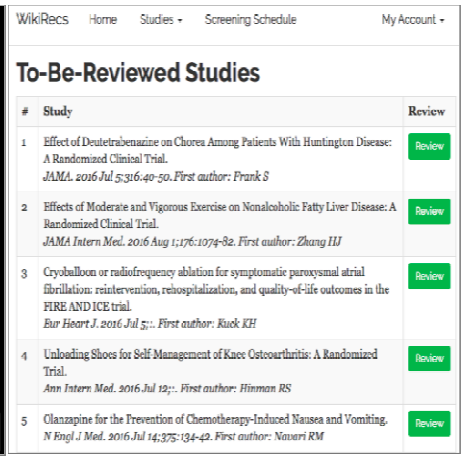
PROCESS

Process overview

BMJ RapidRecs follows a predefined protocol with the following steps, developed in collaboration between the WikiRecs group and the BMJ:

1) We monitor the literature for practice-changing evidence through McMaster Premium LiteratUre Service (PLUS).





2) The WikiRecs executive and the BMJ choose which clinical questions to pursue, based on relevance to a wide audience and likelihood to change current practice.

3) We incorporate the evidence into the existing body of evidence and broader context of clinical practice by:

- Performing a systematic review and meta-analysis on the benefits and harms with a focus on all critical outcomes and considerations that matter to patients.
- Convening an international panel of patient advisers, frontline clinicians, clinical specialists and methodologists to make the recommendations based on said systematic review.
- The systematic review group and the recommendation panel will adhere to standards for trustworthy guidelines(3, 4) and apply the GRADE approach.(5)

Additional research may be conducted, if requested by the guideline panel, including:

- A systematic review of observational studies to identify baseline risk estimates that most closely represent the relevant population. A certain baseline estimate is a key component when calculating the absolute effect of an intervention.(6)
- A systematic review on the typical patient preferences and values, and their variations.(7)

4) Dissemination of the recommendations through:

- Publication of a short recommendation summary in the BMJ.
- Publication of the systematic review(s) in BMJ group journalsPress release and/or marketing to media outlets and relevant parties such as patient groups.
- Links to the BMJ Group's Best Practice point of care resource.
- Publication in full through MAGICapp (for readers wishing to examine in more detail the underlying evidence and rationale and considering local adaptation).(1)

Figure 1: Flowchart of stepwise process in BMJ RapidRecs

Who is involved?
Researchers, systematic review and guideline authors, clinicians, and patients often work in isolation. Academic journals may publish work from any one or combinations of these groups of people, but these groups seldom work together to produce a comprehensive package.

Our collaboration involves:

- The core MAGIC WikiRecs network of researchers coordinating the systematic review group and the recommendation panels.
- The BMJ, which coordinates the editorial process, publishes a synopsis of the recommendations, and help develop user-friendly infographics linking to the MAGICapp for all underlying content.

METHODS FOR THE PRODUCTION OF RAPID RECOMMENDATIONS

BMJ RapidRecs adhere and exceed all standards for trustworthy guidelines with an emphasis on patient involvement, strict management of conflicts of interest, a transparent and systematic process for assessing the quality of evidence, a transparent and systematic process for moving from evidence to recommendations.(3, 4)

Panel member selection and contribution
Panel members are sought and screened through an informal process.
Key considerations for panel composition include:

- At least one but no more than five authors of the underlying systematic reviews.
- At least one patient representative (but ideally more) with lived experience of the disease. This person receives standard patient-oriented training documents to explain the process and one or more patient-liaison panel members help guide the person through the process to empower their contribution.
- A full spectrum of practicing healthcare workers involved in the management of the clinical problem, including frontline practitioners with generalist experience and those with content clinical and research expertise.
- Methodological experts in health research methodology and guideline development.

Any potential conflicts of interest are managed with prudence:

- No panel member may have a financial interest that is judged by the panel or the BMJ team as relevant to the topic.
- Very few panel members can have any intellectual conflict of interest.
- Professional conflicts of interest are minimised and balanced.

Illustrative example: For this BMJ Rapid Recommendation on for arthroscopy for degenerative knee disease, no persons had any financial stake in the recommendations. Two members were judged to have potential intellectual conflicts of interest because they had previously been involved with local guidelines on a related topic (arthroscopic surgery for knee osteoarthritis) informed by older literature. We included three orthopaedic surgeons, who may have a professional conflict, but we also included three patients, three physiotherapists, a rheumatologist, and several generalist physicians to counterbalance any possible professional conflicts.

Meetings and working process

The panels communicate via teleconferences and e-mail exchange of written documents throughout the process. Minutes from teleconferences are audiotaped, transcribed and stored for later documentation (available for peer-reviewers at request).

There will be two or three teleconferences:

- At the initiation of the process to provide feedback on the systematic review protocol (e.g. selection of patient important outcomes and appropriate prespecified analysis of results).
- When the Chair and the methods editor have drafted a GRADE evidence tables based on the systematic review, to discuss, deliberate and reach agreement on the final evidence assessment.
- When moving from evidence to recommendation, to discuss and agree on the final phrasing of the recommendation, its strength and direction, and the underlying content (e.g. GRADE Summary of Findings table, key information, rationale, practical advice).

Lastly, the panel members are invited by e-mail to provide feedback on the final draft before submission to the BMJ. The full panel further reconsiders any substantive changes through the peer review process.

From research to recommendation

What information will be considered?

The panel considers best currently available evidence. Beyond systematic reviews performed in the context of the BMJ RapidRecs, the panel may also consider a number of other research papers or guidelines.

How is a trustworthy guideline made?

The Institute of Medicine (IOM)(8) and the Guidelines International Network (GIN)(4) provide guidance on how trustworthy guidelines should be developed. Table 1 outlines how we aim to meet their trustworthy quality standards for our rapid recommendations.

Table 1: Summary of Institute of Medicine 8 standards for trustworthy guidelines and how the BMJ RapidRecs will meets these standards.

1. Establishing transparency *("The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible"*)*
● The method for BMJ RapidRecs is published as a supplementary file in the BMJ as well as in MAGICapp. ● Peer-reviewers judge the trustworthiness of the recommendations, and the panel will respond to any concerns raised. ● All funding will be reported. We will not use industry funding or any other funding from sources that could bias the recommendation.
2. Managing conflicts of interest *("Prior to selection of the guideline development group, individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity....")*
● The interests of each panel member are declared on a detailed and standardised form prior to involvement and published with the recommendations. ● Potential financial interests in the past three years, or forthcoming 12 months will preclude participation - as judged by the panel Chair, WikiRecs Executive, and The BMJ. ● Intellectual conflicts include having already taken a position on the issue, for example by a written editorial or commentary, conflicts related to performing a primary research study or authoring a previous systematic review on the topic. ● The Chair must have methods expertise, a clinical background, and no financial or intellectual interests. ● Funders and industry have no role in these recommendations. ● Professional conflicts of interest will be reported and minimised
3. Guideline Development Group Composition *("The guideline development group should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG")*
● BMJ RapidRecs will aim to include representation from most or every major geographic region in the world, with specific efforts made to achieve gender balance. ● We will enable patient and public involvement by including patient representatives. We will furthermore make use of systematic reviews on values and preferences to guide outcome choices and relative weights of each outcome, where available. ● Patient representatives will be given priority during panel meetings and will have an explicit role in vetting final judgements on values and preferences. ● The guidelines will include all relevant healthcare worker stakeholders, including allied healthcare professionals
4. Clinical Practice Guideline–Systematic Review Intersection

("CPG developers should use systematic reviews that meet standards set by the IOM. Guideline development group and systematic review team should interact regarding the scope, approach, and output of both processes".
● Each rapid recommendation will be based on one or more linked credible systematic reviews, which will be developed and published in parallel with our recommendation or produced by other authors and reporting sufficient detail to fully trust the review ● The recommendation panel and SR teams will interact, with up to five members participating on both teams to facilitate communication and continuity in the process.
5. Establishing Evidence Foundations for and Rating Strength of Recommendations *("For each recommendation: explain underlying reasoning, including a clear description of potential benefits and harms, a summary of relevant available evidence and description of the quality., explain the part played by values, opinion, theory, and clinical experience in deriving the recommendation, "provide rating of strength of recommendations")*
● We will apply the GRADE framework for establishing evidence foundations and rating the strength of recommendations. For each recommendation, systematic and transparent assessments are made across the following key factors: ○ The balance between the absolute benefits and harms for all patient-important outcomes. ○ Overall quality of the evidence. ○ The typical patient values and preferences and their expected variations. ○ Resources and other considerations (e.g. feasibility, applicability, equity). ● Each outcome will - if data are available through systematic reviews - include an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in GRADE Summary of Findings tables. If such data are not available narrative summaries will be provided. ● A summary of the underlying reasoning and all additional information (e.g. key factors, practical advice, references) will be available in *the BMJ-RapidRecs* article with full content available online in an interactive format at www.magicapp.org. The summary includes descriptions of how theory (e.g. pathophysiology) and clinical experience played into the evidence assessment and recommendation development. ● Recommendations will be rated either weak or strong, as defined by GRADE. ● If the panel disagrees on the evidence assessment or grading of the recommendations, we will follow a structured consensus process customised to the GRADE system and report any final differences of opinion, with their rationale, in the online supplement and at www.magicapp.org.
6. Articulation of recommendations *("Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed, and so that compliance with the recommendation(s) can be evaluated")*
● Each recommendation will appear at the top of the infographic in the BMJ and be

available in standardised formats in MAGICapp.
- The recommendations will be actionable.
- Each summary article in the BMJ will include a statement that these are guiding recommendations. They do not form a mandate of action and should be contextualised to the relevant healthcare system and individual patients.

7. External review

("External reviewers should comprise a full spectrum of relevant stakeholders...., authorship should be kept confidential....., all reviewer comments should be considered....a rationale for modifying or not should be recorded in writing.... a draft of the recommendation should be made available to general public for comment..")

- At least two external peer-reviewers and one patient reviewer will review the recommendation for the BMJ. They will have access to all underlying, online information. They will be asked for general feedback and to assess the trustworthiness of the guideline.
- A BMJ series adviser with methodological and/or statistical expertise will review the BMJ RapidRecs publication and the systematic reviews.
- The panel will be asked to read and respond to the peer review comments and make amendments where reasonable.
- The BMJ and WikiRecs team may, on a case-by-case basis, choose to invite key organisations, agencies, or patient/public representatives to provide and submit public peer-review.
- There will be post-publication public review process where people can provide comments and feedback through theBMJ.com. The Chair will strive to, on behalf of panel members, respond to each publicly available peer-review within 30 days, for a period of six months after publication.

8. Updating

("The date for publication, systematic review and proposed date for future review should be documented, the literature should be monitored regularly and the recommendation should be updated when warranted by new evidence")

- The panel will monitor new research evidence for a published BMJ RapidRecs, aiming to update the recommendation when new evidence suggest a need for change in practice. When relevant, updates will be performed in MAGICapp and submitted to the BMJ for consideration of an updated publication.

REFERENCES:

1 *Vandvik PO, Brandt L, Alonso-Coello P, et al.* Creating clinical practice guidelines we can trust, use, and share: a new era is imminent. Chest 2013; 144: 381-9.
2 *Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO.* Introduction to BMJ Rapid Recommendations. BMJ 2016; 354: i5191.
3 *Laine C, Taichman DB, Mulrow C.* Trustworthy clinical guidelines. Annals of internal medicine 2011; 154: 774-5.
4 *Qaseem A, Forland F, Macbeth F, Ollenschlager G, Phillips S, van der Wees P.* Guidelines International Network: toward international standards for clinical practice guidelines. Annals of internal medicine 2012; 156: 525-31.

5 *Guyatt GH, Oxman AD, Vist GE, et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336: 924-6.
6 *Foroutan F, Guyatt GH, O'Brien K, et al.* Prognosis after surgical replacement with a bioprosthetic aortic valve in patients with severe symptomatic aortic stenosis: systematic review of observational studies. BMJ (Clinical research ed) 2016; 354: i5065.
7 *Lytvyn L, Guyatt GH, Manja V, et al.* Patient values and preferences on transcatheter or surgical aortic valve replacement therapy for aortic stenosis: a systematic review. BMJ Open 2016; 6: e014327.
8 *Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. In:* Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E (Eds.). Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US)

CHAPTER 6: Antiretroviral therapy for pregnant women living with HIV or hepatitis B: a systematic review and meta-analysis

This is a network meta-analysis of medications used to treat HIV and hepatitis B in pregnancy showed that tenofovir probably increases the risk of stillbirth and early neonatal mortality.

Advances:
The focus of the guideline was women living with HIV, but we were guided by the linked guideline panel to look at indirect evidence from women with hepatitis B, and for adverse effects, from non-pregnant adults living with HIV.

Citation:
Siemieniuk RA, Foroutan F, Mirza R, Mah Ming J, Alexander PE, Agarwal A, Lesi O, Merglen A, Chang Y, Zhang Y, Mir H, Hepworth E, Lee Y, Zeraatkar D, Guyatt GH. Antiretroviral therapy for pregnant women living with HIV or hepatitis B: a systematic review and meta-analysis. *BMJ Open*. 2017 Sep 11;7(9):e019022. doi: 10.1136/bmjopen-2017-019022.

BMJ Open

Antiretroviral therapy for pregnant women living with HIV or hepatitis B: a systematic review and meta-analysis

Reed A Siemieniuk,[1,2] Farid Foroutan,[1] Reza Mirza,[3] Jinell Mah Ming,[4] Paul E Alexander,[1,5] Arnav Agarwal,[6] Olufunmilayo Lesi,[7] Arnaud Merglen,[8] Yaping Chang,[1] Yuan Zhang,[1] Hassan Mir,[3] Elliot Hepworth,[3] Yung Lee,[9] Dena Zeraatkar,[1] Gordon H Guyatt[1]

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For numbered affiliations see end of article.

Correspondence to
Professor Gordon H Guyatt;
guyatt@mcmaster.ca

ABSTRACT

Objective To assess the impact of various antiretroviral/antiviral regimens in pregnant women living with HIV or hepatitis B virus (HBV).

Design We performed random effects meta-analysis for HIV-related outcomes and network meta-analysis for HBV outcomes, and used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to assess quality separately for each outcome.

Data sources Embase and Medline to February 2017.

Eligibility criteria For maternal outcomes, we considered randomised controlled trials (RCTs) comparing tenofovir-based regimens with those with alternative nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). For child outcomes, we included RCTs and comparative observational studies of tenofovir-based regimens versus alternative NRTIs regimens or, for HBV, placebo.

Results Ten studies (seven RCTs) met the inclusion criteria for maternal and child outcomes, and an additional 33 studies (12 RCTs) met the inclusion criteria for HBV-specific outcomes. The most common comparison was tenofovir and emtricitabine versus zidovudine and lamivudine. There was no apparent difference between tenofovir-based regimens and alternatives in maternal outcomes, including serious laboratory adverse events (low certainty) and serious clinical adverse events (moderate certainty). There was no difference between NRTIs in vertical transmission of HIV: 1 more per 1000, 8 fewer to 10 more, low certainty; or vertical transmission of HBV: 7 fewer per 1000, 10 fewer to 38 more, moderate certainty. We found moderate certainty evidence that tenofovir/emtricitabine increases the risk of stillbirths and early neonatal mortality (51 more per 1000, 11 more to 150 more) and the risk of early premature delivery at <34 weeks (42 more per 1000, 2 more to 127 more).

Conclusions Tenofovir/emtricitabine is likely to increase stillbirth/early neonatal death and early premature delivery compared with zidovudine/lamivudine, but certainty is low when they are not coprescribed with lopinavir/ritonavir. Other outcomes are likely similar between antiretrovirals.

Trial registration number PROSPERO CRD42017054392

Strengths and limitations of this study

- ► We synthesise the best available evidence to inform choice of HIV and/or hepatitis B therapy for pregnant women.
- ► This review is linked to a *BMJ* Rapid Recommendations project. We conducted the review directed by a guideline panel that included patient representatives. This guideline panel provided detailed input with regard to the patients, interventions and outcomes, and the interpretation of the results from this review.
- ► We paid careful attention to what evidence could be appropriately pooled and which could not.
- ► The evidence for a likely increase of early premature delivery and neonatal mortality with tenofovir and emtricitabine comes mostly from a single study.

BACKGROUND

More than 17 million women are living with HIV, most of whom are of childbearing age.[1] Every year, 1.4 million of these women experience pregnancies, which, without any intervention, carry a risk of vertical transmission to the infant of approximately 15%–45%.[2 3] To reduce the risk of vertical transmission, approximately 80% of pregnant women living with HIV use antiretroviral therapy, primarily combination antiretroviral therapy (cART).[4] The risk of vertical transmission is below 2% in high-income countries and below 5% in several low-income and middle-income countries when cART is universally available and routine HIV screening of pregnant mothers is provided.[5–7] Early initiation of cART may also reduce the risk of serious HIV-related events in all patients living with HIV,[8 9] which has resulted in the WHO recommending cART for all people living with HIV, including pregnant women.[10]

cART typically consists of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)—the 'backbone'—and a third antiretroviral agent. The most frequently used NRTI is tenofovir disoproxil

fumarate (TDF), which is most often coformulated with another NRTI, emtricitabine (FTC) or lamivudine as a convenient once per day medication. Approximately 70% of persons taking cART use a tenofovir-based regimen, both in high-income and low-income and middle-income countries.[11]

In a November 2016 publication, the Promoting Maternal and Infant Survival Everywhere (PROMISE) study randomised pregnant women to either zidovudine (AZT) monotherapy or one of two cART arms with different NRTI backbones: tenofovir/FTC and AZT/lamivudine, each combined with the protease inhibitor lopinavir, boosted with ritonavir (hereafter, LPV/r).[12] The authors reported that both cART regimens reduced vertical transmission more effectively than AZT monotherapy. Notably, tenofovir/FTC, compared with AZT/lamivudine, was associated with an increased risk of early premature labour, early neonatal death and a composite of severe adverse pregnancy outcomes. A subsequent systematic review concluded that tenofovir/FTC appears generally safe in pregnancy, but assumed equal credibility in randomised and observational studies by pooling evidence from all studies.[13]

NRTIs can also be used for indications other than HIV treatment. Tenofovir or lamivudine are often used in the third trimester to reduce the risk of vertical transmission of hepatitis B virus (HBV).[14] HIV-negative women at risk for HIV, many of whom will become pregnant, may also use tenofovir/FTC for pre-exposure prophylaxis (PrEP) to reduce risk of HIV infection.[15] The Joint United Nations Programme on HIV/AIDS (UNAIDS) has set a global target to increase uptake of PrEP to more than 3 million people by 2020.[16]

The WHO and the Centers for Disease Control and Prevention (CDC), despite being aware of the preliminary data from the PROMISE trial presented at a conference in 2015,[17] recommended tenofovir/FTC as first-line therapy for all pregnant women.[10 18] We revisited this issue after publication of the full report[12] that raised concerns about the safety of tenofovir/FTC in pregnancy. Our approach contrasts with a prior effort that pooled randomised controlled trials (RCTs) with far less trustworthy observational studies[13]: our more standard approach deals with these two designs separately. Because of the high prevalence of hepatitis B and HIV coinfection and because the same medications are used for both conditions, we also include an evaluation of the impact of tenofovir versus alternative antivirals in pregnant women living with hepatitis B. This systematic review, along with a systematic review on patient values and preferences,[19] informs a *BMJ* Rapid Recommendation[11] (see box 1). The *BMJ* Rapid Recommendation initiative attempts to provide timely, unconflicted and trustworthy recommendations for clinical situations where new evidence might change practice.[20]

Box 1 Linked articles in this *BMJ* Rapid Recommendations cluster

Siemieniuk R, *et al.* Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline.
- *BMJ* Rapid Recommendation

Lytvyn L, *et al.* Values and preferences of women living with HIV who are pregnant or considering pregnancy on choice of antiretroviral therapy during pregnancy (cosubmitted).
- A systematic review of values and preferences

MAGICapp
- Expanded version of the evidence with multilayered recommendations, evidence summaries and decision aids for use on all devices
- https://www.magicapp.org/goto/guideline/VLpr5E

METHODS

Protocol

We conducted this systematic review based on a registered protocol (PROSPERO CRD42017054392).

Patient involvement

As with all *BMJ* Rapid Recommendations, patients were included in all stages of the research production (see box 2).

Information sources

Our review used three separate search strategies. First, we searched Medline and Embase from 1 January 1996 to 13 January 2017 for observational studies and RCTs that compared a tenofovir-based cART regimen with another regimen with the same non-NRTI antiretroviral in pregnant women, using a mix of keywords and medical subject headings (MeSH) terms for HIV and pregnancy and NRTIs (online supplementary appendix 1a). Second, anticipating that for many *maternal* outcomes there would be only low-quality or very low-quality evidence if we included only direct evidence from pregnant women, we searched for RCTs of non-pregnant adults living with HIV initiating cART with a tenofovir-based regimen or an alternative NRTI-regimen that included the same non-NRTI antiretroviral(s). We updated a comprehensive search conducted on 7 July 2015.[21] We searched from 7 July 2015 to 17 February 2017 and used a mix of MeSH and keywords for HIV and antiretrovirals and RCTs (online supplementary appendix 1b). We also searched the abstracts of recent major conferences, including the

Box 2 Patient involvement

Three women living with HIV, two of whom had children after being diagnosed with HIV and another who is considering having children in the future, participated in the panel. The community representatives received personalised training and support to optimise contributions throughout the guideline development process. These women helped choose the outcomes that were most important to them, all of which were included in our review. The patient panellists approved the review protocol and helped guide interpretation of the results.

Conference of Retroviruses and Opportunistic Infections, the International AIDS Society Conference and the International AIDS Conference on 17 February 2017.

To inform outcomes specific to pregnant women living with chronic HBV infection, we searched for comparative observational studies and RCTs of tenofovir, lamivudine or FTC in pregnant women living with HBV. We built on a systematic search conducted on 11 September 2014.[22] We searched Medline and Embase from 1 January 2014 to 14 January 2017. We used a combination of keywords and MeSH terms for pregnancy and HBV and antivirals (online supplementary appendix 1c).

We also searched reference lists of all included studies, systematic reviews and relevant guidelines. We searched ClinicalTrials.gov for additional studies on 17 February 2017, including unpublished studies. We did not have any language restrictions and had two reviewers fluent in the language of publication assess for inclusion and abstract data if deemed eligible.

Study selection

For child outcomes, we included observational studies and RCTs that compared tenofovir with alternative NRTI regimens in pregnant women. We included studies on women taking NRTIs for PrEP, for treatment of hepatitis B or for HIV infection, in combination with other antiretrovirals as long as the non-NRTI antiretrovirals were the same in both arms. Because for several critical outcomes specific to the mother we anticipated finding no direct evidence or the evidence would be of very low certainty, we also included RCTs that compared tenofovir-based regimens with alternative NRTIs in non-pregnant adults living with HIV. We considered evidence from pregnant women alone before including evidence from non-pregnant adults. For child outcomes, we included studies of PrEP (tenofovir/FTC vs placebo). For outcomes specific to women also living with HBV, we included observational studies and RCTs that compared tenofovir, FTC or lamivudine against each other or, because we anticipated that there would be few head-to-head studies, a control (no antiviral treatment). We excluded studies of NRTIs that are not in widespread use or are not used for HIV infection, including stavudine, didanosine, zalcitabine, adefovir and entecavir. Observational studies included cohort, case–control and any other observational study type that attempted a direct and coincident comparison between any two of the eligible interventions.

Reviewers screened all titles and abstracts independently and in duplicate. If either reviewer felt that a study might meet inclusion criteria, two reviewers independently assessed the full text. Reviewers resolved disagreements through discussion.

Data collection

Two reviewers independently abstracted data and resolved conflicts by discussion. When data were only available in a figure, we digitised the figure.

BMJ Rapid Recommendation process

The semi-independent Rapid Recommendation panel chose outcomes they felt were most likely to influence patient decisions between NRTI regimens; they also identified subgroups in whom effects might differ. As with all *BMJ* Rapid Recommendations,[23–25] the panel was free from financial conflicts, and intellectual and professional conflicts were minimised.[20] The panel included three women living with HIV, clinical experts (two obstetricians, four paediatricians, three infectious diseases specialists, a pharmacist, a hepatologist and a primary care physician with substantial experience treating HIV) and five Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologists.[25] Panellists resided in Africa, Australasia, Europe, North America and South America. The guideline panel provided critical oversight to the review and identified populations, subgroups and outcomes of interest. Panel members provided input at all stages of the systematic review. The patient panel members led the interpretation of the results based on what they expected the typical patient values and preferences to be, as well as the variation between patients. A parallel systematic review of patient values and preferences was also conducted to help with interpretation.[19]

Summary measures

Maternal outcomes included mortality, acceptability (we used drug discontinuation rates as a surrogate), clinical adverse events (grade 2 or higher),[26] laboratory adverse events (grade 2 or higher), detectable viral load 6 months after starting cART as a proxy for viral load at delivery, AIDS-defining illnesses, hepatitis B flares and development of HBV resistance to one or more antivirals. When we included data from RCTs in non-pregnant adults, we used the endpoint closest to 26 weeks after enrolment to approximate the timeline of a woman-starting cART at the beginning of the second trimester. Fetal outcomes included a composite of stillbirth after 20 weeks' gestational age (GA) and early neonatal mortality within the first week, spontaneous abortion, HIV transmission, prematurity <37 weeks, early prematurity <34 weeks, serious birth defects, low birth weight <2500 g, very low birth weight <1500 g, neonatal adverse laboratory event (grade 2 or higher), long-term child growth/development and HBV transmission. We combined stillbirths with early neonatal mortality because of a similar pathophysiology (most early neonatal deaths are caused by pregnancy-related factors) and because we believe that most women would place a similar value on the two events.

Risk of bias and quality of evidence

We used a modified Cochrane Collaboration tool to assess risk of bias for RCTs,[27] which substitutes response options of 'probably low risk' or 'probably high risk' for unclear; empirical evaluation has shown that reviewers can make these judgements accurately.[28] Ultimately, we collapsed the low and probably low, and high and probably high

risk, for presentation. Two reviewers assessed risk of bias independently and resolved disagreements through discussion. We used a modified Ottawa-Newcastle instrument for assessing risk of bias for observational studies.[29]

The GRADE approach provided the framework for rating the certainty of evidence for each outcome.[30] Evidence from RCTs started at high certainty, whereas evidence from observational studies started at low certainty. Concerns with risk of bias, inconsistency, indirectness, imprecision and publication bias lowered certainty. We considered the bodies of evidence from RCTs and observational studies separately.

For the outcomes specific to HBV, we used the GRADE approach for rating certainty of network effect estimates obtained from a network meta-analysis.[31] In brief, we rated the certainty of evidence for direct comparisons using the standard GRADE approach. For indirect comparisons, we rated evidence from the dominant first-order loop by first taking the lowest certainty of the direct comparisons. We then considered further rating down if there were concerns with intransitivity.[31] For mixed estimates (those that included both indirect and direct evidence), we started with the higher of the two certainty ratings and rated down certainty for imprecision or incoherence between the indirect and direct effect estimates.

Subgroups and sensitivity analyses

We planned subgroup analyses if there were at least two studies per group (online supplementary appendix 2). We performed a post hoc sensitivity analysis for pregnancy loss and early infant death as well as premature labour <34 weeks, including PROMISE participants randomised to AZT/lamivudine prior to the introduction of the tenofovir/FTC arm because of concerns that there were fewer events than expected in the AZT/lamivudine arm in the latter part of the study.

Synthesis of results

We used random effects meta-analysis of risk ratios (RRs) and calculated 95% CIs with the DerSimonian and Laird approach. When events were rare across all studies (<2%), we performed meta-analysis directly with the Peto method unless one or more studies had zero events in both arms, in which case we used risk differences (RD) directly. We planned assessment of publication bias with visual inspection of funnel plots for outcomes with 10 or more studies. We present evidence that led to the highest quality using the GRADE framework—for all outcomes, looking first for evidence from RCTs of pregnant women, but if that evidence was either not available or proved of low or very low certainty, then also considering evidence from RCTs of non-pregnant adults and observational studies of pregnant women living with HIV.

For the comparisons of antivirals for HBV infection, we anticipated that there would be few if any direct comparisons between antivirals and therefore performed a network meta-analysis within a frequentist framework using RRs. We added 0.5 events to both arms if one arm had zero events and excluded trials with zero events in both arms because CIs could not be calculated. Direct comparisons were also analysed with standard pairwise DerSimonian and Laird meta-analysis. We used the back-calculation and node splitting methods to estimate the RR and CIs from indirect and direct evidence and to assess for incoherence. Inconsistency was assessed for each pairwise comparison by visual inspection of forest plots and the I^2 statistic for heterogeneity. We also considered the global I^2 for network meta-analyses.[32] We used RevMan V.5.3 for meta-analyses of direct comparisons and Stata V.13 and the netmeta package in R (R project) for network meta-analyses.

We present all outcomes as absolute effects, either calculated directly or by multiplying the RR by the baseline risk. Where possible, we apply the relative risk calculated from RCTs to a baseline risk from observational studies.[33] For outcomes in which trustworthy observational data were not identified, we used the pooled baseline risk from the control group. The Rapid Recommendation panel suggested outcomes in which they expected baseline risk to differ between settings (eg, the panel believed vertical transmission of HBV would be lower in high-resourced health systems than lower resource settings).

RESULTS

We screened 2750 studies in the primary search for comparative studies in pregnant women and included 10 studies (online supplementary appendix 3a). All studies compared a tenofovir-based regimen with placebo or alternative NRTI-based regimens in pregnant women: seven were RCTs (three included women living with HIV,[12 34 35] three evaluated tenofovir/FTC for PrEP in HIV-negative women,[15 36 37] and one evaluated tenofovir alone in pregnant women with HBV infection[38]) and three were observational cohort studies of HIV-positive women[39–41] (table 1). Two of the potentially eligible PrEP RCTs had very low compliance (less than 33%), and we therefore excluded them from further consideration.[36 37] The PrEP RCT that we included had greater than 60% compliance, discouraged pregnancy, tested for pregnancy monthly and discontinued the study medications when pregnancy was detected (at an average of 35 days' GA).[15] Given the very early and limited exposure to antiretroviral medication, we included this study only for the outcome of stillbirth. The RCT of tenofovir versus placebo in pregnant women with HBV infection initiated therapy at 32 weeks' gestation.[38] Given the limited late exposure to the drugs, we included these results only for the outcome of stillbirths, early neonatal deaths and low birth weight. At the request of the *BMJ* Rapid Recommendation panel,[11] we also included evidence from the Antiretroviral Pregnancy Registry for the outcome of birth defects.[42] The registry is a frequently updated non-comparative database that tracks the incidence of birth defects in mothers who have taken antiretrovirals.

Table 1 Study characteristics of comparative studies for tenofovir-containing regimens in pregnant women

Authors, year	Design	Study period	Setting	Population	Sample size	Mother age*	Comparison
Pregnant women living with HIV							
Campbell, 2012[35]	RCT	2005–2007	Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, USA, Zimbabwe	Antiretroviral-naïve, non-pregnant adults, CD4 <350 cells/μL, continued ART if pregnant	42 births	34	TDF/FTC/efavirenz versus AZT/3TC/efavirenz
Fowler *et al*, 2016 (PROMISE)[12]	RCT	2012–2014	India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe	HIV-positive women, ≥14 weeks' gestation, CD4 ≥350 cells/mm^3, 3490	694	Median 26 (IQR 22–30)	TDF/FTC/LPV/r versus AZT/3TC/LPV/r
Gibb, 2012[39]	Obs	2003–2009	Uganda, Zimbabwe	Infants born to HIV-positive mothers on combination ART	173	NR	TDF/AZT/3TC versus ABC/AZT/3TC or NVP/AZT/3TC
Rough *et al*, 2017 (abstract)[40]	Obs	2002–2016	USA	HIV-positive women with birth outcome information in a database	1082	NR	TDF/FTC/LPV/r versus AZT/3TC/LPV/r
Wang, 2016[34]	RCT	2012–2015	China	HIV-positive women, antiretroviral-naïve, 14–28 weeks' gestation, hepatitis B coinfection	31	Mean 28.5 (range 19–39)	TDF/3TC/LPV/r versus AZT/3TC/LPV/r
Zash *et al*, 2017 (abstract)[41]	Obs	2014–2016	Botswana	Births >24 weeks' gestational age to HIV-positive women in maternity wards	2584	34 (IQR 30–38)	TDF/FTC/NVP versus AZT/3TC/NVP and TDF/FTC/LPV/r versus AZT/3TC/LPV/r
At risk but HIV-negative women receiving tenofovir/FTC for PrEP and become pregnant							
Mugo *et al*, 2014[15]	RCT	2008–2013	Kenya, Uganda	HIV serodiscordant heterosexual couples	1785	33 (28–38)	TDF versus TDF/FTC versus placebo (discontinued when pregnancy detected)
Van Damme *et al*, 2012*[37]	RCT	2009–2011	Kenya, South Africa, Tanzania	Women at risk of for HIV acquisition	2120	Mean 24.2	TDF/FTC versus placebo (discontinued when pregnancy detected)
Bunge *et al*, 2015 (abstract)*[36]	RCT	2009–2011	South Africa, Uganda, Zimbabwe	HIV-negative women using contraceptives	428	Median 23 (IQR 21–27)	TDF versus TDF/FTC versus placebo (discontinued when pregnancy confirmed)
Women living with hepatitis B but not HIV							
Pan *et al*, 2016[38]	RCT	2012–2013	China	Women with active hepatitis B virus infection	197	Mean 27.1	TDF versus placebo From 32 weeks

*Excluded post hoc because of very low medication adherence.
3TC, lamivudine; ABC, abacavir; AZT, zidovudine, FTC, emtricitabine; LPV/r, lopinavir boosted with ritonavir; NR, not reprted; NVP, nevirapine; Obs, observational study; PrEP, pre-exposure prophylaxis; PROMISE, Promoting Maternal and Infant Survival Everywhere; RCT, randomised controlled trial; TDF, tenofovir; NR, not reported

RCTs that enrolled pregnant women provided evidence at low risk of bias. The main limitation of the RCTs was the lack of blinding in the PROMISE trial[12] and two smaller RCTs.[34 38] The PROMISE trial was also stopped early, but that decision was based on the reduction in vertical transmission of cART compared with AZT monotherapy and therefore should not bias comparison of tenofovir-based cART versus alternative NRTI-based cART, the focus of this review.[12] The PROMISE trial randomised 823 women, most in Africa, to the comparison of interest. All the observational studies were at high risk of bias because the analyses did not control for most expected key confounders (eg, socioeconomic status and year of cART initiation).

To inform outcomes specific to the mothers in which direct evidence from pregnant women provided only low-quality or very low-quality evidence, we considered indirect evidence from RCTs of tenofovir-based regimens versus alternative NRTI-based regimens in non-pregnant HIV-positive adults (table 2). We screened 297 studies and ultimately included eight RCTs from nine publications with 5353 participants (online supplementary appendix 3b).[12 35 43–49] Four RCTs with 2316 participants compared tenofovir/FTC with AZT/lamivudine,[12 35 43 46] and four with 3037 participants with abacavir/lamivudine. These RCTs were limited primarily by lack of allocation concealment (4 of 8) and lack of blinding (5 of 8) (online supplementary appendix 4a).

Maternal outcomes

Acceptability

Pooled evidence for discontinuation rates from seven RCTs (n=4198) including non-pregnant adults proved of very low certainty due to inconsistency, indirectness because evidence is from non-pregnant adults, and imprecision (online supplementary appendix 5a). Higher certainty evidence addressing acceptability came from medication discontinuation rates in the PROMISE trial,[12] in which there was no important difference between groups: 15 (4.2%, n=356) discontinued in the tenofovir/FTC group and 10 (2.8%, n=360) discontinued in the AZT/lamivudine group (RD 15 more per 1000 discontinued with tenofovir/FTC, CI 9 fewer to 65 more; table 3).

Mortality

For mortality, the PROMISE trial[12] and pooled estimates from RCTs of pregnant women provided moderate certainty evidence of no important difference between alternative cART regimens. No women in the PROMISE trial died[12]: RD 0 per 1000, CI 11 fewer to 11 more. There was no apparent difference between tenofovir/FTC (1.4%, n=2337) and alternative NRTIs (1.6%, n=2313) in mortality in seven RCTs (n=4650) that included non-pregnant adults (RD 2 fewer per 1000 with tenofovir, CI 6 fewer to 2 more; online supplementary appendix 5b).

Clinical maternal adverse events

Although low certainty evidence (very serious imprecision) from the PROMISE trial suggested no difference between groups,[12] higher certainty evidence for clinical maternal adverse events comes from pooled estimates from RCTs of non-pregnant adults. Six RCTs reported adverse effects; three compared AZT/lamivudine versus tenofovir/FTC (n=2139), and three abacavir/lamivudine versus tenofovir/FTC (n=2343). Results suggested a subgroup difference between AZT/lamivudine and abacavir/lamivudine, with relatively more adverse events in the abacavir/lamivudine group than in the AZT/lamivudine group (p for interaction=0.009) (figure 1). Clinical adverse effects were similar for tenofovir/FTC (26.8%, n=1061) and AZT/lamivudine (26.3%, n=1078): RR 1.00, CI 0.90 to 1.12, I^2=0%; RD 0 per 1000 (table 3). There were fewer clinical adverse events in the tenofovir/FTC group (14.1%, n=1173) than the abacavir/lamivudine group (19.6%, n=1170): RR 0.72, CI 0.60 to 0.86, I^2=0%; RD 8 fewer per 1000; moderate certainty due to indirectness. Pain or discomfort (6.0%) and pruritus (2.3%) accounted for most of the difference in one study that combined each with atazanavir/ritonavir.[48]

Maternal laboratory adverse events

Four RCTs (n=2217), three of which were in non-pregnant adults, reported fewer grade 2 or higher laboratory adverse events with tenofovir/FTC than alternatives, but the evidence proved lower certainty evidence than the PROMISE[12] trial alone (inconsistency and indirectness) (figure 2). In the PROMISE trial[12] there was no apparent difference in laboratory adverse events between tenofovir/FTC (10.9%, n=329) and AZT/lamivudine (12.9%, n=333): RR 0.85, CI 0.56 to 1.28; RD 19 fewer per 1000 (table 3).

Undetectable viral load 6 months after starting cART

The PROMISE study did not provide data informing viral load outcomes at birth.[12] We therefore examined indirect evidence in non-pregnant adults living with HIV initiating cART: failure to suppress HIV viral load at 6 months after starting therapy to approximate viral load suppression at delivery for a pregnant woman initiating cART at the start of the second trimester. The pooled results from six RCTs (n=4220) suggested no difference between tenofovir-based cART (19.5%, n=2126) and alternative NRTIs (22.2%, n=2094): RR 0.93, CI 0.71 to 1.23; I^2=77%; RD 16 fewer per 1000 (figure 3, table 3).

Child outcomes

Stillbirth and early neonatal mortality

The evidence from the PROMISE trial[12] and two smaller RCTs reported 21 (6.3%, n=334) stillbirths and early infant deaths in the tenofovir/FTC arm and 5 (1.4%, n=348) in the AZT/lamivudine arm (pooled RR 4.40, CI 1.75 to 11.01; I^2=0%; figure 4). Observational evidence suggests that the baseline risk of stillbirth and early neonatal mortality is approximately 15 per 1000 in high-income countries[50] and approximately 69 per 1000 in low-income countries.[51] The best estimate of the increase in stillbirths and neonatal mortality is therefore

Table 2 Study characteristics of HIV-positive pregnant and non-pregnant adults randomised to different NRTI regimens, combined with the same third antiretroviral agent

Authors, year	Design	Study period	Setting	Population	Sample size	Age	Third ARV	NRTI comparison
Campbell, 2012[35]	RCT	2005–2007	Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, USA, Zimbabwe	Antiretroviral-naïve, CD4 <350 cells/μL	1042	Median 34	Efavirenz	TDF/FTC versus AZT/3TC
Fowler *et al*, 2016 (PROMISE)[12]	RCT	2012–2014	India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe	Pregnant women, CD4 ≥350 cells/μL	694	Median 26 (IQR 22–30)	Lopinavir boosted with ritonavir	TDF/FTC versus AZT/3TC
Gallant, 2006[43]	RCT	2003–2004	France, Germany, Italy, Spain, UK, USA	Antiretroviral-naïve, HIV viral load >10 000 copies/mL	509	Median 36.5	Efavirenz	TDF/FTC versus AZT/3TC
Nishijima, 2013[44]	RCT	2007–2010	Japan	Antiretroviral-naïve, CD4 <350 cells/μL	107	Median 36 (IQR 29–42.5)	Atazanavir boosted with ritonavir	TDF/FTC versus ABC/3TC
Post, 2010[45]	RCT	2007	13 European countries	Antiretroviral-naïve, HIV viral load ≥1000 copies/mL	385	Median 37 (range 18–70)	Efavirenz	TDF/FTC versus ABC/3TC
Rey, 2009[46]	RCT	2005–2006	France	Antiretroviral-naïve, CD4 <350 cells/μL for men and <250 cells/μL for women	71	Mean 41.4 (range 24–74)	Nevirapine	TDF/FTC versus AZT/3TC
Sax, 2009[47 48]	RCT	2005–2007	USA	Antiretroviral-naïve	1857	Median 39 (IQR 32–45)	Atazanavir boosted with ritonavir or efavirenz*	TDF/FTC versus ABC/3TC
Smith, 2009[49]	RCT	2005–2006	Puerto Rico, USA	Antiretroviral-naïve, HIV viral load ≥1000 copies/mL	688	Median 38	Lopinavir boosted with ritonavir	TDF/FTC versus ABC/3TC

*Patients with an HIV viral load <10 000 copies/mL were also randomised to receive atazanavir boosted with ritonavir or efavirenz; patients with higher viral loads all received atazanavir boosted with ritonavir.
3TC, lamivudine; ABC, abacavir; ARV, antiretroviral; AZT, zidovudine; FTC, emtricitabine; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; PROMISE, Promoting Maternal and Infant Survival Everywhere; RCT, randomised controlled trial; TDF, tenofovir disoproxil fumarate.

Table 3 GRADE evidence profile: tenofovir and emtricitabine versus alternative NRTI regimens in pregnant women living with HIV for outcomes that are consistent across settings*

Outcome Time frame	Study results and measurements	Absolute effect estimates Alternative NRTIs	 Tenofovir/FTC-based ART	Certainty in effect estimates (quality of evidence)	Summary
Maternal acceptability* (medication discontinuation)	Relative risk: 1.52 (95% CI 0.69 to 3.33) Based on data from 716 patients in one study	**28 per 1000**	**43 per 1000** **Difference: 15 more per 1000** (95% CI 9 fewer to 65 more)	**Moderate** Due to serious imprecision	There is probably no difference in maternal acceptability.
Maternal mortality	Based on data from 694 patients in one study	**0 per 1000**	**0 per 1000** **Difference: 0 fewer per 1000** (95% CI 11 fewer to 11 more)	**Moderate** Due to serious imprecision	There is probably no important difference in maternal mortality.
Maternal clinical adverse events†	Relative risk: 1.00 (95% CI 0.90 to 1.12) Based on data from 2633 patients in five studies Follow-up 6–18 months	**20 per 1000**	**20 per 1000** **Difference: 0 fewer per 1000** (95% CI 2 fewer to 2 more)	**Moderate** Due to serious indirectness	There is probably no important difference in serious maternal adverse events.
Maternal laboratory adverse events	Relative risk: 0.85 (95% CI 0.56 to 1.28) Based on data from 662 patients in one study Follow-up to delivery	**129 per 1000**	**110 per 1000** **Difference: 19 fewer per 1000** (95% CI 57 fewer to 36 more)	**Moderate** Due to serious imprecision	There is probably no important difference in maternal serious laboratory adverse events.
Detectable viral load 6 months after starting ART	Relative risk: 0.93 (95% CI 0.71 to 1.23) Based on data from 3231 patients in 6 studies of non-pregnant women Follow-up 6 months	**235 per 1000**	**219 per 1000** **Difference: 16 fewer per 1000** (95% CI 68 fewer to 54 more)	**Low** Due to serious inconsistency and indirectness	There may not be an important difference in detectable viral load at delivery.
Vertical HIV transmission	Relative risk: n/a Based on data from 1956 patients in four studies Follow-up 1 week to 1 year	**5 per 1000**	**4 per 1000** **Difference: 1 fewer per 1000** (95% CI 10 fewer to 8 more)	**Low** Observational data	There may not be an important difference in vertical HIV transmission.
Birth defect (with first trimester exposure) 1 year	Relative risk: 0.57 (95% CI 0.15 to 2.16) Based on data from 169 patients in two studies	**8 per 1000**	**5 per 1000** **Difference: 3 fewer per 1000** (95% CI 7 fewer to 9 more)	**Low** Due to serious imprecision and indirectness	There may be no important difference in birth defects.
Spontaneous abortion 20 weeks' gestation	Relative risk: 1.32 (95% CI 0.89 to 1.94) Based on data from 176 patients in one study Follow-up 6–18 months	**323 per 1000**	**426 per 1000** **Difference: 103 fewer per 1000** (95% CI 36 fewer to 304 more)	**Moderate** Due to very serious imprecision	TDF/FTC may increase the risk of spontaneous abortion.

Continued

Table 3 Continued

Outcome Time frame	Study results and measurements	Absolute effect estimates Alternative NRTIs	 Tenofovir/FTC-based ART	Certainty in effect estimates (quality of evidence)	Summary
Prematurity <34 weeks	Relative risk: 2.30 (95% CI 1.06 to 4.97) Based on data from 716 patients in one study	**32 per 1000**	**74 per 1000** **Difference: 42 more per 1000** (95% CI 2 more to 127 more)	**Moderate/low‡** Due to serious imprecision	TDF/FTC probably increases risk of early prematurity.
Prematurity <37 weeks	Relative risk: 0.94 (95% CI 0.69 to 1.28) Based on data from 716 patients in one study	**197 per 1000**	**185 per 1000** **Difference: 12 fewer per 1000** (95% CI 61 fewer to 55 more)	**Moderate/low‡** Due to serious imprecision	There is probably no difference in prematurity under 37 weeks.
Neonatal laboratory adverse events first week of life	Relative risk: 1.08 (95% CI 0.59 to 1.99) Based on data from 687 patients in one study Follow-up 1 week	**59 per 1000**	**64 per 1000** **Difference: 5 more per 1000** (95% CI 24 fewer to 58 more)	**Moderate** Due to serious imprecision	There is probably no difference in serious biochemical adverse events.

Full interactive evidence profile available at https://www.magicapp.org/goto/guideline/VLpr5E.
*Does not include stillbirth/neonatal mortality or vertical transmission of hepatitis B (see table 4).
†Comparator is zidovudine plus lamivudine only. Abacavir may increase risk of maternal clinical adverse events (see text).
‡Certainty in evidence is moderate when combined with lopinavir/ritonavir and low when combined with alternative third antiretrovirals
ART, antiretroviral therapy; FTC, emtricitabine; GRADE, Grading of Recommendations Assessment, Development and Evaluation; n/a, not applicable; NRTIs, nucleoside/nucleotide reverse transcriptase inhibitors; TDF, tenofovir disoproxil fumarate.

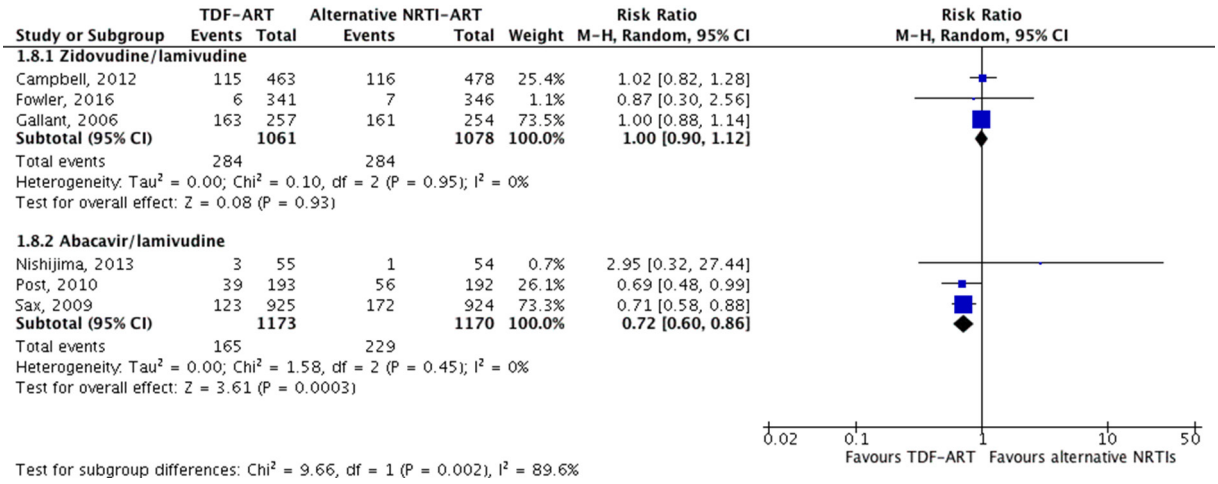

Figure 1 Forest plot of the risk ratio for clinical adverse events (data from randomised trials in non-pregnant adults except Fowler *et al*[12]). ART, antiretroviral therapy; M-H, Mantel-Haenszel; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate.

51 more per 1000 in low-income settings and 235 more per 1000 in high-income settings (table 4). In a post hoc sensitivity analysis that included PROMISE participants[12] randomised to AZT/lamivudine prior to the introduction of the tenofovir/FTC arm, the results remained statistically significant.

Observational studies reported conflicting results (online supplementary appendix 5c). One suggested a higher rate of stillbirth and early neonatal mortality in tenofovir-based regimens than in alternative regimens (combined in a triple NRTI regimen with AZT/lamivudine)[39]; two others found similar results in tenofovir-based and alternative NRTI regimens (combined with either LPV/r or nevirapine)[40 41]; and one reported a lower rate of stillbirths and early neonatal mortality (combined with nevirapine).[41] No study controlled for most of the critical confounders such as socioeconomic status, immune/disease status and cointerventions. Pooled results from these four observational studies suggested no difference between tenofovir-based and alternative regimens, but with a wide CI: RR 0.92, CI 0.52 to 1.64; I^2=68% (online supplementary appendix 5c). Thus, the evidence from observational studies is of very low certainty due to the observational design, imprecision, inconsistency and risk of bias.

Vertical transmission of HIV

Two observational studies including 1850 patients[12 39] and two small RCTs with 75 patients[34 35] reported vertical transmission of HIV. The PROMISE trial did not report vertical transmission in the groups as randomised, and therefore we considered it an observational study for this outcome[12]; there were no other transmission events in any of the other studies. There were two (0.4%, n=472) transmission events in the TDF/FTC-based cART group and seven (0.5%, n=1484) in the alternative NRTI groups: RD 1 fewer per 1000, CI 10 fewer to 8 more; low certainty due to observational design (online supplementary appendix 5d).

Birth defects

The PROMISE trial and a study of PrEP did not detect any difference in birth defects[12 15]: RR 1.05, CI 0.68 to 1.62, RD 0 per 1000, CI 3 fewer to 5 more, moderate certainty because of imprecision. However, women in the PROMISE trial were enrolled at a median of 26 weeks' gestation (IQR 21–31)[12]; thus, the evidence has little or no bearing on exposure in the first trimester. Evidence from two small RCTs with ART exposure in the first trimester did not find any apparent difference in birth defects between tenofovir and alternatives[15 35]: RR 0.57, CI 0.15 to

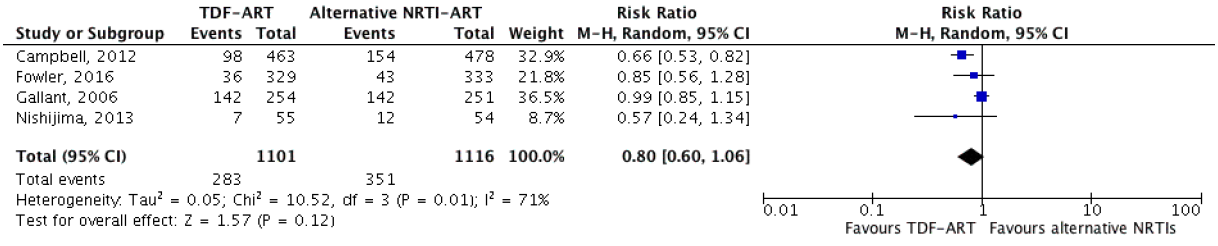

Figure 2 Forest plot of the risk ratio for laboratory adverse events (data from randomised trials in non-pregnant adults except Fowler *et al*[12]). ART, antiretroviral therapy; M-H, Mantel-Haenszel; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate.

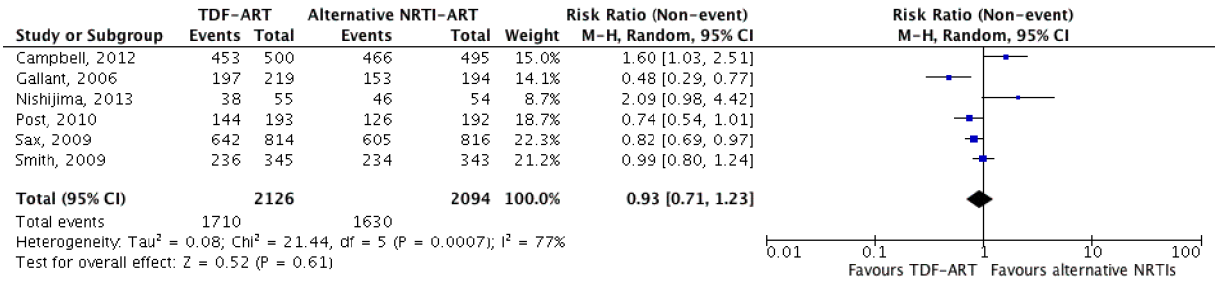

Figure 3 Forest plot of risk ratio for detectable serum viral load 26 weeks after antiretroviral initiation as a proxy for viral load at time of delivery (data from randomised trials of non-pregnant adults). ART, antiretroviral therapy; M-H, Mantel-Haenszel; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate.

2.16; RD 3 fewer per 1000 with TDF-ART, CI 7 fewer to 9 more (table 3). Two observational studies suggested that the overall birth defect rate might be lower with tenofovir-based ART than with alternative NRTIs—a result that was driven by the Antiretroviral Pregnancy Registry,[42] that relies on voluntary reporting and dates back to 1989: RD 9 fewer per 1000, CI 16 fewer to 2 fewer; very low certainty due to the observational design, imprecision, and risk of bias (online supplementary appendix 5e).

Spontaneous abortion

The PROMISE trial did not report any spontaneous abortions, but did not enrol participants prior to 14 weeks' gestation and more than 75% of women were enrolled after 20 weeks' gestation.[12] Evidence from an RCT of HIV PrEP suggested that tenofovir combined with FTC may increase the risk of pregnancy loss, 91% of which were spontaneous abortion: 42.5% (34 in 80 pregnancies) with tenofovir/FTC vs 32.3% (31 in 96 pregnancies) with placebo; RD: 103 more per 1000, CI 36 fewer to 304 more (table 3).[15] Evidence from one observational study was consistent but did not increase certainty (online supplementary appendix 5f).[39]

Prematurity at <34 and<37 weeks' gestation

The PROMISE trial alone provided the highest quality evidence for prematurity.[12] There was an increase in early prematurity <34 weeks' gestation with tenofovir/FTC (6.0%, n=335) compared with AZT/lamivudine (2.6%, n=346): RR 2.30, CI 1.06 to 4.97; RD 42 more per 1000 (table 3). All 35 infants were born after 34 weeks' gestation in one other RCT.[34] The results were similar in a sensitivity analysis that included PROMISE[12] participants randomised to AZT/lamivudine prior to the introduction of the tenofovir/FTC arm. There was no apparent difference in prematurity at <37 weeks' gestation between tenofovir/FTC (18.5%, n=335) and AZT/lamivudine (19.7%, n=346): RR 0.94, CI 0.69 to 1.28; RD 12 fewer per 1000 (table 3).

Three observational studies that included four comparisons (n=3878) suggested that tenofovir-based cART may be associated with reduced risk of premature delivery <37 weeks, but certainty in evidence is very low because of the observational study design and in addition risk of bias from failure to control for key confounders (online supplementary appendix 5g).[39–41] Similarly, there was only very low-quality evidence from the same observational studies addressing very early or early premature delivery (online supplementary appendix 5h).

Low and very low birth weight

The PROMISE trial alone provides the highest quality evidence for low and very low birth weight.[12] There was no apparent increase in low birth weight <2500 g with tenofovir/FTC (16.9%, n=301) and AZT/lamivudine (20.4%, n=319): RR 0.83, CI 0.60 to 1.16; RD 35 fewer per 1000; moderate certainty because of imprecision. There were more neonates born weighing <1500 g with tenofovir/FTC (2.1%, n=335) than with AZT/lamivudine (0.6%, n=346): RR 3.61, CI 0.76 to 17.28; RD 16 more per 1000; moderate certainty due to imprecision. One additional observational study did not improve the certainty in either outcome (online supplementary appendix 5i and j).

Neonatal laboratory adverse events

The best evidence is provided by the PROMISE trial alone.[12] There was no difference in grade 3 or higher

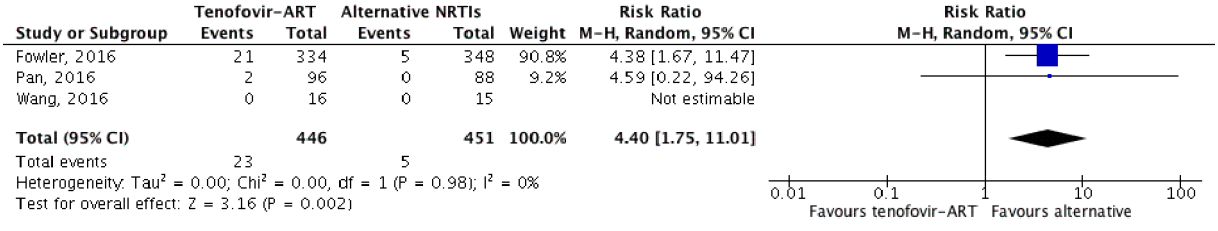

Figure 4 Forest plot of risk ratio for stillbirth and early neonatal mortality from randomised controlled trials. ART, antiretroviral therapy; M-H, Mantel-Haenszel; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor.

Table 4 GRADE evidence profile: tenofovir and emtricitabine versus alternative NRTI regimens in pregnant women living with HIV for outcomes that are different in different settings*

Outcome Time frame	Study results and measurements	Absolute effect estimates Alternative-NRTI ART	 Tenofovir/FTC ART	Certainty in effect estimates (quality of evidence)	Summary
Low and medium resourced settings (high baseline risk of stillbirth and early neonatal mortality, no access to early hepatitis B vaccination series):					
Stillbirth and early neonatal mortality 20 weeks' gestational age to 1 week postpartum	Relative risk: 4.40 (95% CI 1.75 to 11.01) Based on data from 897 patients in three studies Follow-up 1 week postpartum	**69† per 1000** **Difference: 235 more per 1000** (95% CI 52 more to 691 more)	**304 per 1000**	**Moderate/low‡** Due to serious imprecision	Tenofovir/FTC probably increases the risk of stillbirth and early neonatal mortality.
Vertical hepatitis B transmission 6–12 months	Relative risk: 0.26 (95% CI 0.01 to 4.77) Based on data from 1037 patients in nine studies Follow-up neonate to 12 months	**111§ per 1000** **Difference: 82 fewer per 1000** (95% CI 110 fewer to 418 more)	**29 per 1000**	**Low¶** Due to very serious imprecision	There may not be no important difference in vertical hepatitis B transmission.
High-resourced settings (lower baseline risk of stillbirth and early neonatal mortality, access to early hepatitis B vaccination series):					
Stillbirth and early neonatal mortality 20 weeks' gestational age to 1 week postpartum	Relative risk: 4.40 (95% CI 1.75 to 11.01) Based on data from 897 patients in three studies Follow-up 1 week postpartum	**15** per 1000** **Difference: 51 more per 1000** (95% CI 11 more to 150 more)	**66 per 1000**	**Moderate/low‡** Due to serious imprecision	Tenofovir/FTC probably increases the risk of stillbirth and early neonatal mortality.
Vertical hepatitis B transmission 6–12 months	Relative risk: 0.26 (95% CI 0.01 to 4.77) Based on data from 1037 patients in nine studies Follow-up neonate months to 12 months	**10†† per 1000** **Difference: 7 fewer per 1000** (95% CI 10 fewer to 38 more)	**3 per 1000**	**Moderate¶** Due to serious imprecision	There is probably no important difference in vertical hepatitis B transmission.

Full interactive evidence profile available at https://www.magicapp.org/goto/guideline/VLpr5E.
*See table 3 for outcomes consistent across populations.
†Baseline risk is inferred from an observational study in Botswana.[51]
‡Moderate certainty when combined with lopinavir/ritonavir, low certainty when combined with a different third antiretroviral.
§Baseline risk is inferred from an observational study in the USA.[50]
¶We considered rating down for risk of bias because the indirect comparison relies on one study of tenofovir versus placebo that was not adequately blinded.[38] However, we decided not to rate down because any plausible confounding would have favoured the control group (eg, about 8% more infants were delivered by caesarean section in the control group) and all infants received the full early hepatitis B vaccination series and hepatitis B immunoglobulin.
**Estimate of baseline risk comes from an observational study in the USA.[92]
††Estimate of baseline risk is based on the risk ratio of lamivudine versus placebo from our network meta-analysis (0.28) and the baseline risk of hepatitis B transmission without any intervention (38.3%).[83]
ART, antiretroviral therapy; FTC, emtricitabine; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NRTIs, nucleoside/nucleotide reverse transcriptase inhibitors.

laboratory adverse events: 5.9% of 324 with AZT/lamivudine and 6.2% of 315 with tenofovir/FTC: RD 5 more per 1000, CI 24 fewer to 58 more (table 3).

Medium and long-term development

None of the studies reported medium and long-term developmental outcomes.

Hepatitis B outcomes

We screened 1035 titles and abstracts and ultimately included 33 comparative studies of NRTIs (tenofovir, lamivudine and FTC) in pregnant women living with HBV (online supplementary appendix 3c and online supplementary appendix 7).[34 38 52–81] The primary network meta-analysis was restricted to RCTs and included eight RCTs (n=857) comparing lamivudine with a control without antiviral activity (usually placebo)[56 59 66 71 74–76 81] and one RCT (n=180) that compared tenofovir with placebo[38] (online supplementary appendix 6). Two additional RCTs that compared lamivudine with placebo met inclusion criteria but were excluded from the analyses post hoc.[34 82] One included 35 women with HIV and HBV coinfection, but no transmission events occurred in either group.[34] The other, an unpublished study identified in the reference list of a systematic review,[22] was excluded post hoc because the methods and definition of transmission were not described in sufficient detail.[82] The main limitations within the RCTs were possible lack of allocation concealment (all but two RCTs) and lack of blinding (all but two RCTs) (online supplementary appendix 4b).

The secondary network meta-analysis included an additional 22 observational studies with an additional 1522 pregnant women, thus included 31 studies with 2559 pregnant women (online supplementary appendix 6). All 22 observational studies failed to adjust or match for most known confounders, the included populations were probably dissimilar in nine studies, and cointerventions may have been applied differently between the groups in 10 studies (online supplementary appendix 4c). Including the RCTs, 19 studies were conducted primarily in China, 8 in Europe or North America, and 1 in Africa.

Vertical transmission of HBV

There was low global heterogeneity for the network restricted to RCTs and for the network that included observational studies (global I^2=0% for both). There were no concerns of intransitivity. In the network restricted to RCTs (online supplementary appendix 8), lamivudine reduced risk of vertical transmission of HBV more than control (RR 0.28, CI 0.17 to 0.49; high certainty) as did tenofovir, but the CI included no effect (RR 0.07, CI 0.00 to 1.29) (table 4, figure 5). There was no apparent difference between tenofovir and lamivudine: RR 0.26, CI 0.01 to 4.77. Without antiviral therapy, the baseline risk of transmission is approximately 1 in 100[83] in high-income countries and is approximately 380 per 1000 in low-resource countries without access to early neonatal hepatitis B vaccination and hepatitis B immunoglobulin (HBIg).[84] The effect of tenofovir compared with lamivudine on vertical transmission of HBV in high-income countries is 7 fewer per 1000, CI 10 fewer to 38 more, and in low-income countries is 82 fewer per 1000, CI 110 fewer to 418 more (table 4).

When observational studies were included in the network meta-analysis (online supplementary appendix 9), tenofovir reduced risk of vertical transmission of hepatitis B compared with control: RR 0.23, CI 0.10 to 0.54; low certainty because of observational data (figure 5). Tenofovir did not reduce risk of vertical transmission of HBV compared with lamivudine: RR 0.99, 0.38 to 2.59; very low certainty due to observational data and imprecision (online supplementary appendix 9).

The pooled estimates of RCTs are shown in red, the pooled estimate of observational data is shown in yellow, and the pooled mixed estimates shown in blue.`

Other hepatitis B outcomes

Five studies (one RCT, four observational) reported hepatitis B flares, including three that compared tenofovir with control[38 57 63] and two that compared lamivudine with control.[68 72] Four studies defined a hepatitis flare as an increase in serum transaminase levels more than five times the upper limit of normal and one used an increase more than two times the upper limit of normal.[72] All included flares prior to and after stopping antiviral therapy. The network had high global heterogeneity (I^2=63.5%, p=0.042 for inconsistency; online supplementary appendix 10). We found no apparent difference between any of tenofovir, lamivudine or control, but our certainty in the evidence was very low for all comparisons due to observational data, inconsistency and very wide CIs (online supplementary appendix 10). One study reported the development of HBV resistance: HBV lamivudine resistance occurred in 1 of 25 (4.0%, 0.1% to 20.4%) women.[53]

DISCUSSION

The PROMISE trial dominated results for neonatal outcomes.[12] We found moderate certainty evidence of a large absolute increase (point estimate 5%) in stillbirth and early neonatal death with tenofovir/FTC versus AZT/lamivudine when they are combined with LPV/r. Moderate certainty evidence also suggested an increase in prematurity before 34 weeks with tenofovir/FTC plus LPV/r versus AZT/lamivudine (point estimate also approximately 5%). The evidence is indirect when applied to cART regimens in which the third antiretroviral is something other than LPV/r, particularly if it is not a protease inhibitor. In this situation, our certainty is low rather than moderate.

We also summarised the results of observational studies comparing tenofovir-based ART regimens with alternatives on stillbirth and neonatal deaths. Based on similar evidence, our review comes to a different conclusion than another recent meta-analysis.[13] The reason for this

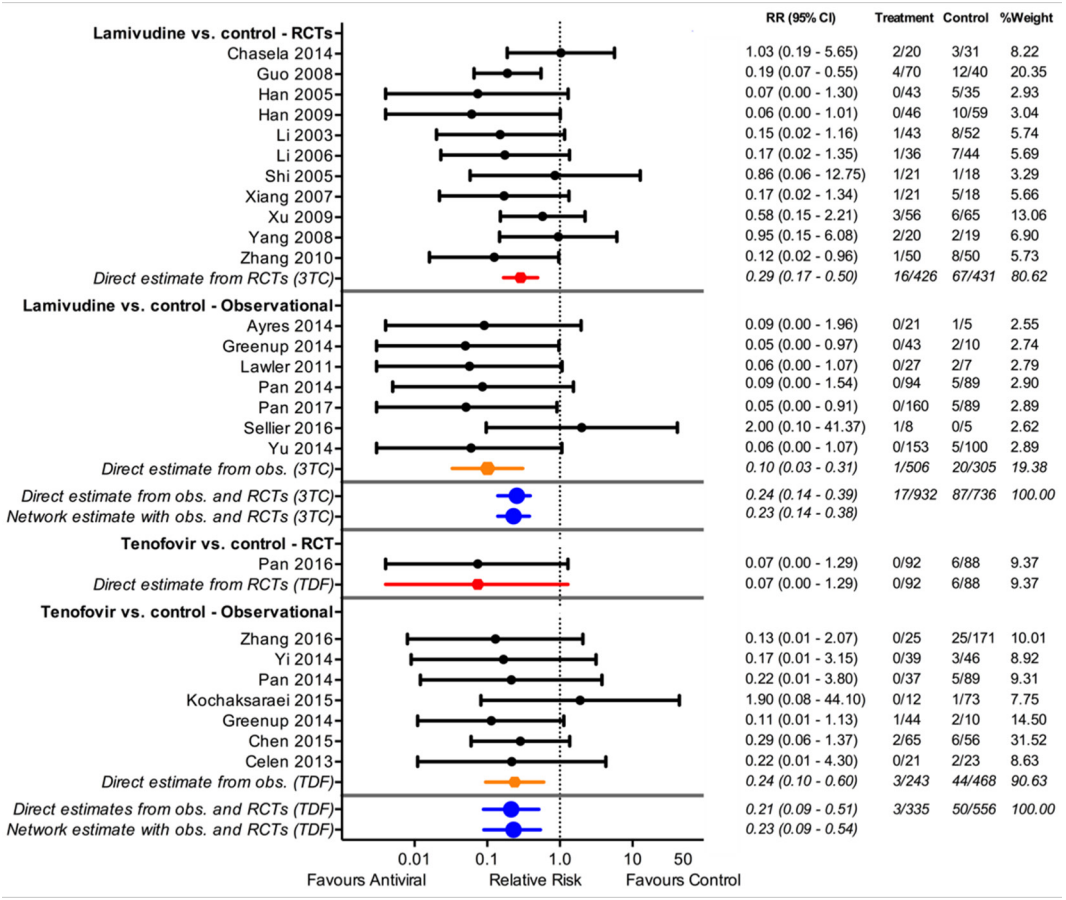

Figure 5 Forest plot of maternal antivirals (lamivudine and tenofovir) versus control (no antiviral) for prevention of vertical transmission of hepatitis B, by study type and antiviral. 3TC, lamivudine; ART, antiretroviral therapy; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; RCT, randomised controlled trial; RR, risk ratio; TDF, tenofovir disoproxil fumarate.

is Nachega and colleagues[13] pooled RCTs and observational studies which, given the much higher certainty associated RCTs, we consider inadvisable and, indeed, inappropriate. This is particularly the case here because the available observational studies, already beginning as low quality using the GRADE framework,[85] were further limited by inconsistent results, imprecise pooled estimates and failure to adjust for important confounders. For instance, AZT/lamivudine is an older drug combination than tenofovir/FTC. Thus, clinical care for women who received AZT/lamivudine was more likely limited or outdated for other aspects of their pregnancy.

For the other key outcomes, there did not appear to be important differences between tenofovir-based regimens and alternatives. Outcomes without evidence of a between group difference include acceptability to pregnant women, clinical and laboratory maternal adverse events, maternal mortality, maternal viral load, vertical transmission of HIV, birth defects, low birth weight and prematurity prior to 37 weeks. Further, in pregnant women with hepatitis B coinfection, tenofovir and lamivudine likely confer a similar large reduction in risk of vertical hepatitis B transmission compared with no maternal intervention, although this is more certain for lamivudine than it is for tenofovir (high versus moderate certainty).

Strengths of our review include the comprehensive search; duplicate assessment of eligibility, risk of bias and data abstraction; summarisation of both RCT and observational studies; careful attention to what findings can or cannot be appropriately pooled; and use of the GRADE framework to address certainty of evidence. The primary limitations of the review are associated with the available evidence. The key results come primarily from a single study of moderate size.[12] Single studies demonstrating large benefits on the basis of small number of events typically yield large overestimates of effect.[86] This is likely true of harm outcomes as well, suggesting that the increase in stillbirths and neonatal deaths with tenofovir/FTC likely represents an overestimate. Because some have raised concerns that the event rates in the AZT/lamivudine arm are lower than might have been anticipated, we also performed a sensitivity analysis that includes participants in the AZT/lamivudine arm who were randomised early in the PROMISE study, before the tenofovir/FTC arm was added.[12]

The results raise challenges in interpretation. The first is the mechanisms that tenofovir/FTC might increase in stillbirths and neonatal mortality. One hypothesis would be that the mediating factor is prematurity. Support from this hypothesis comes from the increase in prematurity

before 34 weeks in the tenofovir group, and that approximately two-thirds of the deaths were attributed to prematurity or sequelae of prematurity.

Another interpretation issue is whether the culprit drug that might cause an increase in stillbirths/early deaths is tenofovir or FTC, and circumstances in which the culprit drug would lead to increases in stillbirths and neonatal deaths. The culprit could be tenofovir or FTC, or the combination of the two.

Another mechanism postulates a role for LPV/r in the increase in stillbirths and neonatal deaths.[87] This cannot be a direct effect: patients in both the tenofovir/FTC and AZT/lamivudine groups received LPV/r.[12] Thus, the only possibility for implicating LPV/r is that it modifies the effect of tenofovir/FTC but not AZT/lamivudine on stillbirths and neonatal mortality. Were this true, tenofovir/FTC would have an adverse effect relative to AZT/lamivudine only when coadministered with LPV/r or similar antiretrovirals. The mechanism of such an interaction is unlikely to be increased LPV drug levels in the presence of tenofovir: if anything, tenofovir decreases LPV drug levels.[88–91] Further, protease inhibitors including LPV/r only slightly increase serum tenofovir levels[88–91] and implicating this drug–drug interaction would nonetheless implicate tenofovir at serum concentrations within the typical therapeutic range (the increase in tenofovir from concurrent LPV/r is a magnitude lower than normal variability between patients).[92] The increased LPV/r dosing used in the PROMISE study during the third trimester provides similar serum drug concentrations to non-pregnant women taking LPV/r.[93] Thus, the hypothesis that the adverse effects on fetal outcomes with tenofovir/FTC occur only with concomitant administration of LPV/r has no evident biological basis. Nevertheless, we conservatively chose to rate down our certainty in the evidence for indirectness from moderate to low for key outcomes when tenofovir/FTC is combined with antiretrovirals other than LPV/r.

Tenofovir is currently the drug of choice for prevention of vertical transmission of HBV. The PROMISE results raise challenges for maternal prophylaxis against vertical transmission of HBV. The evidence that lamivudine results in a large reduction in vertical transmission of HBV compared with no antiviral therapy warrants higher certainty than is the case for tenofovir (although point estimates are similar).[38] The results of our indirect comparisons suggest similar effects with use of tenofovir and lamivudine in decreasing vertical transmission of HBV. Generally, tenofovir is favoured for its lower likelihood of pretreatment HBV resistance and of developing HBV resistance during treatment than lamivudine.[14] These considerations are particularly important in pregnant women who have long-term exposure to lamivudine, are at high risk of vertical transmission and in those who do not have access to early infant HBV vaccination or HBIg.

The results of this review present a dilemma for policymakers. Tenofovir/FTC is convenient as a single pill taken once a day. It is also the currently recommended regimen and allows harmonisation across a wide range of populations, resulting in simplification of cART and widespread provision in low-income and middle-income countries. Moreover, the adverse effect on stillbirths and neonatal mortality is likely an overestimate, and the mechanism and circumstances under which the effect exists remain uncertain. Nevertheless, fully informed pregnant women living with HIV are likely to choose regimens that do not include tenofovir or FTC.

Author affiliations
[1]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada
[2]Department of Medicine, University of Toronto, Toronto, Canada
[3]Department of Medicine, McMaster University, Hamilton, Canada
[4]Southern Alberta HIV Clinic, Alberta Health Services, Calgary, Canada
[5]The Infectious Diseases Society of America, Washington, USA
[6]Faculty of Medicine, University of Toronto, Toronto, Canada
[7]Gastroenterology and Hepatology Unit, College of Medicine, University of Lagos and Lagos University Teaching Hospital, Lagos, Nigeria
[8]Division of General Pediatrics, University Hospitals of Geneva, Geneva, Switzerland
[9]Faculty of Health Sciences, McMaster University, Hamilton, Canada

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REFERENCES

1. World Health Organization. *Number of women living with HIV*. Geneva, Switzerland: World Health Organization, 2017. http://www.who.int/gho/hiv/epidemic_status/cases_adults_women_children/en/ (accessed 20 Mar 2017).
2. Rates of mother-to-child transmission of HIV-1 in Africa, America, and Europe: results from 13 perinatal studies. The Working Group on

Mother-To-Child Transmission of HIV. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;8:506–10.
3. De Cock KM, Fowler MG, Mercier E, *et al*. Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. *JAMA* 2000;283:1175–82.
4. UNAIDS. HIV Fact Sheets, 2017. http://aidsinfo.unaids.org/ (accessed 20 Mar 2017).
5. World Health Organization. Prevention of mother-to-child transmission: World Health Organization, 2017. Available from. http://www.who.int/gho/hiv/epidemic_response/PMTCT_text/en/ (accessed 04 Nov 2017).
6. Forbes JC, Alimenti AM, Singer J, *et al*. A national review of vertical HIV transmission. *AIDS* 2012;26:757–63.
7. World Health Organization. *WHO validates elimination of mother-to-child transmission of HIV and syphilis in Cuba*, 2015.
8. Danel C, Moh R, Gabillard D, *et al*. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med* 2015;373:808–22.
9. Lundgren JD, Babiker AG, Gordin F, *et al*. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med* 2015;373:795–807.
10. World Health Organization. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. 2nd edition, 2016.
11. Siemieniuk RA, Mah Ming J, Guyatt GH, *et al*. Antiretroviral therapy for pregnant women living with HIV. *BMJ*. (Clinical research ed) (Co-submitted).
12. Fowler MG, Qin M, Fiscus SA, *et al*. Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. *N Engl J Med* 2016;375:1726–37.
13. Nachega JB, Uthman OA, Mofenson LM, *et al*. Safety of Tenofovir Disoproxil Fumarate-Based Antiretroviral Therapy Regimens in Pregnancy for HIV-Infected Women and Their Infants: A Systematic Review and Meta-Analysis. *J Acquir Immune Defic Syndr* 2017;76:1–12.
14. Terrault NA, Bzowej NH, Chang KM, *et al*. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology* 2016;63:261–83.
15. Mugo NR, Hong T, Celum C, *et al*. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. *JAMA* 2014;312:362–71.
16. UNAIDS. On the fast-track to end AIDS: UNAIDS 2016-2021 Strategy. 2015.
17. Fowler MG, Qin M, Fiscus SA, *et al*, 2015. PROMISE: Efficacy and Safety of 2 Strategies to Prevent Perinatal HIV Transmission. *Conference on retroviruses and opportunistic infections*. Seattle, USA (Abstract 31LB).
18. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. 2016.
19. Lytvyn L, Siemieniuk RA, Guyatt GH, *et al*. Values and preferences of pregnant women living with HIV considering antiretroviral therapy. *BMJ*. (Co-submitted).
20. Siemieniuk RA, Agoritsas T, Macdonald H, *et al*. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:i5191.
21. Kanters S, Vitoria M, Doherty M, *et al*. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. *Lancet HIV* 2016;3:e510–20.
22. Brown RS, McMahon BJ, Lok AS, *et al*. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis. *Hepatology* 2016;63:319–33.
23. Poolman RW, Agoritsas T, Siemieniuk RA, *et al*. Low intensity pulsed ultrasound (LIPUS) for bone healing: a clinical practice guideline. *BMJ* 2017;356:j576.
24. Vandvik PO, Otto CM, Siemieniuk RA, *et al*. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ* 2016;354:i5085.
25. Siemieniuk RAC, Harris IA, Agoritsas T, *et al*. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *BMJ*. In Press. 2017;357:j1982.
26. U.S. Department of Health and Human Services,National Institutes of Health, Division of AIDS National Institute of Allergy and Infectious Diseases Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. 2014. version 2.0 ed.
27. Busse JWG G. Modification of Cochrane tool to assess risk of bias in randomized trials 2013. https://distillercer.com/wp-content/uploads/2014/02/Tool-to-Assess-Risk-of-Bias-in-Randomized-Controlled-Trials.docx (accessed July 11, 2016).
28. Akl EA, Sun X, Busse JW, *et al*. Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. *J Clin Epidemiol* 2012;65:262–7.
29. Busse JWG G. Modification of Ottawa-Newcastle tool to assess risk of bias in observational studies 2013. (accessed 11 Jul 2016).
30. Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
31. Puhan MA, Schünemann HJ, Murad MH, *et al*. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;349:g5630.
32. Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. *Stat Med* 2012;31:3805–20.
33. Spencer FA, Iorio A, You J, *et al*. Uncertainties in baseline risk estimates and confidence in treatment effects. *BMJ* 2012;345:e7401.
34. Wang L, Wiener J, Bulterys M, *et al*. Hepatitis B Virus (HBV) Load Response to 2 Antiviral Regimens, Tenofovir/Lamivudine and Lamivudine, in HIV/ HBV-Coinfected Pregnant Women in Guangxi, China: The Tenofovir in Pregnancy (TiP) Study. *J Infect Dis* 2016;214:1695–9.
35. Campbell TB, Smeaton LM, Kumarasamy N, *et al*. PEARLS study team of the ACTG. Efficacy and safety of three antiretroviral regimens for initial treatment of HIV-1: a randomized clinical trial in diverse multinational settings. *PLoS Med* 2012;9:e1001290.
36. Bunge K, Balkus J, Noguchi L, *et al*, 2015. Pregnancy incidence and outcomes in women receiving tenofovir-based PrEP in the VOICE trial. *International AIDS conference*. Vancouver, Canada (MOPEC480).
37. Van Damme L, Corneli A, Ahmed K, *et al*. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2012;367:411–22.
38. Pan CQ, Duan Z, Dai E, *et al*. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. *N Engl J Med* 2016;374:2324–34.
39. Gibb DM, Kizito H, Russell EC, *et al*. Pregnancy and infant outcomes among HIV-infected women taking long-term ART with and without tenofovir in the DART trial. *PLoS Med* 2012;9:e1001217.
40. Rough K, Seage GR, Williams PL, *et al*, 2017. TDF/FTC in pregnancy shows no increase in adverse infant birth outcomes in US cohorts. *Conference on Retroviruses and Opportunistic Infections*. Seattle, Washington (Abstract #779).
41. Zash R, Jacobson D, Diseko M, *et al*, 2017. Adverse birth outcomes differ by ART regimen from conception in Botswana. *Conference on Retroviruses and Opportunistic Infections*. Seattle, Washington (Abstract #25).
42. Antiretroviral Pregnancy Registry Steering Committee. 2016. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 July 2016. Wilmington, USA.
43. Gallant JE, DeJesus E, Arribas JR, *et al*. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 2006;354:251–60.
44. Nishijima T, Takano M, Ishisaka M, *et al*. Abacavir/lamivudine versus tenofovir/emtricitabine with atazanavir/ritonavir for treatment-naive Japanese patients with HIV-1 infection: a randomized multicenter trial. *Intern Med* 2013;52:735–44.
45. Post FA, Moyle GJ, Stellbrink HJ, *et al*. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. *J Acquir Immune Defic Syndr* 2010;55:49–57.
46. Rey D, Hoen B, Chavanet P, *et al*. High rate of early virological failure with the once-daily tenofovir/lamivudine/nevirapine combination in naive HIV-1-infected patients. *J Antimicrob Chemother* 2009;63:380–8.
47. Sax PE, Tierney C, Collier AC, *et al*. Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. *J Infect Dis* 2011;204:1191–201.
48. Sax PE, Tierney C, Collier AC, *et al*. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med* 2009;361:2230–40.
49. Smith KY, Patel P, Fine D, *et al*. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS* 2009;23:1547–56.
50. Reddy UM, Laughon SK, Sun L, *et al*. Prepregnancy risk factors for antepartum stillbirth in the United States. *Obstet Gynecol* 2010;116:1119–26.
51. Chen JY, Ribaudo HJ, Souda S, *et al*. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. *J Infect Dis* 2012;206:1695–705.

52. Ayres A, Yuen L, Jackson KM, *et al*. Short duration of lamivudine for the prevention of hepatitis B virus transmission in pregnancy: lack of potency and selection of resistance mutations. *J Viral Hepat* 2014;21:809–17.
53. Ayres A, Yuen L, Manoharan S, *et al*. 736 lamivudine in late pregnancy for prevention of hbv transmission: Effectiveness and detection of antiviral resistance. *J Hepatol* 2011;54:S295–6.
54. Carey I, Lai JC CWW, *et al*. Preventing mother to child transmission of HBV in an ethnically diverse South London population: an effective multidisciplinary clinical pathway (Abstract). *Hepatology* 2016;63:S01.
55. Celen MK, Mert D, Ay M, *et al*. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection. *World J Gastroenterol* 2013;19:9377–82.
56. Chasela CS, Kourtis AP, Wall P, *et al*. Hepatitis B virus infection among HIV-infected pregnant women in Malawi and transmission to infants. *J Hepatol* 2014;60:508–14.
57. Chen HL, Lee CN, Chang CH, *et al*. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. *Hepatology* 2015;62:375–86.
58. Greenup AJ, Tan PK, Nguyen V, *et al*. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus. *J Hepatol* 2014;61:502–7.
59. Guo Y, Sx L, Sl G, *et al*. Effect of lamivudine treatment combined with active–passive immunization on interrupting mother to infant transmission of HBV. *Clinical Focus* 2008;23:1730–1.
60. Han GR, Fang ZX, Zhao W, *et al*. Efficacy and safety of lamivudine treatment on preventing hepatitis B virus vertical transmission in pregnant women. *Chin J Infect Dis* 2009;27:673–6.
61. Han ZH, Chen YH, Lw L, *et al*. Effect and safety of preventing HBV vertical transmission by lamivudine treatment. *Chinese J Intern Med* 2005;44:378.
62. Huang H, Wu Q, Wang Y. Tenofovir Disoproxil: Effective and Safe in Prevention of Mother-to-child Transmission of Hepatitis B Virus. *Hepatology* 2014;60:1088A.
63. Samadi Kochaksaraei G, Castillo E, Osman M, *et al*. Clinical course of 161 untreated and tenofovir-treated chronic hepatitis B pregnant patients in a low hepatitis B virus endemic region. *J Viral Hepat* 2016;23:15–22.
64. Lawler J, Glass A, Chatterjee U, *et al*. Nucleot(s)ide analogues to prevent perinatal transmission of HBV: Lamivudine is effective but tenofovir may be better. *J Gastro Hepato* 2011;26:100.
65. Wf L, Jiang R, Wei Z, *et al*. Clinical effect and safety of lamivudine in interruption of chronic HBV maternal to infant transmission. *Chin Hepatol* 2006;11:106–7.
66. Li XM, Yang YB, Hou HY, *et al*. Interruption of HBV intrauterine transmission: a clinical study. *World J Gastroenterol* 2003;9:1501–3.
67. Pan C, Ta A, Zeng Z. Safety of Tenofovir Disoproxil Fumarate Treatment in Late Pregnancy in Highly Viremic Mothers with Chronic Hepatitis B. *J American Gastro* 2013;108:S156.
68. Pan CQ, Yi W, Liu M, *et al*. Lamivudine therapy during the second vs the third trimester for preventing transmission of chronic hepatitis B. *J Viral Hepat* 2017;24:246–52.
69. Pan CQ, Lan B, Chan S, *et al*. Su1007 Tenofovir or Lamivudine Use in Late Pregnancy Safely Reduces Perinatal Transmission of Hepatitis B Virus in Real-Life Practice. *Gastroenterology* 2014;146:961.
70. Sellier P, Schnepf N, Amarsy R, *et al*. Hepatitis B virus (HBV) status of children born to HIV/HBV co-infected women in a French hospital: a cross-sectional study. *J Int AIDS Soc* 2014;17(4 Suppl 3):19632.
71. Shi MF, Xm L, He J, *et al*. Study of lamivudine in interruption of HBV intrauterine infection. *Clin Med Chin* 2005;21:77–8.
72. Tan PK, Chatterjee U, Glass A, *et al*. Lamivudine in pregnancy: impact on hepatitis flares and HBeAg seroconversion post partum. *J Gastro Hepato* 2012;27:181.
73. Virine B, Osiowy C, Gao S, *et al*. Hepatitis B Virus (HBV) Variants in Untreated and Tenofovir Treated Chronic Hepatitis B (CHB) Patients during Pregnancy and Post-Partum Follow-Up. *PLoS One* 2015;10:e0140070.
74. Xiang GJ, Sun JW, Jiang SQ, *et al*. Evaluation of therapeutic effect in HBV vertical transmission by lamivudine treatment combined with active-passive immunization for pregnant women. *Chin Prac Med* 2007;2:14–16.
75. Wm X, Cui YT, Wang L, *et al*. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. *J viral hepatitis* 2009;16:94–103.
76. Yang S, Liu M, Wang L. Effect of high viral hepatitis B virus DNA loads on vertical transmission of hepatitis B virus in late-pregnant women]. *Zhonghua fu chan ke za zhi* 2008;43:329–31.
77. Yi W, Pan CQ, Liu M, *et al*. Clinical outcomes of tenofovir disoproxil fumarate (TDF) treatment versus no treatment for pregnant women with active chronic hepatitis B (CHB) and elevated alanine aminotransaminase (ALT). *Hepatology* 2014;60:1094A.
78. Mm Y, Jiang Q, Ji Y, *et al*. Comparison of telbivudine versus lamivudine in interrupting perinatal transmission of hepatitis B virus. *J Clin Virol* 2014;61:55–60.
79. Zhang H, Pan CQ, Pang Q, *et al*. Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice. *Hepatology* 2014;60:468–76.
80. Zhang Y, Wu Q, Huang H, *et al*. *J Hepatol* 2016;64:S607 (Abstract FRI-154).
81. Zhang YF. The clinical observation of effect of lamivudine on interrupting mother to infant transmission of chronic HBV on 50 mothers. *J Prat Obst Gynecol* 2010;26:367–8.
82. Shi Z, Li X, Yang Y, *et al*. Clinical research on the interruption of mother to child transmissionof HBV- a randomized, double-blind, placebo-control study. 2008.
83. Schillie S, Walker T, Veselsky S, *et al*. Outcomes of infants born to women infected with hepatitis B. *Pediatrics* 2015;135:e1141–7.
84. Keane E, Funk AL, Shimakawa Y. Systematic review with meta-analysis: the risk of mother-to-child transmission of hepatitis B virus infection in sub-Saharan Africa. *Aliment Pharmacol Ther* 2016;44:1005–17.
85. Guyatt GH, Oxman AD, Kunz R, *et al*. What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008;336:995–8.
86. Montori VM, Devereaux PJ, Adhikari NK, *et al*. Randomized trials stopped early for benefit: a systematic review. *Jama* 2005;294:2203–9.
87. World Health Organization. Press Release: First PROMISE study results confirm WHO recommendations to treat pregnant women and reduce mother-to-child-transmission of HIV. 2014 http://www.who.int/hiv/mediacentre/news/promise-study-result/en/ (accessed 28 Jul 2017).
88. Lack of clinically relevant drug-drug interactions between tenofovir DF and efavirenz, indinavir, lamivudine and lopinavir/ritonavir in healthy subjects. *8th European Conference on Clinical Aspects and Treatment of HIV Infection*.
89. Pharmacokinetic drug interaction of lopinavir/ritonavir in combination with tenofovir in experienced HIV+ patients [abstract A-445]. *44th Interscience Conference on Antimicrobial Agents and Chemotherapy*.
90. Comparison of lopinavir/r plasma levels with and without tenofovir as part of HAART in HIV-1 infected patients. *5th International Workshop on Clinical Pharmacology of HIV Therapy*.
91. Kearney BP, Mathias A, Mittan A, *et al*. Pharmacokinetics and safety of tenofovir disoproxil fumarate on coadministration with lopinavir/ritonavir. *JAIDS* 2006;43:278–83.
92. Kearney BP, Mathias A, Mittan A, *et al*. Pharmacokinetics and safety of tenofovir disoproxil fumarate on coadministration with lopinavir/ritonavir. *J Acquir Immune Defic Syndr* 2006;43:278–83.
93. Best BM, Stek AM, Mirochnick M, *et al*. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. *J Acquir Immune Defic Syndr* 2010;54:381–8.

Appendix to *Antiretroviral therapy for pregnant women living with HIV or hepatitis B: a systematic review*

Appendix 1a

Complete search strategy #1: direct evidence from comparative studies of NRTI therapy in pregnant women living with HIV

Database: Ovid MEDLINE(R) <1996 to January 12, 2017 with daily update>
Search Strategy:
---
1 exp HIV/ (86974)
2 (hiv-infect* or hiv-uninfected or hiv-noninfected or hiv-exposed).mp. [mp=title, abstract, original title, name of
substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease
supplementary concept word, unique identifier] (190210)
3 human immunodeficiency virus.mp. (75380)
4 hiv.mp. (277365)
5 human immune*.mp. or Acquired Immunodeficiency Syndrome/ (38306)
6 human immunodeficiency virus-exposed.mp. (33)
7 HIV Infections/ or HIV prevention.mp. (171100)
8 HIV-exposed uninfected.mp. (261)
9 AIDS.mp. (122315)
10 acquired immun*.mp. (50320)
11 human immun*.mp. (83831)
12 deficiency virus.mp. (404)
13 HIV-infected mothers.mp. (793)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (341888)
15 exp pregnancy/ (441409)
16 (Pregnan* or non-pregnant or infant* or newborn* or neonate).mp. [mp=title, abstract, original title, name of
substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease
supplementary concept word, unique identifier] (1088445)
17 (breastf* or breast fe*).mp. [mp=title, abstract, original title, name of substance word, subject heading word,
keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
(30930)

18 Fetal Growth Retardation/ or maternal.mp. (184127)
19 (prenatal* or prenatal exposure or perinatal*).mp. [mp=title, abstract, original title, name of substance word,
subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept
word, unique identifier] (147078)
20 lactat*.mp. (102104)
21 In utero exposure.mp. (1992)
22 (gestation* or congenital).mp. [mp=title, abstract, original title, name of substance word, subject heading word,
keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
(292851)
23 (MTCT or Mother-to-child transmission or Mother to child transmission or Mother-to-infant transmission or
Infectious disease transmission, vertical or Vertical transmission or disease transmission, vertical or Adult to child
transmission or mother-to-infant).mp. [mp=title, abstract, original title, name of substance word, subject heading word,
keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
(21275)
24 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (1321676)
25 14 and 24 (34559)
26 exp tenofovir/ (3395)
27 exp antiretroviral therapy/ (21906)
28 TDF.mp. (1626)
29 exp emtricitabine/ (1201)
30 FTC.mp. (1936)
31 Combination TDF FTC.mp. (4)
32 Tenofovir emtricitabine efavirenz.mp. (31)
33 Antiretroviral Therapy, Highly Active/ or Drug Resistance, Viral/ or Zidovudine/ or NRTI.mp. or Anti-HIV Agents/
or HIV Reverse Transcriptase/ (71025)
34 NRTIs.mp. (1548)
35 nucleotide reverse transcriptase inhibitor.mp. (142)
36 (preexposure prophylaxis or Pre-Exposure Prophylaxis or PrEP).mp. [mp=title, abstract,

original title, name of
substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease
supplementary concept word, unique identifier] (3209)
37 (Combination ART or Combination antiretroviral therapy or triple ART or triple antiretroviral therapy).mp.
[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol
supplementary concept word, rare disease supplementary concept word, unique identifier] (3178)
38 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 (77227)
39 25 and 38 (7767)
40 limit 39 to (humans and yr="1996 -Current") (7554)
41 limit 40 to (clinical study or clinical trial, all or clinical trial or comparative study or controlled clinical
trial or observational study or randomized controlled trial) (1577)

Database: Embase <1996 to 2017 January 13>
Search Strategy:
---
1 exp HIV/ (210953)
2 (hiv-infect* or hiv-uninfected or hiv-noninfected or hiv-exposed or human immunodeficiency virus or human
immune*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer,
device trade name, keyword, floating subheading] (337799)
3 (HIV-exposed uninfected or AIDS or acquired immun*).mp. [mp=title, abstract, heading word, drug trade name,
original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (147854)
4 exp pregnancy/ (404194)
5 (Pregnan* or non-pregnant or infant* or newborn* or neonate).mp. [mp=title, abstract, heading word, drug trade

name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (1100463)
6 breastf*.mp. (23599)
7 (prenatal exposure or perinatal*).mp. [mp=title, abstract, heading word, drug trade name, original title, device
manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (110164)
8 (In utero exposure or gestation*).mp. [mp=title, abstract, heading word, drug trade name, original title, device
manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (205557)
9 (MTCT or Mother-to-child transmission or Mother to child transmission or Mother-to-infant transmission or
Infectious disease transmission, vertical or Vertical transmission or disease transmission, vertical or Adult to child
transmission or mother-to-infant).mp. [mp=title, abstract, heading word, drug trade name, original title, device
manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (21091)
10 1 or 2 or 3 (396132)
11 4 or 5 or 6 or 7 or 8 or 9 (1156675)
12 10 and 11 (35782)
13 exp tenofovir/ (15120)
14 exp antiretroviral therapy/ (36372)
15 tenofovir disoproxil/ or TDF.mp. (6694)
16 exp emtricitabine/ (7239)
17 (FTC or Combination TDF FTC or Tenofovir emtricitabine efavirenz).mp. [mp=title, abstract, heading word, drug
trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
(3498)
18 (AZT or 3TC).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug
manufacturer, device trade name, keyword, floating subheading] (5159)
19 efavirenz.mp. or efavirenz plus emtricitabine plus tenofovir disoproxil/ or efavirenz plus lamivudine plus
zidovudine/ or efavirenz plus lamivudine plus tenofovir disoproxil/ (17412)
20 (nucleoside reverse transcriptase inhibitor or nucleotide reverse transcriptase inhibitor or reverse
transcriptase inhibitors).mp. [mp=title, abstract, heading word, drug trade name, original title,

device manufacturer,
drug manufacturer, device trade name, keyword, floating subheading] (7580)
21 (preexposure prophylaxis or Pre-Exposure Prophylaxis or PrEP or Combination ART or Combination antiretroviral
therapy).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer,
device trade name, keyword, floating subheading] (9760)
22 (Anti-HIV Agents or triple ART or triple antiretroviral therapy or maternal triple antiretrovirals or mART
NRTI).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer,
device trade name, keyword, floating subheading] (1156)
23 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (75195)
24 12 and 23 (6143)
25 limit 24 to (human and yr="1996 -Current") (5867)
26 limit 25 to (clinical trial or randomized controlled trial or controlled clinical trial) (1032)

Appendix 1b

Complete search strategy #2: indirect evidence about viral load suppression and adverse effects from randomised controlled trials in non-pregnant adults living with HIV. The search was adapted from *Kanters S et al. Lancet HIV. 2016;3(11):e510-e520.*

Database: Ovid MEDLINE(R) <July 7 2015 to February Week 1 2017>
Search Strategy:
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1 exp HIV/ or exp HIV Infection/ (284680)
2 (HIV Infections or HIV?1* or HIV?2* or HIV infect* or human immune?deficiency virus or human immune?deficiency virus).ti,ab. (87275)
3 (human immun* and deficiency virus).ti,ab. (481)
4 (acquired immuno?deficiency syndrome or AIDS or acquired immunedeficiency syndrome or acquired immune deficiency).ti,ab. (131687)
5 (acquired immun* and deficiency syndrome).ti,ab. (5207)
6 Salvage therapy.ti,ab. (3872)
7 exp Treatment Failure/ (30593)
8 (Treatment-experienced or Antiretroviral experienced or ART-experienced or Experienced patients).ti,ab. (2412)
9 treatment switch*.ti,ab. (280)
10 (or/1-5) not (or/6-9) (324871)
11 exp Antiretroviral Therapy, Highly Active/ (19002)
12 exp Integrase Inhibitors/ (2110)
13 exp HIV Reverse Transcriptase/ (5271)
14 exp Reverse Transcriptase Inhibitors/ (30089)
15 exp Anti-HIV Agents/ (59829)
16 exp HIV Protease Inhibitors/ (12154)
17 (atazanavir or Reyataz or a603019 or BMS-232632 or atv*).ti,ab. (1994)
18 (cobicistat or GS-9350 or Tybost).ti,ab. (142)
19 (dolutegravir or Tivicay or a613043 or S?GSK1349572 or GSK1349572).ti,ab. (284)
20 (darunavir or Prezista or TMC114 or a607042 or drv*).ti,ab. (1401)
21 (Elvitegravir or GS-9137 or Vitekta).ti,ab. (334)
22 (emtricitabine or Emtriva or Coviracil or a604004).ti,ab. (1446)
23 (lopinavir or ABT-378 or a602015 or lpv*).ti,ab. (2382)
24 (nevirapine or Viramune or a600035).ti,ab. (3484)
25 (ritonavir or Norvir or a696029).ti,ab. (4885)

26 (raltegravir or Isentress or MK-0518 or a608004).ti,ab. (1279)
27 (efavirenz or Efavir or Sustiva or Stocrin or Efcure or Efferven or Estiva or Evirenz or Viranz or a699004).ti,ab. (3221)
28 (Trizivir or Aluvia or Kaletra or Stribild or triumeq).ti,ab. (201)
29 or/11-28 (81501)
30 Tenofovir.ti,ab. (3901)
31 Viread.ti,ab. (50)
32 or/30-31 (3914)
33 29 and 32 (3529)
34 (Randomized Controlled Trial or Controlled Clinical Trial).pt. (534746)
35 (Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt. (536698)
36 Multicenter Study.pt. (218538)
37 Randomized Controlled Trial/ or Randomized Controlled Trials as Topic/ or "Randomized Controlled Trial (topic)"/ (551676)
38 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ or "Controlled Clinical Trial (topic)"/ (97156)
39 Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ (508028)
40 Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ (193281)
41 "Clinical Trial (topic)"/ or "Phase 2 Clinical Trial (topic)"/ or "Phase 3 Clinical Trial (topic)"/ or "Phase 4 Clinical Trial (topic)"/ (0)
42 or/34-41 (1108160)
43 10 and 33 and 42 (865)
44 (healthy adj3 volunteer*).ti,ab. (79538)
45 (healthy adj3 subject*).ti,ab. (112666)
46 (cohort or observational study or case-control*).ti,ab. (422308)
47 43 not (44 or 45 or 46) (751)
48 47 not (cost minimi* or cost-utilit* or health utility* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab. (751)
49 48 not (review or letter or meta-analysis or case report or case series or posters or News or Newspaper article or meeting abstracts or lectures or interview or historical article or handbooks or guidelines or guidebooks or essays or editorial or comment or clinical conference or catalogs or case reports).pt. (633)
50 limit 49 to ed=20150705-20170217 (157)

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Database: **Embase** <July 7 2015 to 2017 February 16>

Search Strategy:

---

1 exp HIV/ or exp HIV Infection/ (439172)

2 (HIV Infections or HIV?1* or HIV?2* or HIV infect* or human immune?deficiency virus or human immune?deficiency virus).ti,ab. (116054)

3 (human immun* and deficiency virus).ti,ab. (688)

4 (acquired immuno?deficiency syndrome or AIDS or acquired immunedeficiency syndrome or acquired immune deficiency).ti,ab. (159421)

5 (acquired immun* and deficiency syndrome).ti,ab. (5910)

6 Salvage therapy.ti,ab. (7322)

7 exp Treatment Failure/ (115102)

8 (Treatment-experienced or Antiretroviral experienced or ART-experienced or Experienced patients).ti,ab. (4914)

9 treatment switch*.ti,ab. (738)

10 (or/1-5) not (or/6-9) (475830)

11 exp Antiretroviral Therapy, Highly Active/ (36524)

12 exp Integrase Inhibitors/ (7636)

13 exp HIV Reverse Transcriptase/ (18528)

14 exp Reverse Transcriptase Inhibitors/ (96826)

15 exp Anti-HIV Agents/ (139471)

16 exp HIV Protease Inhibitors/ (35217)

17 (atazanavir or Reyataz or a603019 or BMS-232632 or atv*).ti,ab. (3765)

18 (cobicistat or GS-9350 or Tybost).ti,ab. (419)

19 (dolutegravir or Tivicay or a613043 or S?GSK1349572 or GSK1349572).ti,ab. (639)

20 (darunavir or Prezista or TMC114 or a607042 or drv*).ti,ab. (2946)

21 (Elvitegravir or GS-9137 or Vitekta).ti,ab. (681)

22 (emtricitabine or Emtriva or Coviracil or a604004).ti,ab. (2937)

23 (lopinavir or ABT-378 or a602015 or lpv*).ti,ab. (3848)

24 (nevirapine or Viramune or a600035).ti,ab. (4721)

25 (ritonavir or Norvir or a696029).ti,ab. (7394)

26 (raltegravir or Isentress or MK-0518 or a608004).ti,ab. (2452)

27 (efavirenz or Efavir or Sustiva or Stocrin or Efcure or Efferven or Estiva or Evirenz or Viranz or a699004).ti,ab. (5163)

28 (Trizivir or Aluvia or Kaletra or Stribild or triumeq).ti,ab. (379)

29 or/11-28 (183039)
30 Tenofovir.ti,ab. (8260)
31 Viread.ti,ab. (75)
32 or/30-31 (8276)
33 29 and 32 (8220)
34 (Randomized Controlled Trial or Controlled Clinical Trial).pt. (0)
35 (Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt. (0)
36 Multicenter Study.pt. (0)
37 Randomized Controlled Trial/ or Randomized Controlled Trials as Topic/ or "Randomized Controlled Trial (topic)"/ (593351)
38 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ or "Controlled Clinical Trial (topic)"/ (486075)
39 Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ (1091163)
40 Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ (121968)
41 "Clinical Trial (topic)"/ or "Phase 2 Clinical Trial (topic)"/ or "Phase 3 Clinical Trial (topic)"/ or "Phase 4 Clinical Trial (topic)"/ (161831)
42 or/34-41 (1486152)
43 10 and 33 and 42 (1516)
44 (healthy adj3 volunteer*).ti,ab. (117167)
45 (healthy adj3 subject*).ti,ab. (164272)
46 (cohort or observational study or case-control*).ti,ab. (769550)
47 43 not (44 or 45 or 46) (1295)
48 47 not (cost minimi* or cost-utilit* or health utility* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab. (1288)
49 48 not (review or letter or meta-analysis or case report or case series or posters or News or Newspaper article or meeting abstracts or lectures or interview or historical article or handbooks or guidelines or guidebooks or essays or editorial or comment or clinical conference or catalogs or case reports).pt. (1066)
50 (201507* or 201508* or 201509* or 201510* or 201511* or 201512* or 201512* or 201601* or 201602* or 201603* or 201604* or 201605* or 201606* or 201607* or 201608* or 201609* or 201610* or 201611* or 201612* or 201701* or 201702*).dd. (1789047)
51 49 and 50 (245)

Appendix 1c

Complete search strategy #3: Search for comparative studies of lamivudine, tenofovir, emtricitabine for hepatitis B infection in pregnant women

Search to from January 1, 2014 to January 14, 2017

OVID & MEDLINE

1. exp Hepatitis B/
2. (HBV or "hepatitis B" or "serum hepatitis" or "hippie hepatitis" or "injection hepatitis" or "hepatitis type B").mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
3. 1 or 2
4. exp Antiviral Agents/
5. exp antivirus agent/
6. (tenofovir or "tenofovir disoproxil" or TDF or "tenofovir alafenamide" or lamivudine or 3TC or emtricitabine or "Emtricitabine/tenofovir" or Viread or Genvoya or truvada or Emtriva or Coviracil or epivir).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
7. 4 or 5 or 6
8. exp Pregnancy/
9. (pregnan* or gestation* or "child bearing" or childbearing or infant* or newborn* or neonate or breastf* or "breast fe*" or maternal or prenatal* or "prenatal exposure" or perinatal* or lactat* or "in utero" or "In utero exposure" or gestation* or congenital MTCT or "Mother-to-child transmission" or "Mother to child transmission" or "Mother-to-infant transmission" or "Infectious disease transmission" or "Vertical transmission disease transmission, vertical" or "vertical Adult to child transmission" or mother-to-infant).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
10. exp Vertical Transmission/
11. 8 or 9 or 10
12. exp evidence based medicine/
13. exp meta analysis/
14. exp Meta-Analysis as Topic/
15. exp "systematic review"/
16. exp "systematic review"/
17. exp Practice Guideline/
18. exp Randomized Controlled Trial/
19. exp triple blind procedure/
20. exp Double-Blind Method/

21. exp Single-Blind Method/
22. exp latin square design/
23. exp Placebos/
24. exp comparative study/
25. exp Cross-Sectional Studies/
26. exp Cross-Over Studies/
27. exp Cohort Studies/
28. exp longitudinal study/
29. exp retrospective study/
30. exp retrospective study/
31. exp population research/
32. exp observational study/
33. exp clinical trial/
34. clinical study.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
35. exp Evaluation Studies/
36. exp quantitative study/
37. exp validation studies/
38. exp experimental study/
39. exp quasi experimental study/
40. exp field study/
41. in vivo study.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
42. exp panel study/
43. exp Pilot Projects/
44. exp pilot study/
45. exp prevention study/
46. exp replication study/
47. exp Feasibility Studies/
48. exp Models, Theoretical/
49. exp trend study/
50. exp correlational study/
51. exp confidence interval/
52. exp regression analysis/
53. exp proportional hazards model/
54. exp multivariate analysis/
55. exp follow up studies/
56. odds ratio.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]

57. ((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or guideline* or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo or random* or control* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or compar* or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analys*" or "cross-sectional survey*" or "cross-sectional design*" or "prevalence study" or "prevalence analys*" or "prevalence survey*" or "disease frequency study" or "disease frequency analys*" or "disease frequency survey*" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or longitudinal* or "retrospective study" or "retrospective survey" or "retrospective analysis" or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "population study" or "population survey" or "population analysis" or "concurrent study" or "concurrent survey" or "concurrent analysis" or "incidence study" or "incidence survey" or "incidence analysis" or "follow-up study" or "follow-up survey" or "follow-up analysis" or "observational study" or "observational survey" or "observational analysis" or "case study" or "case series" or "clinical series" or "case studies" or "clinical study" or "clinical trial" or "evaluation study" or "evaluation survey" or "evaluation analysis" or "twin study" or "twin survey" or "twin analysis" or "quantitative study" or "quantitative analys*" or "validation study" or "validation survey" or "validation analysis" or "experimental study" or "experimental analysis " or "quasi experimental study" or "quasi experimental analysis" or "quasiexperimental study" or "quasiexperimental analysis" or "field study" or "field survey" or "field analysis" or "in vivo study" or "in vivo analysis" or "panel study" or "panel survey" or "panel analysis" or "prevention study" or "prevention survey" or "prevention analysis" or "replication study" or "replication analysis " or "theoretical study" or "theoretical analysis " or "feasibility study" or "feasibility analysis " or "trend study" or "trend survey" or "trend analysis" or (correlation* adj2 study) or (correlation* adj2 analys*) or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case compeer study" or "case comparison study" or study or trial or pilot or "odds ratio" or "confidence interval" or "regression analysis" or "hazards model" or "change analysis").mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
58. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58

59. 3 and 7 and 11 and 59
60. limit 60 to (book or book series or editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts)
61. 60 not 61
62. 62 not (exp animals/ not exp humans/)
63. remove duplicates from 63
64. exp HIV infections/
65. exp AIDS/
66. (HIV or "hiv-infect*" or "hiv-noninfected" or "hiv-exposed" or "human immunodeficiency virus" or "human immune*" or "human immunodeficiency" or "virusexposed" or "HIV prevention" or "HIV-exposed" or "uninfected AIDS" or "acquired immun* human" or "immun* deficiency virus" or "HIV-infected mothers" or "Viral load").mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fs, nm, kf, px, rx, ui]
67. 65 or 66 or 67
68. 64 and 68
69. limit 64 to yr="2014-2017"
70. 69 or 70

Appendix 2. Methods continued

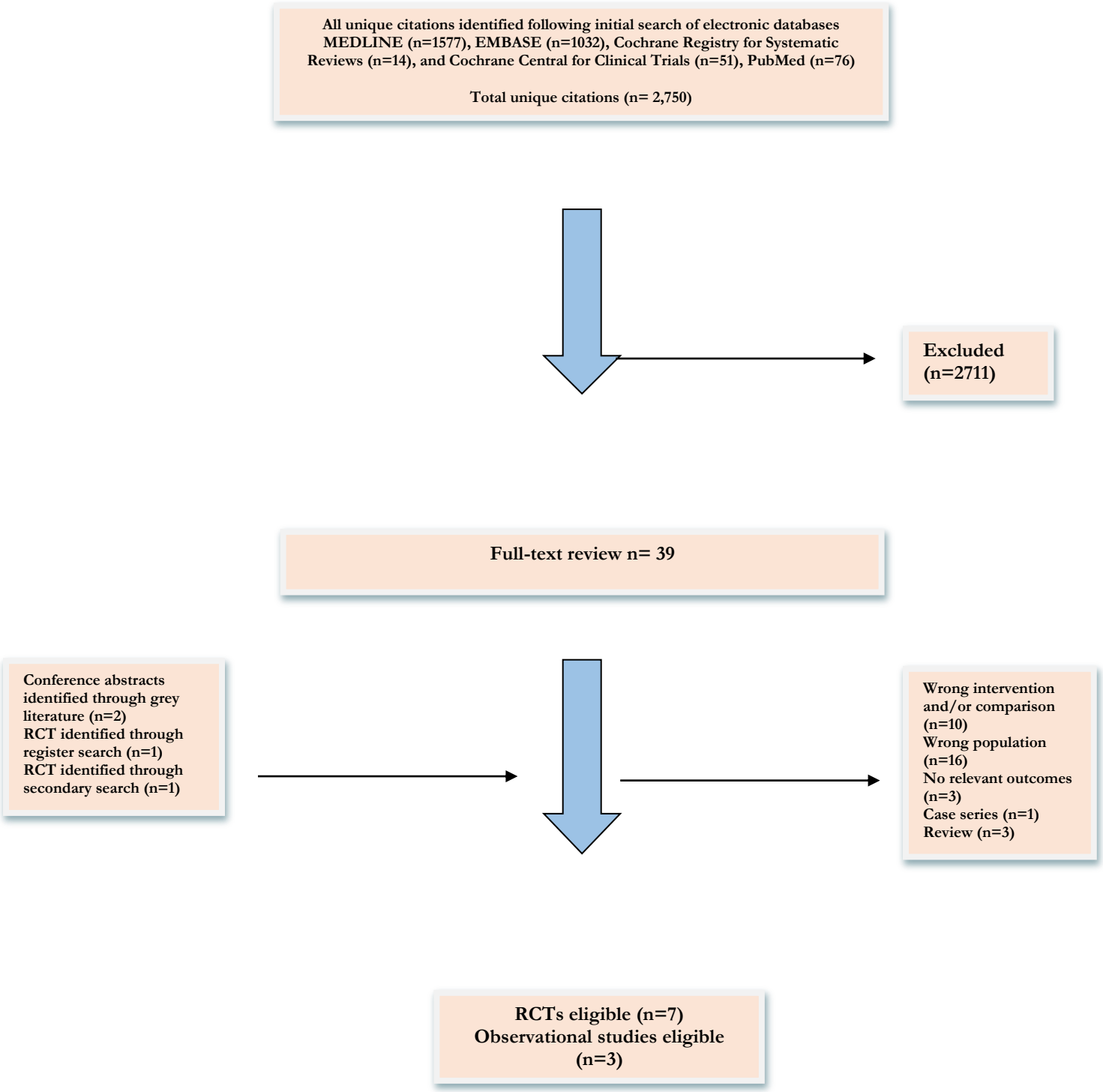
Subgroups

We planned to use published criteria for assessing the certainty of any subgroup effect (Xin Sun's subgroup BMJ study). We prespecified the expected direction of effect for each of the subgroup analyses for each outcome. Our planned sub-group analyses were:

- Low vs. high risk of bias
- Placebo control vs. dual NRTI control
- Intervention arm that includes both tenofovir/FTC vs. tenofovir or FTC alone
- Class of third antiretroviral
    - Protease inhibitors
    - Non-nucleoside reverse transcriptase inhibitors
    - Integrase strand inhibitors
- Low and middle income settings vs. high income settings
- HIV-positive versus pre-exposure prophylaxis (PrEP)
- Mother starting CD4<350 vs CD4 >350 cells/mm^3
- Alternative NRTI (abacavir/lamivudine or AZT/lamivudine)

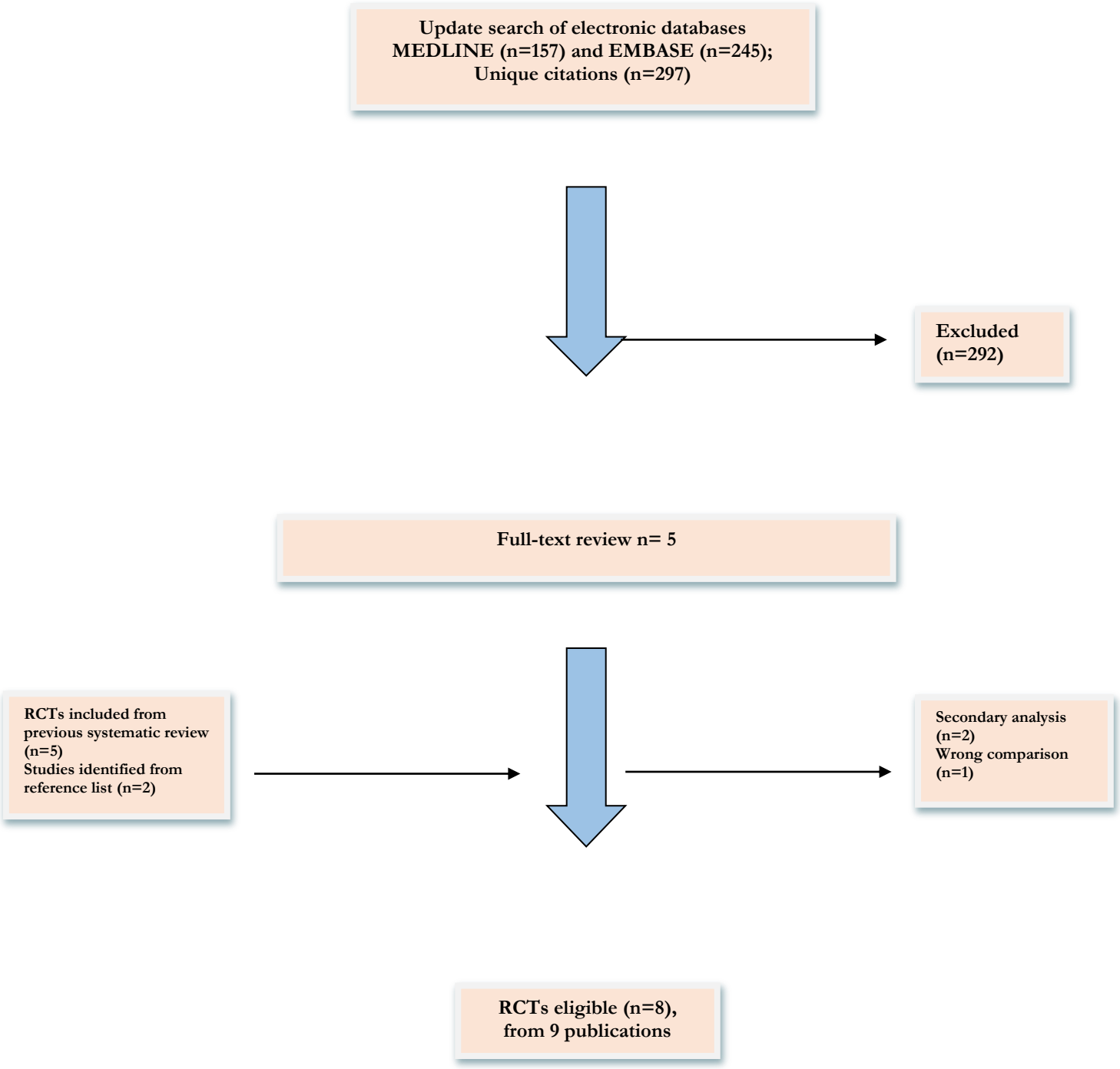
Appendix 3a

Figure. PRISMA Flow diagram of evidence for comparative studies of nucleoside reverse transcriptase inhibitors in pregnancy



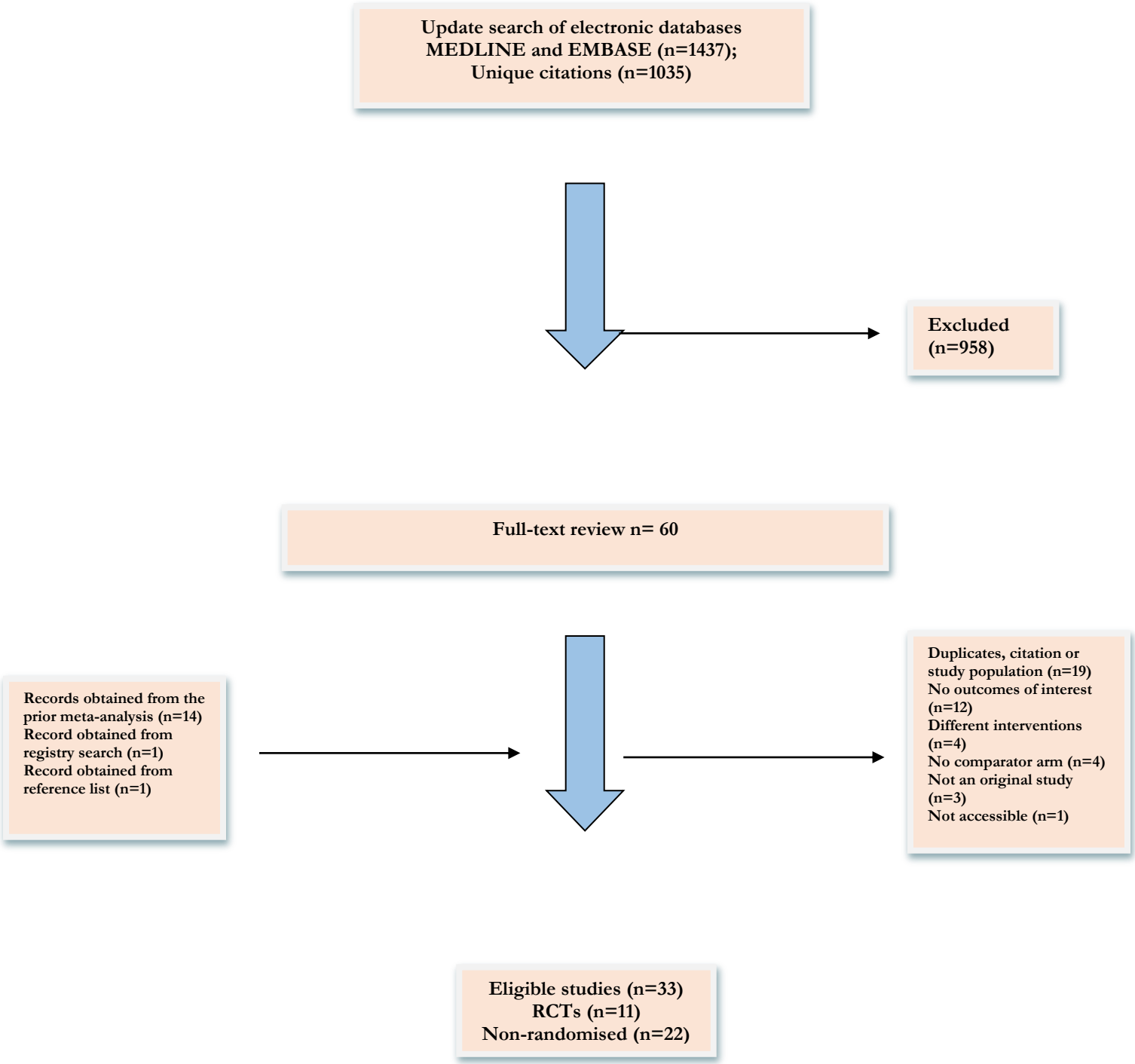
Appendix 3b

Figure. PRISMA flow diagram for randomised controlled trials comparing two different NRTI regimens with the same non-NRTI antiretroviral



Appendix 3c

Figure. PRISMA flow diagram for randomised controlled trials comparing NRTI regimens in pregnant women with hepatitis B infection



Appendix 4a

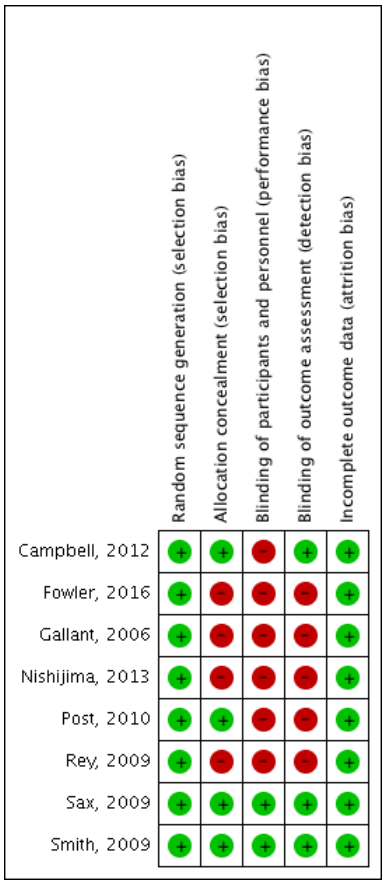


Figure. Risk of bias summary of randomised trials comparing different NRTI regimens in HIV-positive adults

Appendix 4b

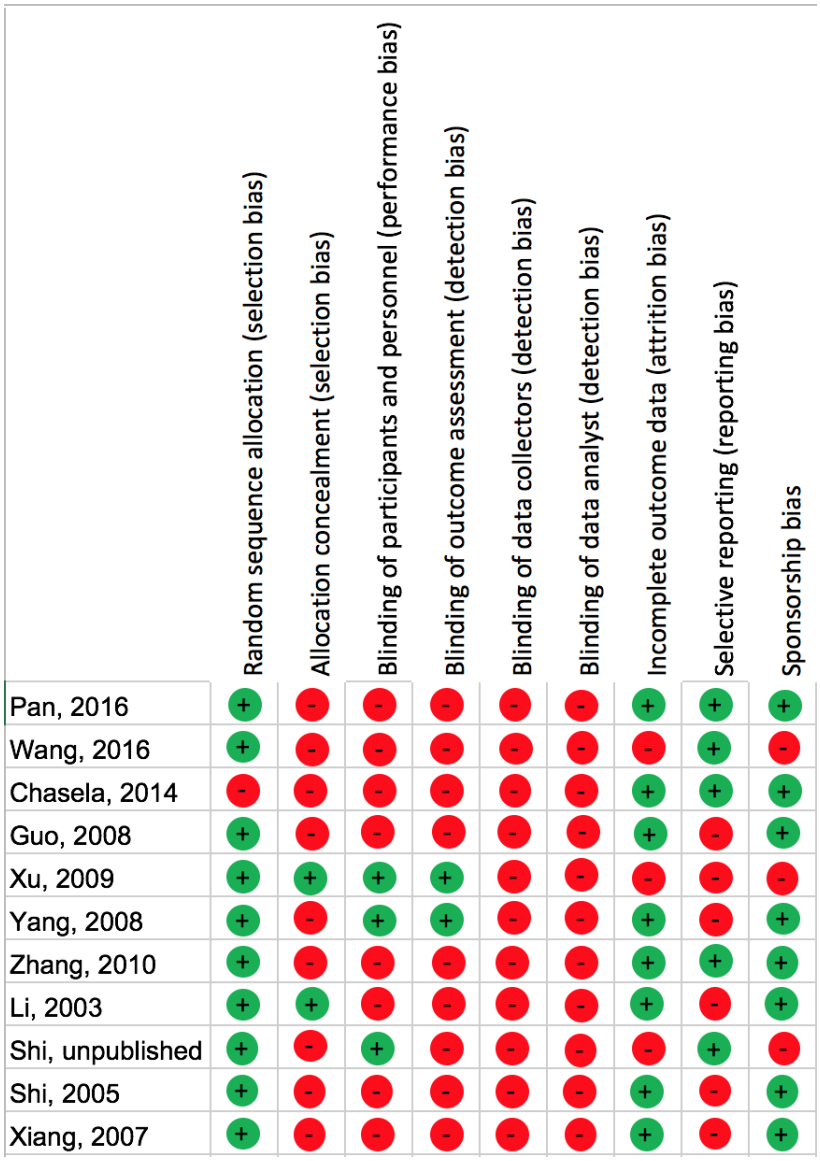

Random sequence allocation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Blinding of data collectors (detection bias)
Blinding of data analyst (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Sponsorship bias
Pan, 2016
Wang, 2016
Chasela, 2014
Guo, 2008
Xu, 2009
Yang, 2008
Zhang, 2010
Li, 2003
Shi, unpublished
Shi, 2005
Xiang, 2007

Figure. Risk of bias for randomised controlled trials of antiviral therapy in pregnant women with hepatitis B

Appendix 4c

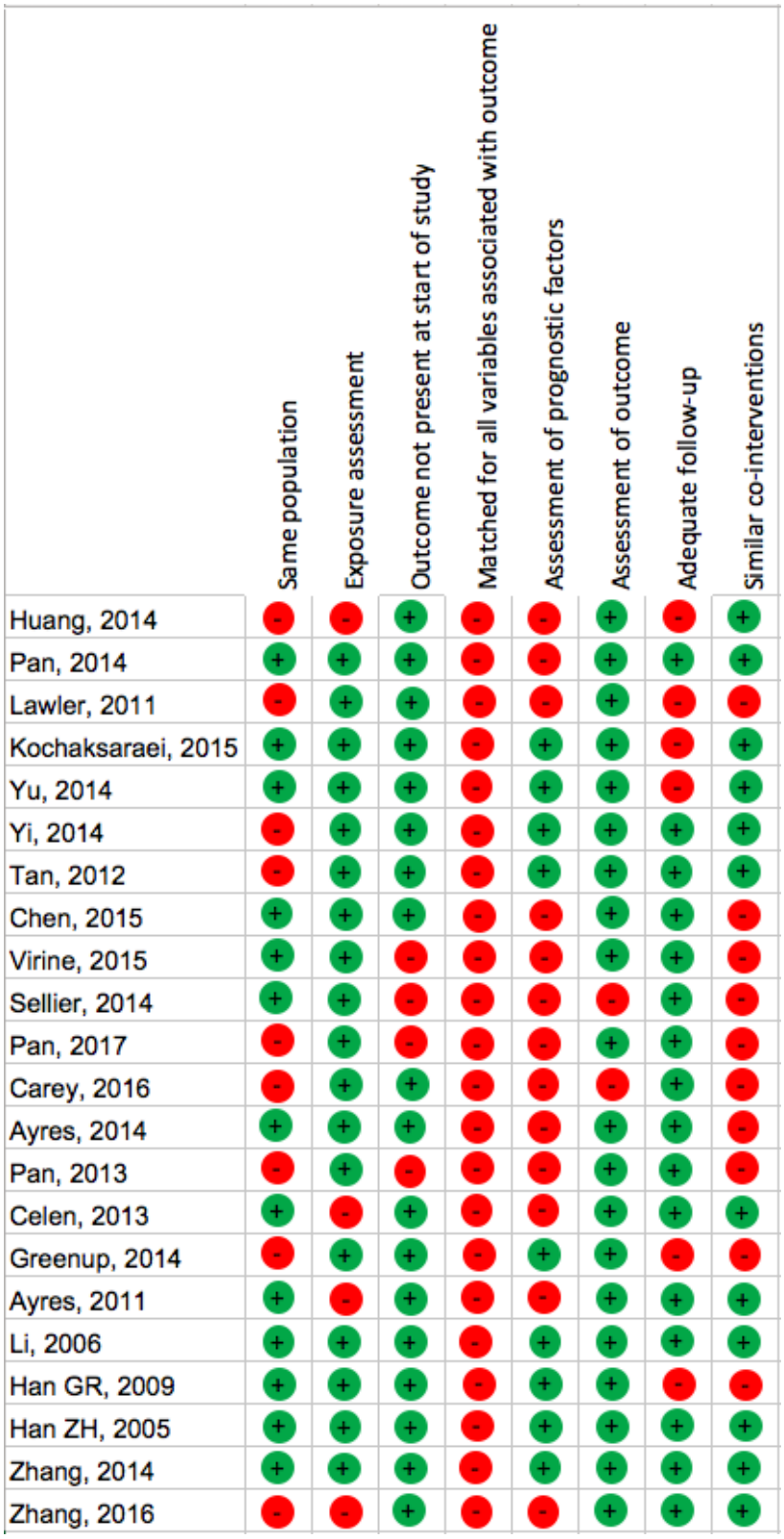

Same population
Exposure assessment
Outcome not present at start of study
Matched for all variables associated with outcome
Assessment of prognostic factors
Assessment of outcome
Adequate follow-up
Similar co-interventions
Huang, 2014
Pan, 2014
Lawler, 2011
Kochaksaraei, 2015
Yu, 2014
Yi, 2014
Tan, 2012
Chen, 2015
Virine, 2015
Sellier, 2014
Pan, 2017
Carey, 2016
Ayres, 2014
Pan, 2013
Celen, 2013
Greenup, 2014
Ayres, 2011
Li, 2006
Han GR, 2009
Han ZH, 2005
Zhang, 2014
Zhang, 2016

Figure. Risk of bias for observational studies of antiviral therapy in pregnant women with hepatitis B

Appendix 5a

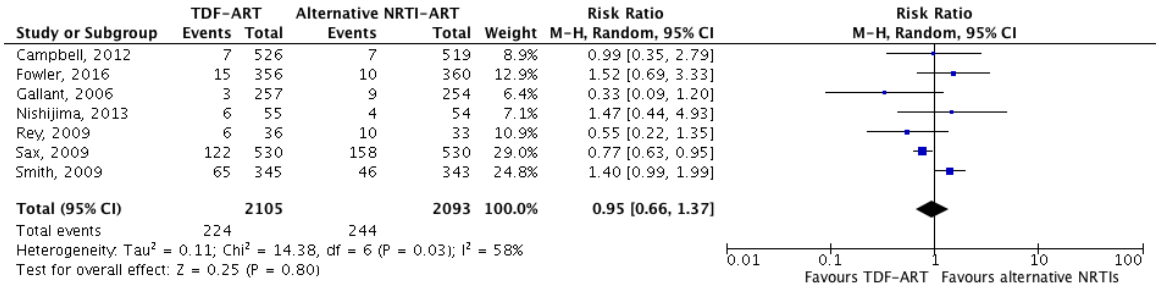


Figure. Forest plot of risk ratio for study medication discontinuations because of patient decision or clinical adverse events in randomised trials comparing different NRTI regimens in HIV-positive adults

TDF-ART, tenofovir disoproxil fumarate-based antiretroviral therapy; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; M-H, Mantel-Haenszel; CI, confidence interval

Appendix 5b

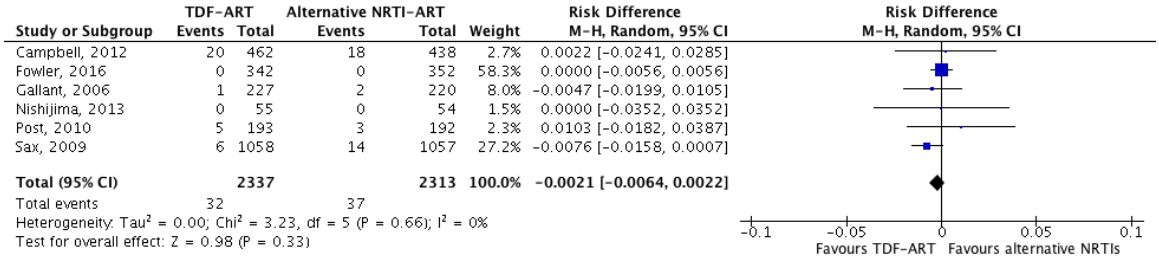


Figure. Forest plot of risk difference in mortality in randomised trials comparing different NRTI regimens in HIV-positive adults

TDF-ART, tenofovir disoproxil fumarate-based antiretroviral therapy; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; M-H, Mantel-Haenszel; CI, confidence interval

Appendix 5c

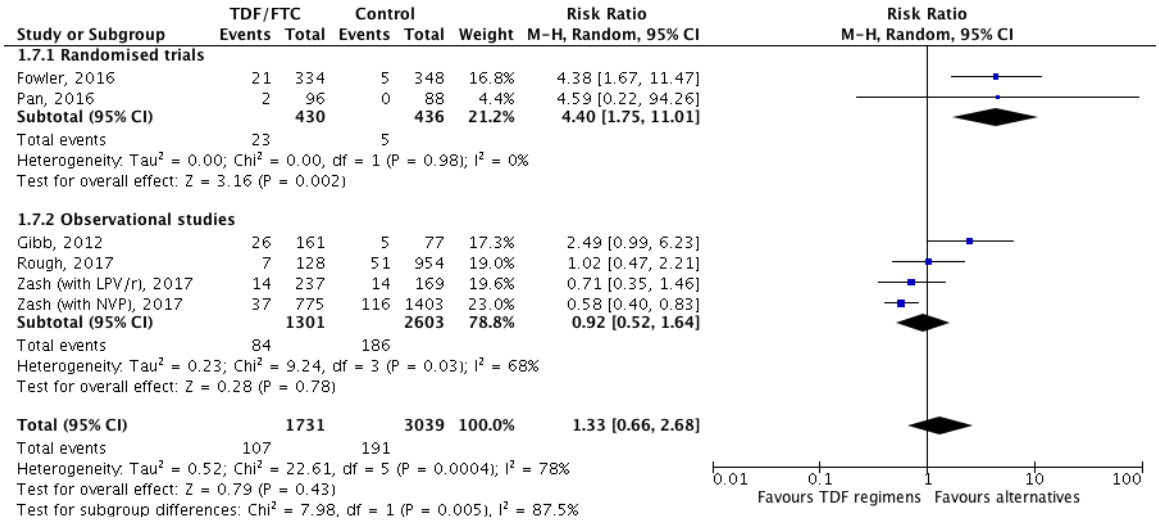


Figure. Forest plot of risk ration for stillbirth and early neonatal mortality of tenofovir-based antiretroviral therapy, by study design

TDF-ART, tenofovir disoproxil fumarate-based antiretroviral therapy; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; M-H, Mantel-Haenszel; CI, confidence interval

Appendix 5d

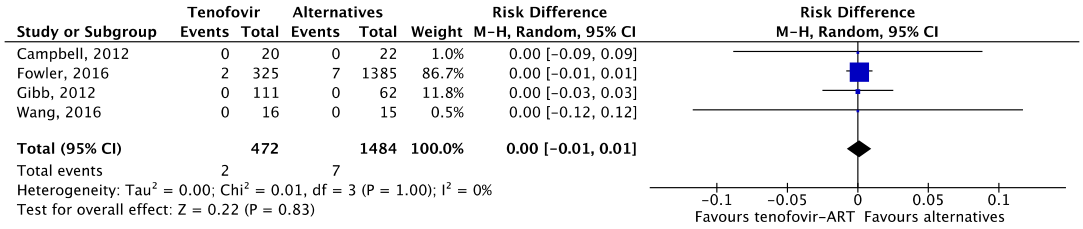


Figure. Forest plot of risk difference in vertical transmission of HIV with tenofovir-based ART from randomised and observational studies

M-H, Mantel-Haenszel; ART, antiretroviral therapy

Appendix 5e

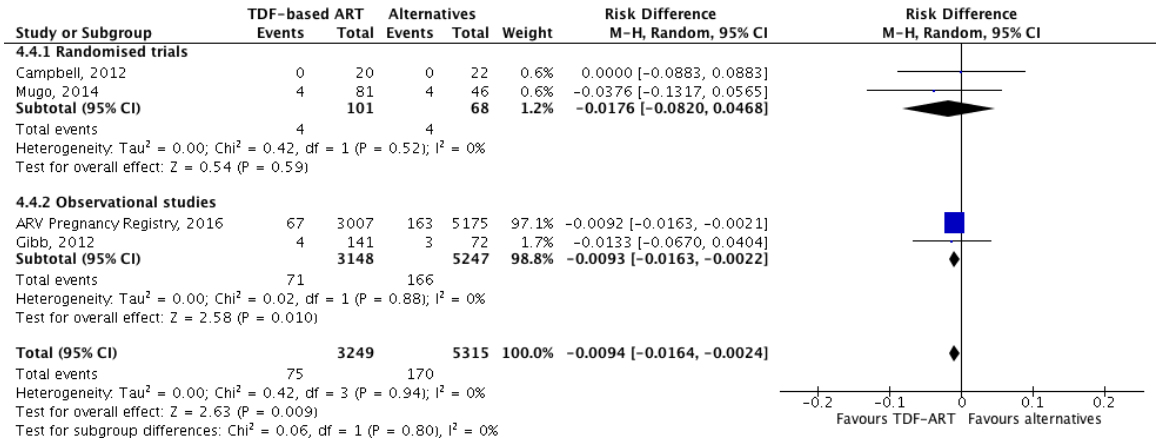


Figure. Forest plot of risk difference in birth defects in fetuses exposed to tenofovir and alternative antiretroviral therapies in the first trimester, by study design

ART, antiretroviral therapy; M-H, Mantel-Haenszel; ARV, antiretroviral; TDF, tenofovir disoproxil fumarate

Appendix 5f

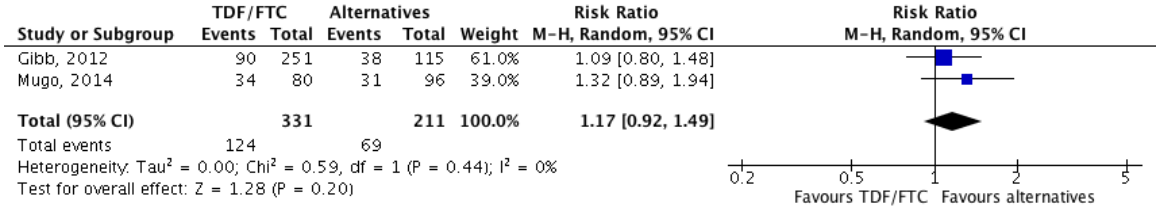


Figure. Forest plot of risk ratio for spontaneous abortion with tenofovir/FTC versus alternative NRTIs in studies with first trimester antiretroviral exposure. Mugo randomised HIV-negative women to tenofovir/emtricitabine or placebo; Gibb observed risk of spontaneous abortion in fetuses exposed to tenfovir versus no tenofovir-containing ART.

M-H, Mantel-Haenszel; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ART, antiretroviral therapy

Appendix 5g

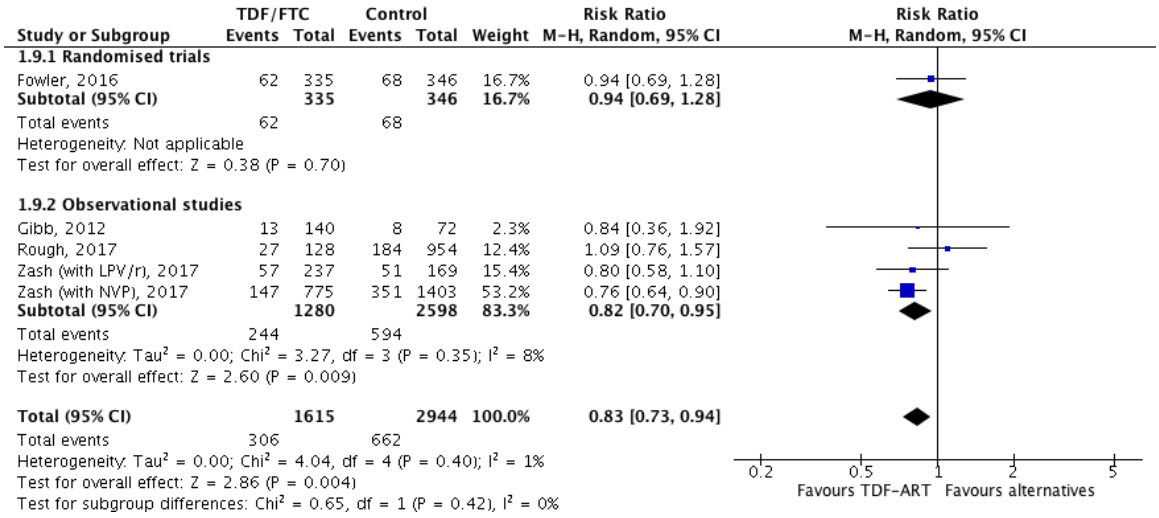


Figure. Forest plot of risk ratio for premature delivery <37 weeks gestation, by study design..

M-H, Mantel-Haenszel; TDF, tenofovir disoproxil fumarate; ART, antiretroviral therapy

Appendix 5h

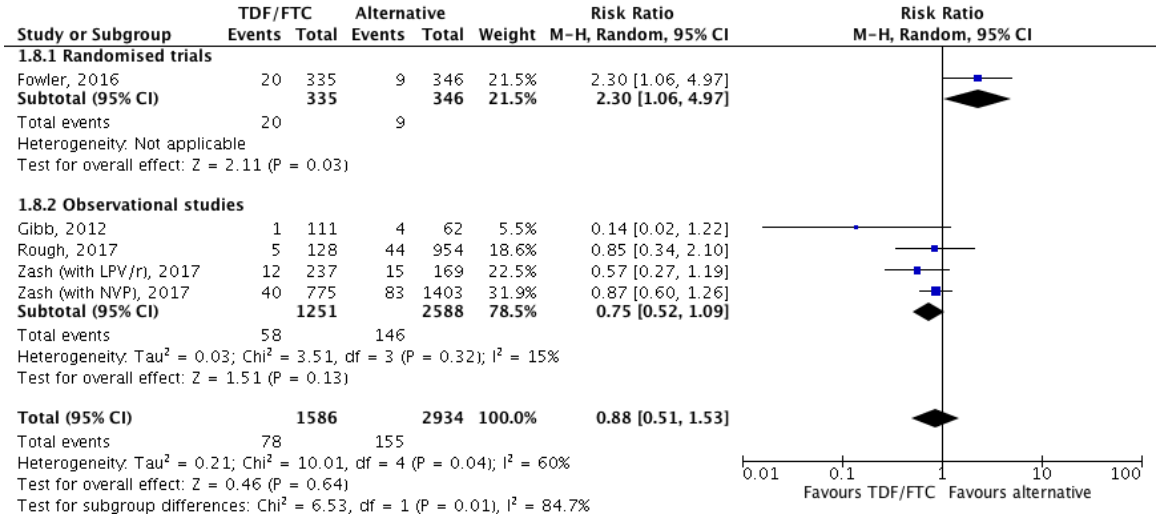


Figure. Forest plot of risk ratio for early or very early premature delivery <32 to <34 weeks gestation, by study design.

M-H, Mantel-Haenszel; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ART, antiretroviral therapy

Appendix 5i

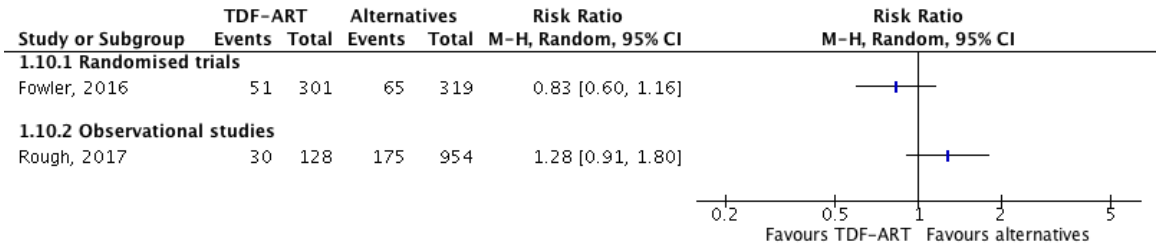


Figure. Forest plot of risk ratio for low birth weight <2500g, by study design.

M-H, Mantel-Haenszel; TDF, tenofovir disoproxil fumarate; ART, antiretroviral therapy

Appendix 5j

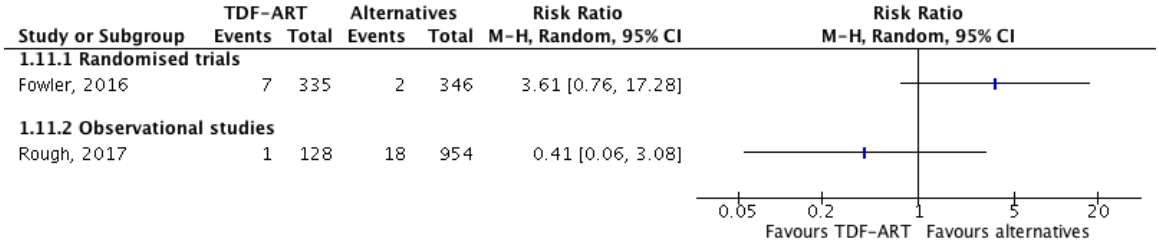


Figure. Forest plot of risk ratio for very low birth weight <1500g, by study design.

M-H, Mantel-Haenszel; TDF, tenofovir disoproxil fumarate; ART, antiretroviral therapy

Appendix 6

Table. Study characteristics of comparative studies of antivirals in pregnant women living with hepatitis B

Study	Design	Comparison	Country	Maternal viral inclusion criteria	Gestational age at start	Infant follow-up	Maternal Sample Size	Maternal Age*
Chasela, 2014[1]	RCT	3TC vs. control	Malawi	HIV & HBsAg+	≤30 weeks	48 wks.	72	25 (22-29)
Guo, 2008[2]	RCT	3TC vs. control	China	HBsAg+	28 weeks	26-52 wks.	110	27 (4.9)
Li, 2003[3]	RCT	3TC vs. control	China	HBsAg+	28 weeks	24h	151	NR
Pan, 2016[4]	RCT	TDF vs. control	China	HBeAg+ & >200,000IU/mL	30-32 weeks	28 wks.	200	27.4 (3.0)
Shi, 2005[5]	RCT	3TC vs. control	China	NR	28 weeks	24h	39	27.9 (2.9)
Wang, 2016[6]	RCT	TDF/3TC vs 3TC	China	HIV & HBV	14-27 weeks	--	35	29 (24 - 36)
Xiang, 2007[7]	RCT	3TC vs. control	China	NR	28 weeks	24h	86	27.6 (2.3)
Xu, 2009[8]	RCT	3TC vs. control	China and Philippines	>1000 MEq/mL	30-34 weeks	52 wks.	150	19-36
Yang, 2008[9]	RCT	3TC vs. control	China	NR	24 weeks	26-52 wks.	40	27
Zhang, 2010[10]	RCT	3TC vs. control	China	NR	28 weeks	26-52 wks.	100	NR
Ayres, 2011[11]	Observational	3TC vs. control	UK	$>10^8$ IU/mL	32 weeks	--	59	NR
Ayres, 2014[12]	Observational	3TC vs. control	Australia	$>10^7$ IU/mL	32 weeks	36 wks.	26	NR
Carey, 2016[13]	Observational	TDF vs. control	UK	>200,000 IU/mL	30 weeks	52 wks.	401	30
Celen, 2013[14]	Observational	TDF vs. control	Turkey	HBeAg+ & >200,000 IU/mL	18-27 weeks	28 wks.	45	27.5 (3.5)
Chen, 2015[15]	Observational	TDF vs. control	Taiwan	$>10^{7.5}$ IU/mL	30-32 weeks	26 wks.	118	27.27 (1.37)
Greenup, 2014[16]	Observational	3TC vs. TDF vs. control	China	$>10^{6.5}$ IU/mL	32 weeks	48 wks.	120	28
Han G., 2009[17]	Observational	3TC vs. control	China	NR	20 weeks	26-52 wks.	123	27 (3)
Han Z., 2005[18]	Observational	3TC vs. control	China	NR	28 weeks	26-52 wks.	78	NR
Huang, 2014[19]	Observational	TDF vs. TDF/3TC	NR	HBeAg+	Anytime	20-48 wks.	38	NR
Kochaksaraei, 2016[20]	Observational	TDF vs. control	Canada	$>10^7$ IU/mL	28-32 weeks	13-26 wks.	161	30 (28 - 34)
Lawler, 2011[21]	Observational	3TC vs. TDF vs. control	NR	NR	NR	NR	67	NR
Li, 2006[22]	Observational	3TC vs. control	China	$>10^7$ IU/mL	32 weeks	39 wks.	80	NR
Pan C., 2013[23]	Observational	TDF vs. control	NR	All HBV	33 weeks	28 wks.	34	NR
Pan Q., 2014[24]	Observational	3TC vs. TDF vs. control	China and USA	HBeAg+ & $>10^6$ copies/mL	NR	28-58 wks.	220	27.7 (4.4)
Pan C., 2017[25]	Observational	3TC vs. control	China	HBeAg+ & $>10^6$ copies/mL	NR	40-52 wks.	249	27.3 (3.9)
Sellier, 2014[26]	Observational	3TC vs. control	France	HIV & HBV	NR	104 wks.	49	NR
Tan, 2012[27]	Observational	3TC vs. control	Australia	High HBV viral load	32 weeks	>13 wks.	64	NR
Virine, 2015[28]	Observational	TDF vs. control	Canada	All HBV	NR	26-52 wks.	21	31 (21 - 37)

Yi, 2014[29]	Observational	TDF vs. control	China	All HBV	1st trimester	28 wks.	85	30.46 (3.24)
Yu, 2014[30]	Observational	3TC vs. HBIG	China	HBeAg+ & >10^6 copies/mL	8-32 weeks	4 wks.	487	26.81 (3.85)
Zhang, 2016[31]	Observational	TDF vs. control	China	HBeAg+ & >10^6 copies/mL	28-38 weeks	26 wks.	289	NR
Zhang, 2014[32]	Non-randomized interventional trial	3TC vs. control	China	HBeAg+ & >10^6 copies/mL	28-30 weeks	52 wks.	700	29 (4.7)

*Mean and (standard deviation) or Median and (interquartile range)

RCT, randomised controlled trial; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine; TDF, emtricitabine; HBIG, hepatitis B immunoglobulin; HIV, human immunodeficiency virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; NR, not report

Appendix 7

Table. Study outcomes for comparative studies of antivirals in pregnant women living with hepatitis B

Study	Design	Vertical transmission lamivudine	Vertical transmission tenofovir	Vertical transmission dual	Vertical transmission control	HBV flare lamivudine	HBV flare tenofovir	HBV flare control	Lamivudine resistance
Chasela, 2014[1]	RCT	2/20			3/31				
Guo, 2008[2]	RCT	4/70			12/40				
Li, 2003[3]	RCT	1/43			8/52				
Pan, 2016[4]	RCT		0/92		6/88		6/97	9/100	
Shi, 2005[5]	RCT	1/21			1/18				
Wang, 2016[6]	RCT		0/15	0/16 (TDF/3TC)					
Xiang, 2007[7]	RCT	1/21			5/18				
Xu, 2009[8]	RCT	3/46			5/36				
Yang, 2008[9]	RCT	2/20			2/19				
Zhang, 2010[10]	RCT	1/50			8/50				
Ayres, 2011[11]	Observational								1/25
Ayres, 2014[12]	Observational	0/18			1/3				
Carey, 2016[13]	Observational		0/48		0/306				
Celen, 2013[14]	Observational		0/21		2/23				
Chen, 2015[15]	Observational		2/62		6/56		2/62	7/56	
Greenup, 2014[16]	Observational	0/43	1/44		2/10				
Han G., 2009[17]	Observational	0/46							
Han Z., 2005[18]	Observational	0/43			5/35				
Huang, 2014[19]	Observational		0/21	0/14 (TDF/3TC)					
Kochaksaraei, 2016[20]	Observational		0/12		1/73		4/23	7/138	
Lawler, 2011[21]	Observational	0/27	0/0		2/7				

Li, 2006[22]	Observational	1/36			7/44		
Pan C., 2013[23]	Observational		0/9		0/4		
Pan Q., 2014[24]	Observational	5/89	0/37		0/94		
Pan C., 2017[25]	Observational	0/160			5/89	5/160	1/89
Sellier, 2014[26]	Observational	1/9		0/11 (TDF/FTC)	0/5		
Tan, 2012[27]	Observational	NR	NR		NR	14/48	3/16
Virine, 2015[28]	Observational	NR	NR		NR		
Yi, 2014[29]	Observational		0/39		3/46		
Yu, 2014[30]	Observational	0/153					
Zhang, 2016[31]	Observational		0/25		25/171		
Zhang, 2014[32]	Non-randomized interventional trial	0/52			10/352		

HBV, hepatitis B virus; RCT, ranodmised controlled trial; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine; FTC, emtricitabine; NR, not reported

Appendix 8

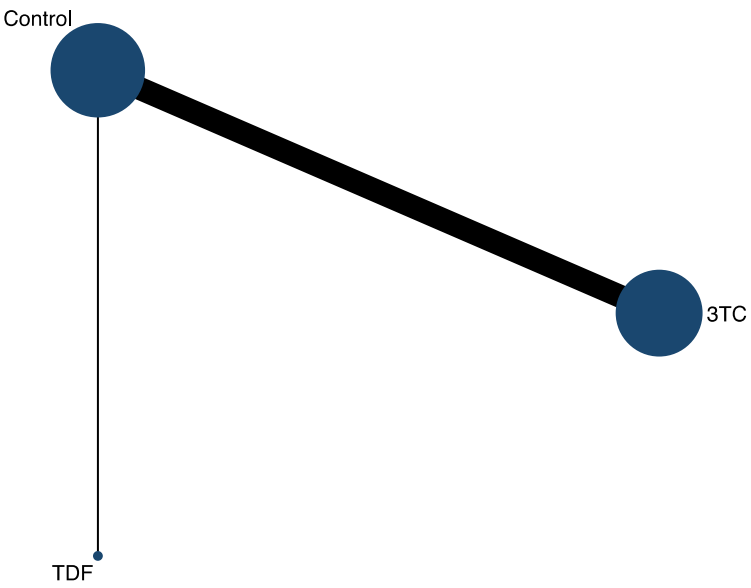


Figure. Network plot of randomised controlled trials for maternal antiviral therapy to prevent vertical transmission of hepatitis B. The size of the treatment nodes represents number of patients and width of the lines represents the number of randomised trials.

TDF, tenofovir disoproxil fumarate; Control, no active antiviral therapy; 3TC, lamivudine

Table. Network meta-analysis results of antiviral therapy for the prevention of vertical transmission of hepatitis B, randomised trials only.

	Lamivudine	Tenofovir	No antiviral
Lamivudine	Lamivudine	0.26 (0.01,4.77)	**3.52 (2.05,6.05)**
Tenofovir	3.86 (0.21,70.97)	Tenofovir	13.59 (0.77,237.69)
No antiviral	**0.28 (0.17,0.49)**	0.07 (0.00,1.29)	No antiviral

All results presented with relative risk, 95% confidence interval.

Relative risk <1 favour the column.

Global I^2=0%, p for inconsistency = 0.51

Appendix 9

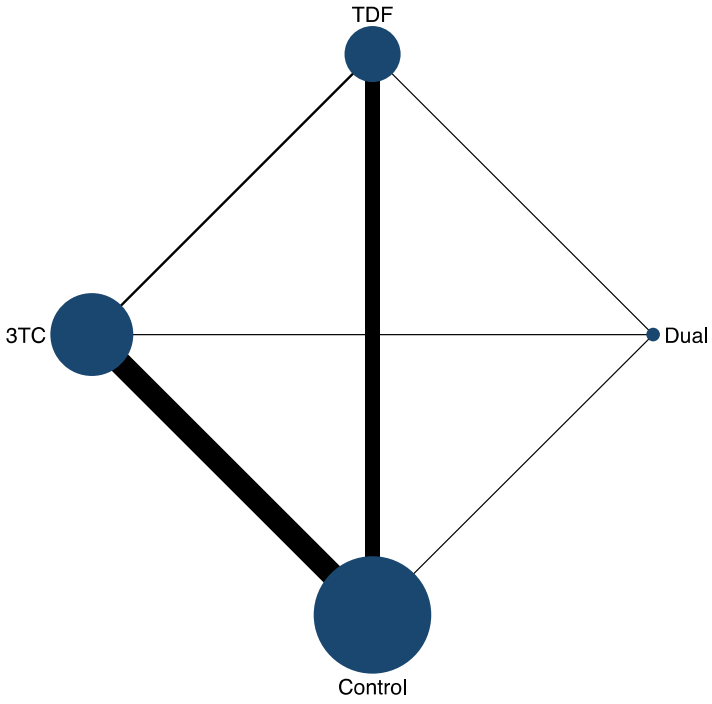


Figure. Network plot of RCTs and comparative observational studies of maternal antiviral therapy to prevent vertical transmission of hepatitis B. The size of the treatment nodes represents number of patients and width of the lines represents the number of studies.

TDF, tenofovir disoproxil fumarate; dual, dual antiviral therapy; Control, no active antiviral therapy; 3TC, lamivudine

Table. Network meta-analysis results of antiviral therapy for the prevention of vertical transmission of hepatitis B, including observational data.

	Lamivudine	Tenofovir	Dual antivirals	No antiviral
Lamivudine	Lamivudine	0.99 (0.38,2.59)	0.48 (0.02,9.43)	**4.29 (2.63,6.96)**
Tenofovir	1.01 (0.39,2.66)	Tenofovir	0.49 (0.02,10.94)	**4.34 (1.86,10.94)**
Dual antivirals	2.08 (0.11,40.95)	2.06 (0.09,46.31)	Dual antivirals	8.93 (0.45,179.27)
No antiviral	**0.23 (0.14,0.38)**	**0.23 (0.10,0.54)**	0.11 (0.01,2.25)	No antiviral

Relative risk <1 favour the column.

Global I^2=0%, p for inconsistency = 0.76

Appendix 10

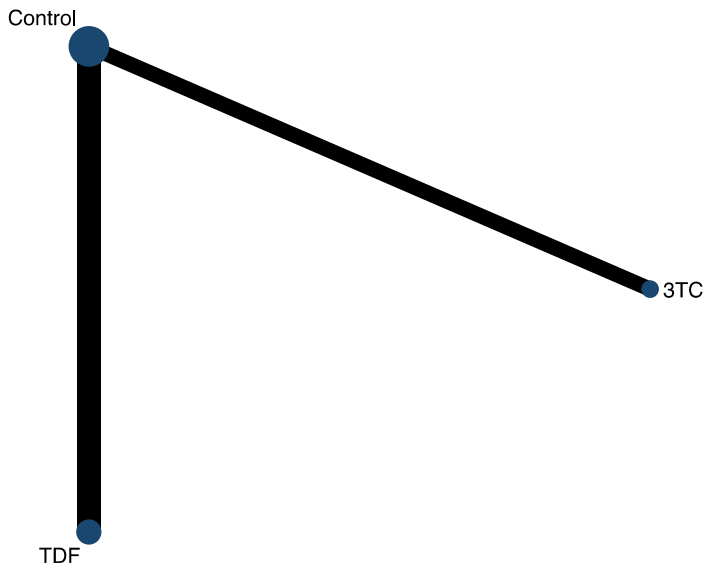


Figure. Network plot of randomised controlled trials and comparative observational studies reporting maternal hepatitis B flares in women who took antivirals in pregnancy. The size of the treatment nodes represents number of patients and width of the lines represents the number of studies.

TDF, tenofovir disoproxil fumarate; dual, dual antiviral therapy; Control, no active antiviral therapy; 3TC, lamivudine

Table. Network meta-analysis results of risk of hepatitis B flares with antiviral therapy during pregnancy, randomised and observational studies.

	Lamivudine	Tenofovir	No antiviral
Lamivudine	Lamivudine	0.48 (0.06,3.70)	0.52 (0.10,2.71)
Tenofovir	2.10 (0.27,16.39)	Tenofovir	1.10 (0.32,3.73)
No antiviral	1.92 (0.37,9.97)	0.91 (0.27,3.10)	No antiviral

All results presented with relative risk, 95% confidence interval.

Relative risk <1 favour the column.

Global I^2=63.5%, p for inconsistency = 0.042

References

1. Chasela CS, Kourtis AP, Wall P, et al. Hepatitis B virus infection among HIV-infected pregnant women in Malawi and transmission to infants. *Journal of hepatology* 2014;60(3):508-14. doi: 10.1016/j.jhep.2013.10.029 [published Online First: 2013/11/12]
2. Guo Y, Li SX, Ge SL, et al. Effect of lamivudine treatment combined with active–passive immunization on interrupting mother to infant transmission of HBV. *Clinical Focus* 2008;23:1730-1.
3. Li XM, Yang YB, Hou HY, et al. Interruption of HBV intrauterine transmission: a clinical study. *World journal of gastroenterology* 2003;9(7):1501-3. [published Online First: 2003/07/11]
4. Pan CQ, Duan Z, Dai E, et al. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. *The New England journal of medicine* 2016;374(24):2324-34. doi: 10.1056/NEJMoa1508660 [published Online First: 2016/06/16]
5. Shi MF, Li XM, He J, et al. Study of lamivudine in interruption of HBV intrauterine infection. *Clin Med Chin* 2005;21:77-78.
6. Wang L, Wiener J, Bulterys M, et al. Hepatitis B Virus (HBV) Load Response to 2 Antiviral Regimens, Tenofovir/Lamivudine and Lamivudine, in HIV/ HBV-Coinfected Pregnant Women in Guangxi, China: The Tenofovir in Pregnancy (TiP) Study. *The Journal of infectious diseases* 2016;214(11):1695-99. doi: 10.1093/infdis/jiw439 [published Online First: 2016/09/24]
7. Xiang GJ, Sun JW, Jiang SQ, et al. Evaluation of therapeutic effect in HBV vertical transmission by lamivudine treatment combined with active-passive immunization for pregnant women. *Chin Prac Med* 2007;2(14-16)
8. Xu WM, Cui YT, Wang L, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. *Journal of viral hepatitis* 2009;16(2):94-103. doi: 10.1111/j.1365-2893.2008.01056.x [published Online First: 2009/01/30]
9. Yang S, Liu M, Wang L. [Effect of high viral hepatitis B virus DNA loads on vertical transmission of hepatitis B virus in late-pregnant women]. *Zhonghua fu chan ke za zhi* 2008;43(5):329-31. [published Online First: 2008/10/29]
10. Zhang YF. The clinical observation of effect of lamivudine on interrupting mother to infant transmission of chronic HBV on 50 mothers. *J Prat Obst Gynecol* 2010;26:367-68.
11. Ayres A, Yuen L, Manoharan S, et al. 736 LAMIVUDINE IN LATE PREGNANCY FOR PREVENTION OF HBV TRANSMISSION: EFFECTIVENESS AND DETECTION OF ANTIVIRAL RESISTANCE. *Journal of hepatology* 2011;54:S295-S96.
12. Ayres A, Yuen L, Jackson KM, et al. Short duration of lamivudine for the prevention of hepatitis B virus transmission in pregnancy: lack of potency and selection of resistance

mutations. *Journal of viral hepatitis* 2014;21(11):809-17. doi: 10.1111/jvh.12212 [published Online First: 2013/12/18]

13. Carey I, Lai JC, C.W. W, et al. Preventing mother to child transmission of HBV in an ethnically diverse South London population: an effective multidisciplinary clinical pathway (Abstract). *Hepatology (Baltimore, Md)* 2016;63:S01.
14. Celen MK, Mert D, Ay M, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection. *World journal of gastroenterology* 2013;19(48):9377-82. doi: 10.3748/wjg.v19.i48.9377 [published Online First: 2014/01/11]
15. Chen HL, Lee CN, Chang CH, et al. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. *Hepatology (Baltimore, Md)* 2015;62(2):375-86. doi: 10.1002/hep.27837 [published Online First: 2015/04/09]
16. Greenup AJ, Tan PK, Nguyen V, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus. *Journal of hepatology* 2014;61(3):502-7. doi: 10.1016/j.jhep.2014.04.038 [published Online First: 2014/05/08]
17. Han GR, Fang ZX, Zhao W, et al. Efficacy and safety of lamivudine treatment on preventing hepatitis B virus vertical transmission in pregnant women. *Chin J Infect Dis* 2009;27:673-76.
18. Han ZH, Chen YH, Li LW, et al. Effect and safety of preventing HBV vertical transmission by lamivudine treatment. *Chinese J Intern Med* 2005;44:378.
19. Huang H, Wu Q, Wang Y. Tenofovir Disoproxil: Effective and Safe in Prevention of Mother-to-child Transmission of Hepatitis B Virus. *Hepatology (Baltimore, Md)* 2014;60:1088A.
20. Kochaksaraei SG, Castillo E, Osman M, et al. Clinical course of 161 untreated and tenofovir-treated chronic hepatitis B pregnant patients in a low hepatitis B virus endemic region. *Journal of viral hepatitis* 2016;23(1):15-22. doi: 10.1111/jvh.12436 [published Online First: 2015/07/21]
21. Lawler J, Glass A, Chatterjee U, et al. Nucleot(s)ide analogues to prevent perinatal transmission of HBV: Lamivudine is effective but tenofovir may be better. *Journal of Gastroenterology and Hepatology* 2011;26:100.
22. Li WF, Jiang R, Wei Z, et al. Clinical effect and safety of lamivudine in interruption of chronic HBV maternal to infant transmission. *Chin Hepatol* 2006;11:106-07.
23. Pan C, Ta A, Zeng Z. Safety of Tenofovir Disoproxil Fumarate Treatment in Late Pregnancy in Highly Viremic Mothers with Chronic Hepatitis B. *American Journal of Gastroenterology* 2013;108:S156.

24. Pan QP, Lan B, Chan S, et al. Su1007 Tenofovir or Lamivudine Use in Late Pregnancy Safely Reduces Perinatal Transmission of Hepatitis B Virus in Real-Life Practice. *Gastroenterology* 2014;146(5 (Supplement 1)):S-961.
25. Pan CQ, Yi W, Liu M, et al. Lamivudine therapy during the second vs the third trimester for preventing transmission of chronic hepatitis B. *Journal of viral hepatitis* 2017;24(3):246-52. doi: 10.1111/jvh.12640 [published Online First: 2016/12/28]
26. Sellier P, Schnepf N, Amarsy R, et al. Hepatitis B virus (HBV) status of children born to HIV/HBV co-infected women in a French hospital: a cross-sectional study. *Journal of the International AIDS Society* 2014;17(4 Suppl 3):19632. doi: 10.7448/ias.17.4.19632 [published Online First: 2014/11/14]
27. Tan PK, Chatterjee U, Glass A, et al. Lamivudine in pregnancy: Impact on hepatitis flares and HBeAg seroconversion post partum. *Journal of Gastroenterology and Hepatology* 2012;27:181.
28. Virine B, Osiowy C, Gao S, et al. Hepatitis B Virus (HBV) Variants in Untreated and Tenofovir Treated Chronic Hepatitis B (CHB) Patients during Pregnancy and Post-Partum Follow-Up. *PloS one* 2015;10(10):e0140070. doi: 10.1371/journal.pone.0140070 [published Online First: 2015/10/17]
29. Yi W, Pan CQ, Liu M, et al. Clinical outcomes of tenofovir disoproxil fumarate (TDF) treatment versus no treatment for pregnant women with active chronic hepatitis B (CHB) and elevated alanine aminotransaminase (ALT). *Hepatology (Baltimore, Md)* 2014;60:1094A.
30. Yu MM, Jiang Q, Ji Y, et al. Comparison of telbivudine versus lamivudine in interrupting perinatal transmission of hepatitis B virus. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology* 2014;61(1):55-60. doi: 10.1016/j.jcv.2014.06.005 [published Online First: 2014/07/06]
31. Zhang Y, Wu Q, Huang H, et al. 2016. *Journal of hepatology* 2016;64(2(Supplement)):S607 (Abstract FRI-154).
32. Zhang H, Pan CQ, Pang Q, et al. Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice. *Hepatology (Baltimore, Md)* 2014;60(2):468-76.

CHAPTER 7: Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline

This is a *Rapid Recommendation* on medications for pregnant women living with HIV. The review above found that a tenofovir probably increases risk of stillbirth. Another linked systematic review provided evidence that pregnant women living with HIV place an extremely high value on avoiding stillbirth. With these two key pieces of information, we were able to make a defensible recommendation against tenofovir. This recommendation contradicted guidelines from the World Health Organization (WHO) and others, which took a public health perspective and recommend tenofovir because of resource use and feasibility. A linked editorial called on the WHO to reprioritize the needs of women when making recommendations.

Citation:
Siemieniuk RAC, Lytvyn L, Mah Ming J, Mullen RM, Anam F, Otieno T, Guyatt GH, Taylor GP, Beltrán-Arroyave C, Okwen PM, Nduati R, Kinuthia J, Luma HN, Kirpalani H, Merglen A, Lesi OA, Vandvik PO, Agoritsas T, Bewley S. Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline. *BMJ*. 2017 Sep 11;358:j3961. doi: 10.1136/bmj.j3961.

RAPID RECOMMENDATIONS

Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline

Reed A C Siemieniuk,[1] Lyubov Lytvyn,[2] Jinell Mah Ming,[3] Rhonda Marama Mullen,[4] Florence Anam,[5] Teresia Otieno,[6] Gordon H Guyatt,[1] Graham P Taylor,[7] Claudia Beltrán-Arroyave,[8] Patrick Mbah Okwen,[9] Ruth Nduati,[10] John Kinuthia,[11] Henry Namme Luma,[12] Haresh Kirpalani,[13] Arnaud Merglen,[14] Olufunmilayo A Lesi,[15] Per Olav Vandvik,[16] Thomas Agoritsas,[17] Susan Bewley[18]

Full author details can be found at the end of the article

Correspondence to: R Siemieniuk reed.siemieniuk@medportal.ca

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This BMJ Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. BMJ Rapid Recommendations represent a collaborative effort between the MAGIC group (www.magicproject.org) and The BMJ. A summary is offered here and the full version including decision aids is on the MAGICapp (www.magicapp.org), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualisation of our recommendations to local contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact The BMJ for permission to reuse content in this article.

Drug names

There are a large number of different antiretroviral drugs used by people with HIV. These drug names and abbreviations will be used throughout this article.

Nucleoside reverse transcriptase inhibitors (NRTIs)

- TDF — Tenofovir
- FTC — Emtricitabine
- AZT — Zidovudine
- 3TC — Lamivudine
- ABC — Abacavir

Protease inhibitors (PIs)

- LPV/r — Lopinavir (boosted with ritonavir)
- ATZ/r — Atazanavir (boosted with ritonavir)
- DRV/r — Darunavir (boosted with ritonavir)

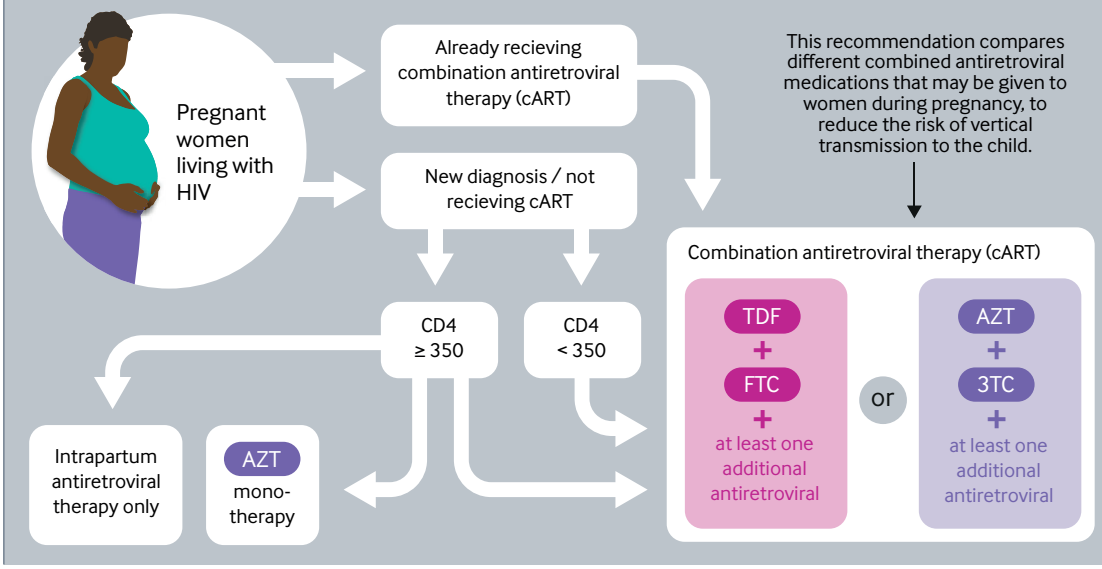
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

- EFV — Efavirenz
- RPV — Rilpivirine

Integrase inhibitors

- RAL — Raltegravir

Population



Comparison 1

TDF + FTC-based therapy

Tenofovir + emtricitabine-based antiretroviral therapy.

Treatment backbone: TDF + FTC

Combined with one of: DRV/r, ATZ/r, RAL, EFV, RPV

or

AZT + 3TC-based therapy

Zidovudine + lamivudine-based antiretroviral therapy.

Treatment backbone: AZT + 3TC

Combined with one of: LPV/r, DRV/r, ATZ/r, RAL, EFV, RPV, ABC

Favours TDF + FTC cART			Favours AZT + 3TC cART	
Strong	Weak		Weak	Strong

Applies to

All

We suggest a zidovudine and lamivudine-based antiretroviral regimen over one that includes tenofovir and emtricitabine

Comparison of benefits and harms

Favours TDF + FTC cART | No important difference | Favours AZT + 3TC cART

All settings	Events per 1000 people			Evidence quality
HIV vertical transmission	4	No important difference	5	★★☆☆ Low
Maternal laboratory AEs	117	No important difference	138	★★☆☆ Low
Maternal clinical AEs	20	No important difference	20	★★★☆ Moderate
Premature births (<34 weeks)	74	42 fewer	32	★★☆☆ Low
Low/medium resourced settings	**Events per 1000 people**			**Evidence quality**
Hepatitis B vertical transmission	29	No important difference	111	★★☆☆ Low
Stillbirth/neonatal mortality	304	235 fewer	69	★★☆☆ Low
High resourced settings	**Events per 1000 people**			**Evidence quality**
Hepatitis B vertical transmission	3	No important difference	10	★★★☆ Moderate
Stillbirth/neonatal mortality	66	51 fewer	15	★★☆☆ Low

Preferences and values

Women in these situations might be more likely to choose regimens with a tenofovir/emtricitabine backbone:

- Severe anemia
- Lamivudine-resistant hepatitis B
- Drug allergy
- Lamivudine-resistant HIV
- Alternatives are not available
- Zidovudine-resistant HIV
- Women taking other medications with serious interactions
- Women who place a high value on a once-daily regimen

Other considerations

The evidence applies less in areas with high hepatitis B disease activity, high resource settings, or where access to one of the options is limited.

Resourcing

Zidovudine /lamivudine is available as a low-cost generic around the world, while tenofovir/emtricitabine remains on patent in several countries.

Comparison 2

TDF + FTC + LPV/r

The specific combination of drugs tested in the PROMISE trial

Treatment backbone: TDF + FTC

Combined with: LPV/r

or

AZT + 3TC-based therapy

Zidovudine + lamivudine-based antiretroviral therapy.

Treatment backbone: AZT + 3TC

Combined with one of: LPV/r, DRV/r, ATZ/r, RAL, EFV, RPV, ABC

Favours TDF + FTC + LPV/r — **Favours AZT + 3TC cART**

Applies to All

Strong | Weak | Weak | Strong

We recommend a zidovudine and lamivudine-based antiretroviral regimen over tenofovir and emtricitabine with ritonavir-boosted lopinavir

Comparison of benefits and harms

Favours TDF + FTC cART | No important difference | Favours AZT + 3TC cART

All settings	Events per 1000 people			Evidence quality
HIV vertical transmission	4	No important difference	5	★★☆☆ Low
Maternal laboratory AEs	117	No important difference	138	★★★☆ Moderate
Maternal clinical AEs	20	No important difference	20	★★★☆ Moderate
Premature births (<34 weeks)	74	42 fewer	32	★★★☆ Moderate

Low/medium resourced settings	Events per 1000 people			Evidence quality
Hepatitis B vertical transmission	29	No important difference	111	★★☆☆ Low
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High resourced settings	Events per 1000 people			Evidence quality
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Preferences and values

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- Women taking other medications with serious interactions
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Other considerations

The evidence applies less in areas with high hepatitis B disease activity, high resource settings, or where access to one of the options is limited.

Resourcing

Zidovudine /lamivudine is available as a low-cost generic around the world, while tenofovir/emtricitabine remains on patent in several countries.

Approximately 1.4 million women living with HIV become pregnant every year. Most women use antiretroviral therapy, to reduce the risk of vertical transmission or for personal health reasons. Using the GRADE framework according to the BMJ Rapid Recommendation process, we make recommendations for optimal choice of combination antiretroviral regimen considering patient values and preferences, the balance of desirable and undesirable outcomes, their uncertainty, and practical issues. We suggest a zidovudine and lamivudine-based regimen over one that includes tenofovir or emtricitabine (weak recommendation). We recommend alternatives over the combination of tenofovir, emtricitabine, and lopinavir/ritonavir (strong recommendation).

The use of the most common combination antiretroviral medicines in pregnancy was questioned when the results of the Promoting Maternal and Infant Survival Everywhere (PROMISE) trial were published in late 2016.[1] The primary efficacy outcome demonstrated that two common combination antiretroviral therapy regimens confer similar reductions in vertical HIV transmission compared with zidovudine (AZT) monotherapy. However, a planned analysis of a composite safety outcome raised the possibility that the combination regimen with tenofovir plus emtricitabine (FTC) may increase early prematurity, stillbirth, and neonatal death compared with zidovudine plus lamivudine when combined with ritonavir-boosted lopinavir.[1] We aimed to appraise the totality of evidence about combination antiretroviral therapy for pregnant women infected with HIV and make women-centred recommendations.

Every year, about 1.4 million women living with HIV become pregnant and 1.1 million pregnant women use antiretroviral therapy.[2] Without any intervention, approximately 15-45% of children born to mothers with HIV acquire HIV in the antenatal, intrapartum, and postpartum periods.[3]

Women may be offered antiretroviral therapy while pregnant to prevent vertical transmission[4] and, in some cases, to reduce the maternal risk of AIDS defining events.[5] Combination antiretroviral therapy is the most effective among several options to reduce the risk of vertical transmission. Many of these options can be implemented simultaneously (box 1). They have different burdens and adverse effects.

Maternal combination antiretroviral therapy, when initiated before the third trimester, confers a vertical transmission rate of less than 5 per 1000 births.[7] Most combination antiretroviral therapy regimens include a "backbone" of two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) in combination with a third antiretroviral, often with a different mechanism of action.[8-10]

Major guidelines currently recommend the NRTI combination of tenofovir disoproxil fumarate and emtricitabine as a first line therapy in pregnant women (table 1). For simplicity, we refer to tenofovir disoproxil fumarate as tenofovir, recognising that the discussion may not apply to the related agent tenofovir alafenamide. Tenofovir is usually combined with emtricitabine and is currently the most widely used antiretroviral worldwide (fig 1). In 2016, revenues from tenofovir and tenofovir-containing products reached US$13bn (approximately £10bn).[16]

Some antiretrovirals, including tenofovir and lamivudine, also have activity against hepatitis B virus (HBV). HBV infection is common among women with HIV, especially in women born in areas where HBV is endemic.[17]

WHAT YOU NEED TO KNOW

- The guideline panel make a weak recommendation for zidovudine and lamivudine instead of tenofovir or emtricitabine for pregnant women living with HIV when they are combined with most antiretrovirals, and a strong recommendation when these drugs are combined with lopinavir/ritonavir
- Tenofovir and emtricitabine probably increase the risk of early neonatal death and preterm delivery <34 weeks compared with zidovudine and lamivudine; this is more certain when they are combined with lopinavir/ritonavir
- Almost all women place an extremely high value on avoiding early neonatal deaths, and most do not consider pill burden very important in pregnancy
- Women with active hepatitis B and high risk of vertical hepatitis B transmission, severe anaemia, drug allergies or intolerances, or zidovudine or lamivudine resistant HIV or hepatitis B may be more likely to choose treatment based on tenofovir and emtricitabine
- Recommendations that take a public health perspective (rather than an individual patient perspective) need to consider resource use and might make different recommendations based on the same evidence

LINKED ARTICLES IN THIS *BMJ* RAPID RECOMMENDATIONS CLUSTER

- Siemieniuk RAC, Lytvyn L, Mah Ming J, et al. Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline. *BMJ* 2017;358:j3961. doi:10.1136/bmj.j3961
  - Summary of the results from the Rapid Recommendation process
- Siemieniuk RA, Foroutan F, Mirza R, et al. Antiretroviral therapy for pregnant women living with HIV or hepatitis B: a systematic review and meta-analysis. *BMJ Open* 2017;7:e019022. doi:10.1136/bmjopen-2017-019022
  - Systematic review of antiretroviral therapies in pregnant women
- Lytvyn L, Siemieniuk RA, Dilmitis S, et al. Values and preferences of women living with HIV who are pregnant, postpartum, or considering pregnancy on choice of antiretroviral therapy during pregnancy. *BMJ Open* 2017;7:e019023. doi:10.1136/bmjopen-2017-019023
  - Systematic review of values and preferences
- MAGICapp (www.magicapp.org/goto/guideline/VLpr5E)
  - Expanded version of the evidence with multilayered recommendations, evidence summaries, and decision aids for use on all devices

Box 1 | Interventions that reduce vertical transmission of HIV

- Maternal antiretroviral therapy:
  - Antiretroviral monotherapy
  - Combination antiretroviral therapy
  - Intrapartum antiretroviral therapy
- Pre-labour, pre-rupture of membranes caesarean section[6]
- Infant antiretroviral therapy prophylaxis
- Formula feeding rather than breastfeeding
- Maternal antiretroviral therapy during breastfeeding
- Infant nevirapine therapy during breastfeeding

Vertical transmission of HBV occurs in approximately 38% of children born to mothers with active HBV infection in settings where prophylactic measures are not available.[18] The transmission rate is reduced to about 1% in children who receive prophylaxis with hepatitis B immunoglobulin and early hepatitis B vaccination.[19] When transmission does occur, it is almost always in the minority of mothers with high HBV disease activity—such as a detectable serum hepatitis B envelope antigen (found in the early phase of infection) or high HBV viral load (>1 million copies/mL).[19 20]

The evidence

To inform the recommendations, the panel requested two systematic reviews, which are linked to this publication (see linked articles in this cluster) on the following questions:

- What are the relative benefits and harms of different NRTI regimens for pregnant women with HIV?[21]
- What evidence describes the values and preferences of women considering antiretroviral therapy?[22]

Understanding the recommendation

Benefit and harm

The most credible and relevant evidence comes from the PROMISE study, which randomised 816 women from Africa, who were at least 14 weeks pregnant, to tenofovir/emtricitabine or zidovudine/lamivudine.[1] Both groups also received the protease inhibitor combination of lopinavir/ritonavir at a standard dose until the third trimester, when the dose was increased by 50% until delivery. Fig 2 shows details of the study and characteristics of included patients.

Based on the linked systematic review,[21] the panel judged that there was moderate certainty that tenofovir/emtricitabine—when combined with lopinavir/ritonavir in the doses used in the PROMISE trial—increases stillbirth and early neonatal mortality compared with zidovudine/lamivudine, as well as early premature labour before 34 weeks gestational age (see infographic). Certainty is moderate rather than high because of imprecision around the best estimate of the absolute effect and because most of the evidence comes from a single study where the event rate in the zidovudine/lamivudine arm may have been lower than expected.[1] The authors of the PROMISE trial argued that the event rate in the zidovudine/lamivudine arm might have been lower than expected because of "some unknown confounder" that resulted in fewer early premature deliveries and early infant deaths in the zidovudine/lamivudine arm during the second phase of the study when tenofovir/emtricitabine was available—and that the confounder was not present before the introduction of the tenofovir/emtricitabine arm.[1] The panel think this is unlikely, and, even if there was an unknown confounder in the study, until that confounder is identified, the risk estimates apply to all pregnant women living with HIV. The available evidence suggested that there was no difference for any of the other pre-specified outcomes (low to moderate certainty; see infographic).

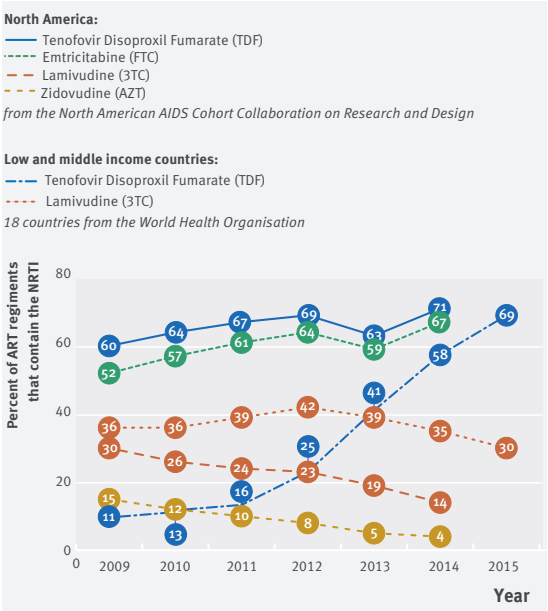

Fig 1 | Trends in the use of nucleoside or nucleotide reverse transcriptase inhibitors. ART=antiretroviral therapy; NRTI=nucleoside or nucleotide reverse transcriptase inhibitor; TDF=tenofovir disoproxil fumarate; AZT=zidovudine; 3TC=lamivudine; FTC=emtricitabine Dashed lines represent NRTI use in 18 low and middle income countries[14]; solid lines represent NRTI use in North America.[15]

Table 1 | Statements from current guidelines on antiretroviral therapy for pregnant women living with HIV

Guideline	Preferred options	Alternative options	Recommend against	Preferred third antiretroviral
EACS, 2016[10]	TDF/FTC TAF/FTC ABC/3TC	—	d4T ddI	Lopinavir/ritonavir Atazanavir/ritonavir Rilpivirine
US DHHS, 2016[9]	TDF/FTC TDF/3TC ABC/3TC	AZT/3TC	TAF d4T ddI	Atazanavir/ritonavir Darunavir/ritonavir Raltegravir
WHO, 2016[8]	TDF/FTC TDF/3TC	AZT/3TC	—	Efavirenz
BHIVA, 2014[11]	TDF/FTC ABC/3TC AZT/3TC	—	—	Lopinavir/ritonavir Atazanavir/ritonavir Efavirenz
Ireland, 2011[12]	AZT/3TC HBV co-infection: TDF/FTC TDF/3TC	—	—	Lopinavir/ritonavir Saquinavir/ritonavir Atazanavir/ritonavir Nevirapine
Thailand, 2010[13]	AZT/3TC	d4T/3TC	—	Lopinavir/ritonavir

EACS=European AIDS Clinical Society; US DHHS=US Department of Health and Human Services; WHO=World Health Organization; BHIVA=British HIV Association.
TDF= tenofovir disoproxil fumarate; FTC=emtricitabine; 3TC=lamivudine; AZT=zidovudine; ABC=abacavir; TAF=tenofovir alafenamide; d4T=stavudine; ddI=didanosine; HBV=hepatitis B virus.

HOW THE RECOMMENDATIONS WERE CREATED

This independent international panel included women living with HIV, adult and paediatric infectious disease specialists, general practitioners, paediatricians, obstetricians, a hepatologist, a pharmacist, and research methodologists (see appendix 1 on bmj.com for list of panel members). Panel members were recruited based on their work on the topic, with the focus on achieving a balanced panel representing all viewpoints. No person had any financial conflicts of interest; intellectual and professional conflicts were minimal (see appendix 2 on bmj.com).

The panel followed the *BMJ* Rapid Recommendations process for creating a trustworthy recommendation, such as using the GRADE approach to evaluate the evidence and create recommendations (appendix 3).[31-35] The panel considered the typical and expected variation in patient values and preferences, the balance of benefits, harms and burdens of the combination antiretroviral regimens, the quality of the evidence for each outcome, and treatment acceptability. With GRADE, recommendations can be strong or weak.[36 37] Weak recommendations imply that there is likely to be variation in what informed patients would choose, thus emphasising the need for an explicit shared decision-making process between patient and healthcare provider.

NRTIs are often combined with antiretrovirals other than lopinavir/ritonavir (table 1). It is possible but unlikely that a drug-drug interaction between lopinavir/ritonavir and tenofovir contributed to the increase in infant mortality. When tenofovir and lopinavir/ritonavir are used together, serum lopinavir/ritonavir concentrations are not increased and tenofovir levels are only marginally increased (much less than normal variation between patients).[23] Moreover, the increased lopinavir/ritonavir dose used in the third trimester in the PROMISE study provided serum drug concentrations similar to those of non-pregnant women taking the typical dose,[24] although some experts argue that no dose increase is required during pregnancy.[25] For combinations with a third antiretroviral agent other than lopinavir/ritonavir, the best evidence informing the comparison of tenofovir/emtricitabine versus alternative NRTIs is therefore indirect because the best evidence comes almost entirely from a study that used lopinavir/ritonavir. In this circumstance, certainty in the evidence was rated down from moderate to low for several key outcomes, including stillbirth and early neonatal death.

Whether the culprit medication is tenofovir or emtricitabine, and the circumstances in which an increase in stillbirths and neonatal death occurs, remain uncertain. Some evidence from observational studies might suggest that tenofovir/emtricitabine is safe in pregnancy.[8 26] However, in addition to the inevitable residual confounding inherent to observational studies,[27] the available studies also failed to adjust for important confounders, had inconsistent results, and their pooled estimate of effect was imprecise.[21] The observational evidence thus provides only very low certainty evidence and does not provide reassurance that tenofovir/emtricitabine is safe in pregnancy. Indeed, even adequately powered observational studies that control for known and measurable confounders would be unlikely to provide adequate assurance of safety in the face of the current randomised trial evidence suggesting harm.

Hepatitis B co-infection—Tenofovir and lamivudine both have antiviral activity against HBV. In the linked network meta-analysis, there was no apparent difference between tenofovir and lamivudine for preventing vertical transmission of hepatitis B, but the certainty is low because there were very few patients and events in the single randomised controlled trial with tenofovir.[21] The impact of tenofovir compared with lamivudine on the risk of antiviral resistance and flares in hepatitis B disease is uncertain in this context.

Practical issues

Tenofovir/emtricitabine (as well as abacavir/lamivudine) are typically administered once per day, whereas zidovudine/lamivudine is administered twice daily. Antiretrovirals are often co-formulated into single tablets for ease of administration in an attempt to optimise adherence. Tenofovir/emtricitabine and abacavir/lamivudine are available as co-formulations with several other antiretrovirals in single once daily tablets (tenofovir/emtricitabine is co-formulated with efavirenz, rilpivirine, or elvitegravir/cobicistat); zidovudine/lamivudine is not co-formulated into any single once daily tablets, and is instead available in a single tablet co-formulated with abacavir to be taken twice per day. Therefore, tenofovir based regimens may be simpler than zidovudine/lamivudine based combination antiretroviral therapy (see fig 3).

Values and preferences

Our linked systematic review of qualitative studies report several consistent themes that are important or very

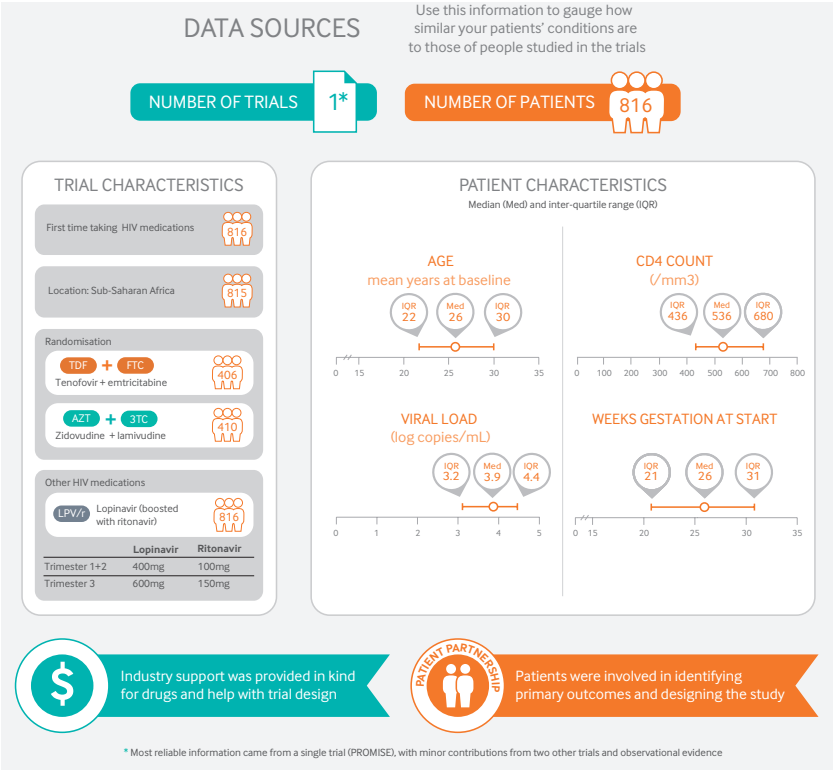

Fig 2| Characteristics of patients and details of PROMISE study

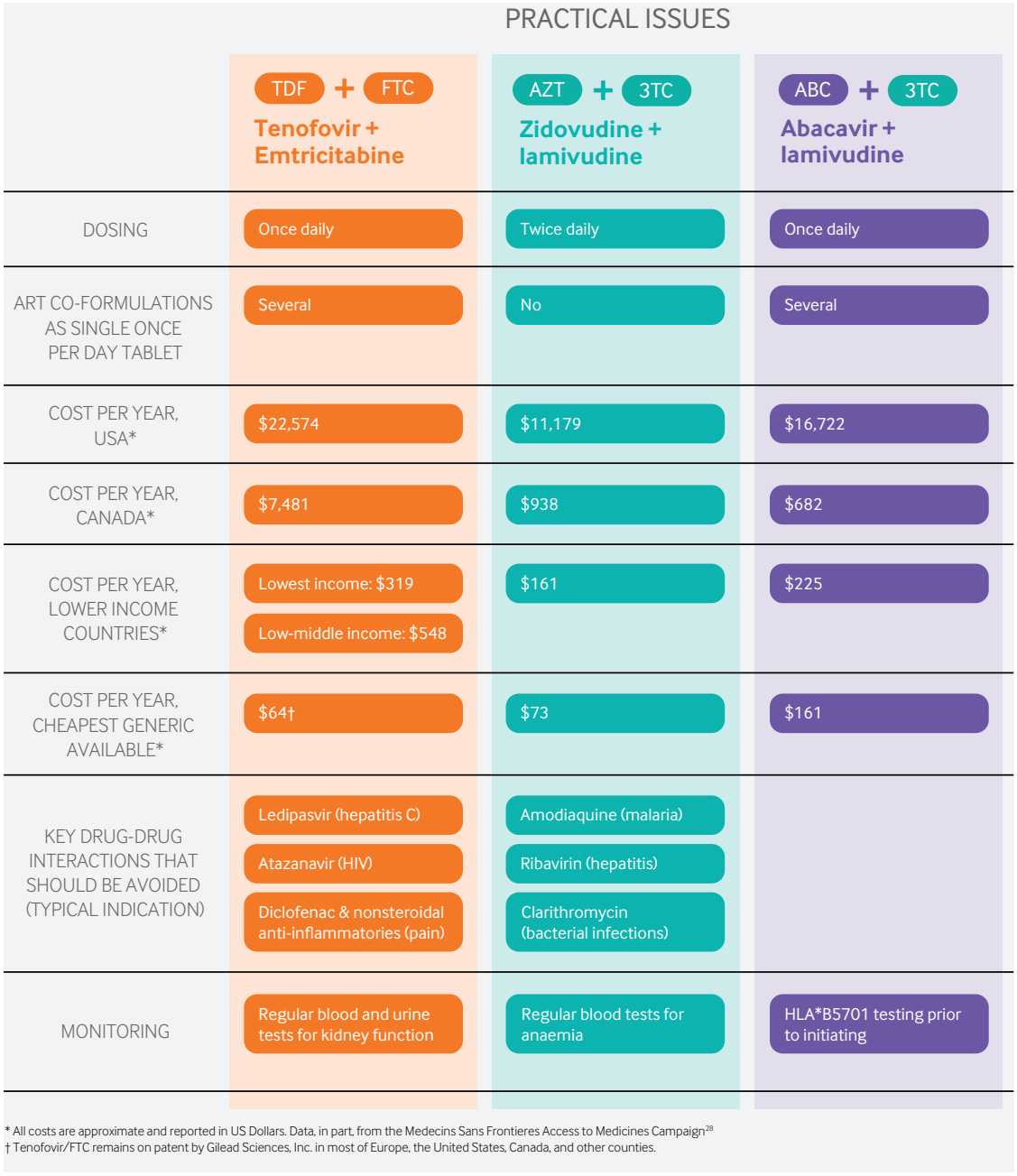

Fig 3| Practical issues about use of combination antiretroviral therapy

important to women when considering combination antiretroviral therapy during pregnancy.[22] These themes concur with the experience of those panellists living with HIV, as well as the healthcare worker panellists' observations from interactions with patients.

Women described a strong desire to optimise the health of their child. This desire encouraged mothers to use antiretroviral therapy to reduce vertical HIV transmission, but also proved a barrier for some because of concerns about adverse effects on the child.[22] More specifically, almost all women place an extremely high value on avoiding stillbirth and neonatal mortality, and most women place a very high or extremely high value on avoiding early preterm labour. With some exceptions, women probably place little or very little importance on simplifying the combination antiretroviral therapy dosing regimen from twice daily to once daily.[22] Thus our recommendations apply to women who share these values.

Practical advice

Empowering women

The recommendations are meant to support shared decision making between pregnant women and their healthcare provider. Healthcare providers should make all necessary efforts to inform women of all of the benefits and harms for all reasonable treatment options. The linked decision aids, available through MagicApp can help facilitate this conversation (www.magicapp.org/goto/guideline/VLpr5E). Patient support organisations can also play a critical role in patient education.

Alternative NRTIs

A reasonable NRTI backbone is zidovudine/lamivudine. This is because evidence from randomised controlled trials is directly applicable only to zidovudine/lamivudine as an alternative to tenofovir/emtricitabine, although other NRTI combinations such as abacavir/lamivudine are available.

A new formulation of tenofovir, tenofovir alafenamide, is now available; tenofovir alafenamide may have improved renal and bone safety compared with tenofovir disoproxil fumarate in adults because of reduced plasma concentrations.[29] In the absence of randomised trial data in pregnancy, whether tenofovir alafenamide and tenofovir disoproxil fumarate carry similar risks to the fetus is speculative.

The third antiretroviral agent

Typically, a third antiretroviral is added to a dual NRTI backbone to complete the combination antiretroviral therapy regimen. A triple NRTI regimen, with zidovudine/lamivudine plus abacavir, is one reasonable option, although there are several others. Current guidelines differ substantially in their recommendations for the third antiretroviral agent (table 1). The linked systematic review did not formally address the third antiretroviral agent, but evidence from a randomised trial of 540 pregnant women in Botswana suggests that, when combined with zidovudine/lamivudine, abacavir might confer a lower risk of premature delivery than lopinavir/ritonavir (15% *v* 23%, but with a 95% confidence interval of the difference of <1% to 16%).[30] Other outcomes, including vertical transmission of HIV, were similar between abacavir and lopinavir/ritonavir. The impact of other combination antiretroviral therapy regimens on key outcomes in pregnancy is very uncertain.

Some women may have other compelling reasons to choose a specific single or combination antiretroviral therapy regimen. The virus should be susceptible to the prescribed antiretrovirals. Further, specific antiretroviral therapy agents should be avoided if a woman is allergic, intolerant to side effects, or has had a serious adverse reaction to that agent in the past. Abacavir should be avoided in women with the HLA B*5701 genotype.

Recommendations in context

The number of antiretroviral therapy options that women can choose from and can be prescribed varies considerably throughout the world. The most widely available regimen in low resource settings is tenofovir with emtricitabine or lamivudine, combined with efavirenz. In many settings, zidovudine/lamivudine may not be available, despite it being older and generally cheaper. Our first recommendation can only apply to settings where women have access to zidovudine and lamivudine. In light of this evidence, healthcare administrators should be encouraged to prioritise making zidovudine and lamivudine available to pregnant women in settings where zidovudine/lamivudine based combination antiretroviral therapy regimens are not currently available.

These recommendations, like all *BMJ* Rapid Recommendations,[31] take a patient centred perspective. Guidelines that take a public health perspective, such as the WHO guideline,[8] may issue different recommendations based on the same evidence. Many HIV treatment programmes, especially in low resource settings, are underfunded and have difficulty meeting antiretroviral therapy demand. In some situations, these operational pressures have been partially alleviated by simplifying the treatment regimen to be used as first line therapy for all patients, including women with HIV who are pregnant or who may be expected to become pregnant. The 2016 WHO guidelines explicitly state that "simplifying operational demands" was one reason that "the same once-per-day combination pill is now recommended for all adults".[8] The WHO currently recommends a single tablet combination of tenofovir/emtricitabine plus efavirenz as the first line combination antiretroviral therapy regimen for all adults.[8] Recommending alternative treatment options for women living with HIV who are pregnant may introduce operational challenges. For example, many treatment programmes negotiate more affordable medication purchases in bulk. Other influential guidelines either have not yet had the opportunity to consider the evidence from the PROMISE trial or did not have the opportunity to consider the evidence systematically.[9 10]

Hepatitis B co-infection

In women co-infected with HBV, there is a risk that the HBV becomes resistant and that treatment fails, a risk that may be particularly important in women taking lamivudine for a prolonged period.[32] Lamivudine may be less effective at preventing vertical transmission of HBV in mothers with lamivudine resistance than in mothers without resistance. However, the degree to which this is true is uncertain. In women with low HBV disease activity or who have access to neonatal hepatitis B immunoglobulin and early infant HBV vaccination, the risk of HBV transmission is already low (approximately 1 in 100), so any speculative difference in vertical transmission rates between tenofovir and lamivudine in lamivudine-resistant HBV will be small. On the other hand, the speculative benefit of tenofovir over lamivudine in preventing vertical transmission in women with lamivudine-resistant HBV might be larger in situations with a higher baseline risk of HBV transmission—particularly when there is high maternal HBV activity (such as >200 000 IU/mL or 1 million copies/mL) and where there is unreliable infant access to hepatitis B immunoglobulin or early HBV vaccination.

Cost and resources

In the commonest situation, where women do not pay directly for antiretroviral therapy, cost is not their concern. In settings where tenofovir/emtricitabine and its one tablet once per day combination pills remain on patent, we expect there to be considerable cost savings to the payer with the routine use of zidovudine/lamivudine over tenofovir/emtricitabine. In settings where generic tenofovir/emtricitabine is available and routinely prescribed, the impact on costs to the payer is uncertain (fig 3).

Uncertainty

There is a lack of data on the safety and efficacy of most commonly used combination antiretroviral therapy regimens in pregnant women living with HIV. To date,

Table 2 | New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article				

EDUCATION INTO PRACTICE

- How many women in your practice receive tenofovir or emtricitabine while pregnant?
- How will you share this information with women infected with HIV?
- To what extent might you use information in this article to alter the conversations you have with women living with HIV?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

In addition to the systematic review of the values and preferences of women living with HIV, three women living with HIV were full panel members, participated in the teleconferences and email discussions, and met all authorship criteria. These panel members identified important outcomes, led the discussions about values and preferences, and helped to interpret and provide context for the evidence.

most information has been gleaned from observational studies, rather than randomised controlled trials. Even if adequately powered and carefully controlled for known confounders, observational studies are unlikely to provide sufficient reassurance on the safety of any particular regimen when randomised trial evidence suggests harm—even when the randomised trial data informs decisions indirectly and the effect estimates are imprecise. Speculative arguments about antiretroviral dosing, serum levels, drug interactions, and mechanisms that might cause antiretroviral therapy-related harm in pregnancy need further basic science and observational research, complemented by safety confirmation in randomised controlled trials. The PROMISE trial serves as a reminder of the importance of randomised evidence to inform treatment options in pregnant women with HIV.

The outcomes reported in many of the studies were narrow in scope. Future studies should consider all outcomes important to patients—such as medium to long term child development. Future primary studies and secondary reviews must consider all reasonable and available interventions, including zidovudine monotherapy, not simply combination antiretroviral therapy.

Implementation research and efforts may be required to overcome the current operational challenges so that availability of the right choice of combination antiretroviral therapy is aligned with the best available evidence for almost all pregnant women living with HIV.

Updates to this article

Table 2 shows evidence which has emerged since the publication of this article. As new evidence is published, a group will assess the new evidence and make a judgment on to what extent it is expected to alter the recommendation.

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Competing interests: All authors have completed the *BMJ* Rapid Recommendations interests form. The *BMJ* Rapid Recommendations team judged that no panel member declared financial, professional, or academic interests that precluded authorship. The declared interests for each panel member are in appendix 2 on bmj.com. No panel members declared any financial conflicts of interest related to this clinical question. This article was edited by H MacDonald at *The BMJ* who had no relevant financial or intellectual interests.

Transparency: R A C Siemieniuk affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

1 Fowler MG, Qin M, Fiscus SA, et al. IMPAACT 1077BF/1077FF PROMISE Study Team. Benefits and risks of antiretroviral therapy for perinatal HIV prevention. *N Engl J Med* 2016;375:1726-37. doi:10.1056/NEJMoa1511691 pmid:27806243.
2 UNAIDS. AIDSInfo Data Sheets 2016. http://aidsinfo.unaids.org/.
3 The Working Group on Mother-To-Child Transmission of HIV. Rates of mother-to-child transmission of HIV-1 in Africa, America, and Europe: results from 13 perinatal studies. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;8:506-10. doi:10.1097/00042560-199504120-00011 pmid:7697448.
4 Siegfried N, van der Merwe L, Brocklehurst P, Sint TT. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database Syst Rev* 2011;(7):CD003510.pmid:21735394.
5 Lundgren JD, Babiker AG, Gordin F, et al. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015;373:795-807. doi:10.1056/NEJMoa1506816 pmid:26192873.
6 European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet* 1999;353:1035-9. doi:10.1016/S0140-6736(98)08084-2 pmid:10199349.
7 Forbes JC, Alimenti AM, Singer J, et al. Canadian Pediatric AIDS Research Group (CPARG). A national review of vertical HIV transmission. *AIDS* 2012;26:757-63. doi:10.1097/QAD.0b013e328350995c pmid:22210635.
8 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. 2016. www.who.int/hiv/pub/arv/arv-2016/en/.
9 Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 2016. https://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.
10 European AIDS Clinical Society. EACS guidelines. 2017. www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html.
11 de Ruiter A, Taylor GP, Clayden P, et al. British HIV Association. British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). *HIV Med* 2014;15(Suppl 4):1-77. doi:10.1111/hiv.12185 pmid:25604045.
12 Health Service Executive. Irish guidelines for antiretroviral treatment in children 2011. www.hse.ie/eng/about/Who/clinical/natclinprog/obsandgynaeprogramme/guide10.pdf.
13 Phanuphak N, Lolekha R, Chokephaibulkit K, et al. Thailand national guidelines for the prevention of mother-to-child transmission of HIV: March 2010. 2010. www.researchgate.net/publication/317745187_Thailand_national_guidelines_for_the_prevention_of_mother-to-child_transmission_of_HIV_2016.
14 Habiyambere V, AIDS Medicines and Diagnostic Services (AMDS) Strategic Information and Planning Unit. WHO global ARVs and diagnostic use survey in 2015 in low & middle-income countries: ARV use situation by end of 2014 preliminary results. 2016. www.who.int/hiv/amds/amds2016-ppt-WHO-2015ARVUseSurvey.pdf?ua=1.
15 North American AIDS Cohort Collaboration on Research and Design. ART use: international epidemiology database to evaluate AIDS. 2017. https://statepiaps7.jhsph.edu/naaccord/.
16 Gilead Sciences announces fourth quarter and full year 2016 financial results [press release]. 2017. www.gilead.com/news/press-releases/2017/2/gilead-sciences-announces-fourth-quarter-and-full-year-2016-financial-results.
17 Barth RE, Huijgen Q, Taljaard J, Hoepelman AI. Hepatitis B/C and HIV in sub-Saharan Africa: an association between highly prevalent infectious diseases. A systematic review and meta-analysis. *Int J Infect Dis* 2010;14:e1024-31. doi:10.1016/j.ijid.2010.06.013 pmid:20870439.
18 Keane E, Funk AL, Shimakawa Y. Systematic review with meta-analysis: the risk of mother-to-child transmission of hepatitis B virus infection in sub-Saharan Africa. *Aliment Pharmacol Ther* 2016;44:1005-17. doi:10.1111/apt.13795 pmid:27630001.

19 Schillie S, Walker T, Veselsky S, et al. Outcomes of infants born to women infected with hepatitis B. *Pediatrics* 2015;135:e1141-7. doi:10.1542/peds.2014-3213 pmid:25896839.
20 Wiseman E, Fraser MA, Holden S, et al. Perinatal transmission of hepatitis B virus: an Australian experience. *Med J Aust* 2009;190:489-92.pmid:19413519.
21 Siemieniuk RA, Foroutan F, Mirza R, et al. Antiretroviral therapy for pregnant women living with HIV or hepatitis B: a systematic review and meta-analysis. *BMJ Open* 2017;7:e019022. doi:10.1136/bmjopen-2017-019022.
22 Lytvyn L, Siemieniuk RA, Dilmitis S, et al. Values and preferences of women living with HIV who are pregnant, postpartum, or considering pregnancy on choice of antiretroviral therapy during pregnancy. *BMJ Open* 2017;7:e019023. doi:10.1136/bmjopen-2017-019023.
23 Kearney BP, Mathias A, Mittan A, Sayre J, Ebrahimi R, Cheng AK. Pharmacokinetics and safety of tenofovir disoproxil fumarate on coadministration with lopinavir/ritonavir. *J Acquir Immune Defic Syndr* 2006;43:278-83. doi:10.1097/01.qai.0000243103.03265.2b pmid:17079992.
24 Best BM, Stek AM, Mirochnick M, et al. International Maternal Pediatric Adolescent AIDS Clinical Trials Group 1026s Study Team. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. *J Acquir Immune Defic Syndr* 2010;54:381-8. doi:10.1097/QAI.0b013e3181d6c9ed pmid:20632458.
25 Salem AH, Jones AK, Santini-Oliveira M, et al. No need for lopinavir dose adjustment during pregnancy: a population pharmacokinetic and exposure-response analysis in pregnant and nonpregnant HIV-infected subjects. *Antimicrob Agents Chemother* 2015;60:400-8. doi:10.1128/AAC.01197-15 pmid:26525798.
26 Mofenson LM, Baggaley RC, Mameletzis I. Tenofovir disoproxil fumarate safety for women and their infants during pregnancy and breastfeeding. *AIDS* 2017;31:213-32. doi:10.1097/QAD.0000000000001313 pmid:27831952.
27 Agoritsas T, Merglen A, Shah ND, O'Donnell M, Guyatt GH. Adjusted analyses in studies addressing therapy and harm: users' guides to the medical literature. *JAMA* 2017;317:748-59. doi:10.1001/jama.2016.20029 pmid:28241362.
28 Médecins Sans Frontières Access Campaign. *Untangling the web of antiretroviral price reductions.*Médecins Sans Frontières, 2016.
29 Wang H, Lu X, Yang X, Xu N. The efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate in antiretroviral regimens for HIV-1 therapy: meta-analysis. *Medicine (Baltimore)* 2016;95:e5146. doi:10.1097/MD.0000000000005146 pmid:27741146.
30 Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *N Engl J Med* 2010;362:2282-94. doi:10.1056/NEJMoa0907736 pmid:20554983.
31 Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:i5191. doi:10.1136/bmj.i5191 pmid:27680768.
32 Lok AS, Lai CL, Leung N, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003;125:1714-22. doi:10.1053/j.gastro.2003.09.033 pmid:14724824.
33 Poolman RW, Agoritsas T, Siemieniuk RA, et al. Low intensity pulsed ultrasound (LIPUS) for bone healing: a clinical practice guideline. *BMJ* 2017;356:j576. doi:10.1136/bmj.j576 pmid:28228381.
34 Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ* 2016;354:i5085. doi:10.1136/bmj.i5085 pmid:27680583.
35 Siemieniuk RAC, Harris IA, Agoritsas T, et al. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *BMJ* 2017;357:j1982. doi:10.1136/bmj.j1982 pmid:28490431.
36 Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. Going from evidence to recommendations. *BMJ* 2008;336:1049-51. doi:10.1136/bmj.39493.646875.AE pmid:18467413.
37 Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. doi:10.1136/bmj.39489.470347.AD pmid:18436948.

[1]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada; Department of Medicine, University of Toronto, Toronto, Canada
[2]Oslo University Hospital, Forskningsveien 2b, Blindern 0317 Oslo, Norway
[3]Southern Alberta HIV Clinic, Calgary, Canada
[4]INA (Māori, Indigenous & South Pacific) HIV/AIDS Foundation, Tirau, New Zealand
[5]International Community of Women living with HIV (ICW-Global), Nairobi, Kenya
[6]ATHENA Network, Seattle, USA
[7]Imperial College London, London, UK
[8]Universidad de Antioquia, Medellin, Colombia
[9]Bali District Hospital, Yaoundé, Cameroon
[10]University of Nairobi, Nairobi, Kenya
[11]Kenyatta National Hospital, Nairobi, Kenya
[12]University of Yaoundé, Yaoundé, Cameroon
[13]University of Pennsylvania, Philadelphia, *USA*
[14]Geneva University Hospitals, Geneva, Switzerland
[15]Lagos University Teaching Hospital, Lagos, Nigeria; College of Medicine, University of Lagos, Nigeria
[16]Institute of Health and Society, Faculty of Medicine, University of Oslo, 0318 Oslo, Norway; Department of Medicine, Innlandet Hospital Trust-division, Gjøvik, Norway
[17]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada; Division General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, CH-1211, Geneva, Switzerland
[18]Women's Health Academic Centre, King's College London, London, UK

CHAPTER 8: Corticosteroids for treatment of sore throat: systematic review and meta-analysis of randomised trials

This is a review that showed that an ultra-short course of corticosteroids were more effective than placebo at reducing severity and duration of symptoms in patients with sore throat, without substantially increasing the risk of adverse effects. It informed a practice-changing *Rapid Recommendations* suggesting the use of a modest dose of a corticosteroid for most patients with sore throat.

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*Joint first authors

Corticosteroids for treatment of sore throat: systematic review and meta-analysis of randomised trials

Behnam Sadeghirad,[1,2] Reed A C Siemieniuk,[1] Romina Brignardello-Petersen,[1,3] Davide Papola,[4] Lyubov Lytvyn,[5] Per Olav Vandvik,[6,7] Arnaud Merglen,[8] Gordon H Guyatt,[1] Thomas Agoritsas[1,9]

[1]Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Hamilton, ON, Canada
[2]HIV/STI Surveillance Research Centre, and WHO Collaborating Centre for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
[3]Faculty of Dentistry, University of Chile, Santiago, Chile
[4]Department of Public Health and Community Medicine, Section of Psychiatry, University of Verona, Italy
[5]Oslo University Hospital, Oslo, Norway
[6]Department of Medicine, Innlandet Hospital Trust, Division Gjøvik, Oslo, Norway
[7]Institute of Health and Society, Faculty of Medicine, University of Oslo, Norway
[8]Division of General Paediatrics, University Hospitals of Geneva and Faculty of Medicine, University of Geneva, Geneva, Switzerland
[9]Division of General Internal Medicine and Division of Clinical Epidemiology, University Hospitals of Geneva, Switzerland

Correspondence to:
B Sadeghirad
sadeghb@mcmaster.ca

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ABSTRACT

OBJECTIVE

To estimate the benefits and harms of using corticosteroids as an adjunct treatment for sore throat.

DESIGN

Systematic review and meta-analysis of randomised control trials.

DATA SOURCES

Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), trial registries up to May 2017, reference lists of eligible trials, related reviews.

STUDY SELECTION

Randomised controlled trials of the addition of corticosteroids to standard clinical care for patients aged 5 or older in emergency department and primary care settings with clinical signs of acute tonsillitis, pharyngitis, or the clinical syndrome of sore throat. Trials were included irrespective of language or publication status.

REVIEW METHODS

Reviewers identified studies, extracted data, and assessed the quality of the evidence, independently and in duplicate. A parallel guideline committee (*BMJ* Rapid Recommendation) provided input on the design and interpretation of the systematic review, including the selection of outcomes important to patients. Random effects model was used for meta-analyses. Quality of evidence was assessed with the GRADE approach.

RESULTS

10 eligible trials enrolled 1426 individuals. Patients who received single low dose corticosteroids (the most common intervention was oral dexamethasone with a maximum dose of 10 mg) were twice as likely to experience pain relief after 24 hours (relative risk 2.2, 95% confidence interval 1.2 to 4.3; risk difference 12.4%; moderate quality evidence) and 1.5 times more likely to have no pain at 48 hours (1.5, 1.3 to 1.8; risk difference 18.3%; high quality). The mean time to onset of pain relief in patients treated with corticosteroids was 4.8 hours earlier (95% confidence interval −1.9 to −7.8; moderate quality) and the mean time to complete resolution of pain was 11.1 hours earlier (−0.4 to −21.8; low quality) than in those treated with placebo. The absolute pain reduction at 24 hours (visual analogue scale 0-10) was greater in patients treated with corticosteroids (mean difference 1.3, 95% confidence interval 0.7 to 1.9; moderate quality). Nine of the 10 trials sought information regarding adverse events. Six studies reported no adverse effects, and three studies reported few adverse events, which were mostly complications related to disease, with a similar incidence in both groups.

CONCLUSION

Single low dose corticosteroids can provide pain relief in patients with sore throat, with no increase in serious adverse effects. Included trials did not assess the potential risks of larger cumulative doses in patients with recurrent episodes of acute sore throat.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42017067808.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Short course corticosteroids are one adjunct treatment option for relief of symptoms in patients with sore throat

Corticosteroids are not commonly prescribed as clinicians are uncertain about the balance of benefits and harms and the applicability of the evidence to patients with less severe disease

WHAT THIS STUDY ADDS

Moderate to high quality evidence suggests the addition of one (or two) dose(s) of corticosteroids reduces the intensity and duration of pain in patients with sore throat with no increase in serious adverse effects

The mean time to complete pain resolution was about 11 hours shorter with corticosteroids, and about 18% more patients experienced complete pain relief at 48 hours

There were no subgroup effects between patients consulting at the emergency departments or primary care family practice

Introduction

Sore throat is among the most common presenting complaints in both emergency departments and outpatient care settings. It is the cause of about 5% of medical visits in children and about 2% of all outpatient visits in adults.[1-3] The most common cause of sore throat is acute pharyngitis caused by self limiting viral infections. Pain management with paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs (NSAIDs) therefore represents the mainstay of care.[4 5] These drugs provide limited pain relief but also sometimes cause serious harm.[6 7]

Treatment of sore throat with antibiotics also provides modest benefit in reduction of symptoms and fever when the infection is bacterial, but their use could contribute to antibiotic resistance.[8 9] Although most cases of sore throat have a viral aetiology, and the risk of secondary complications is low, clinicians commonly prescribe antibiotics.[4 10] Though this could be because clinicians think that patients seeking care expect a course of antibiotics, in reality pain relief might be more important to them.[10]

Corticosteroids represent an additional therapeutic option for symptom relief. Randomised control trials

suggest that a short course of low-to-moderate dose corticosteroids probably provides symptomatic benefit to patients with sore throat.[11-14] Despite this evidence, clinicians do not commonly use steroids. Reasons might include uncertain applicability of the evidence to patients with less severe disease, as the initial studies enrolled only patients with severe sore throat presenting to emergency departments, almost all of whom received antibiotics.

This systematic review is part of the *BMJ* Rapid Recommendations project, a collaborative effort from the MAGIC research and innovation programme (www.magicproject.org) and *BMJ*. The aim of the project is to respond to new potentially practice changing evidence and provide a trustworthy practice guideline in a timely manner.[15] In this case, the stimulus was the recent TOAST (Treatment Options without Antibiotics for Sore Throat) trial, which randomised over 500 patients with sore throat presenting to their primary care clinician who were not initially prescribed antibiotics; the TOAST authors reported beneficial effects of corticosteroids.[16] In the light of this new potentially practice changing evidence, we updated the latest Cochrane review[12] dealing with the effectiveness and safety of corticosteroids as an adjunct treatment for sore throat in addition to standard care compared with standard care alone. This systematic review informed the parallel guideline published in a multilayered electronic format on *bmj.com*[17] and MAGICapp (https://www.magicapp.org/goto/guideline/JjXYAL/section/j79pvn).

Methods

Guideline panel and patient involvement

According to the *BMJ* Rapid Recommendations process,[15] a guideline panel provided critical oversight to the review and identified populations, subgroups, and outcomes of interest. The panel included clinicians, methodologists, and patients with experience of sore throat. Patients received personal training and support to optimise contributions throughout the guideline development process. The patients on the panel led the interpretation of the results based on what they expected the typical patient values and preferences to be, as well as the variation between patients. Five patient representatives were full members of the guideline panel and contributed to the selection and prioritisation of outcomes, values and preferences assessments, and critical feedback to the protocol for the systematic review and the *BMJ* Rapid Recommendations manuscript.

Search strategy

We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) for relevant published randomised controlled trials based on the strategy reported in the most recent Cochrane systematic review,[12] modified under the guidance of a research librarian (appendix 1). We limited the search from 1 January 2010, which included a two month overlap with the previous Cochrane review search,[12] to 1 May 2017. There were no language restrictions. We reviewed reference lists from eligible new trials and related reviews for additional eligible trials and searched ClinicalTrials.gov for ongoing or unpublished trials and for additional data from published trials.

Study selection

Reviewers (BS, RACS, DP, RBP) independently and in duplicate screened the titles and abstracts of all identified studies using a priori selection criteria. Subsequently, the samereviewersindependently assessed eligibility of the full texts of potentially eligible studies. Reviewers resolved discrepancies through discussion or, if needed, by adjudication from a third reviewer.

We included randomised controlled trials that compared corticosteroids with standard of care or placebo and enrolled adults and/or children aged 5 and over in emergency departments and primary care settings with a clinical syndrome of sore throat (painful throat, odynophagia, or pharyngitis).

We excluded studies of participants who were admitted to hospital or immunocompromised and those with infectious mononucleosis, sore throat after any surgery or intubation (postoperative sore throat), gastroesophageal reflux disease, croup, or peritonsillar abscess. We also excluded studies that enrolled children aged under 5 because they would not be able to provide trustworthy outcome measurements, especially for self reported pain.

Our outcomes of interest were complete resolution of pain at 24 and 48 hours; mean time to onset of pain relief; mean time to complete resolution of pain; absolute reduction of pain at 24 hours; duration of bad/non-tolerable symptoms (such as problems for eating, drinking, swallowing); recurrence/relapse of symptoms; days missed from school or work; need for antibiotics; and rate of adverse events related to treatment. We included any adverse events reported by the authors.

Data abstraction and risk of bias assessment

Reviewers extracted the following data, independently and in duplicate: general study information (authors, publication year, and study location); study population details (sample size, age, diagnosis, and percentage of participants with confirmed group A β haemolytic streptococcus (GAS) pharyngitis or culture positive for bacterial pathogens); setting (primary care versus hospital emergency department); details on the intervention and comparison (for example, type, form, duration, and dose of corticosteroids; type of control group); co-interventions (proportion of participants who received antibiotics and/or analgesics); and outcomes as listed above.

In randomised controlled trials with more than two arms, we extracted data from the arm closest to a single dose regimen or data from the arm that received corticosteroid as adjunct treatment to standard of care rather than instead of standard of care. In trials with data for both oral and parenteral corticosteroids, we

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used oral data for the main analysis and intramuscular data for the appropriate subgroup analysis.

Two reviewers independently assessed risk of bias using the modified Cochrane risk of bias instrument,[18 19] which deals with random sequence generation; allocation concealment; blinding of study participants, healthcare providers, and outcome assessors; incomplete outcome data; and other potential sources of bias. Reviewers classified studies at high risk of bias when they had rated at least one item as high risk of bias.

To assess the quality of evidence, we used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach that classifies evidence as high, moderate, low, or very low quality based on considerations of risk of bias, consistency, directness, precision, and publication bias.[20] We resolved disagreements between reviewers in data extraction and assessments of risk of bias or quality of evidence by discussion and, if needed, by third party adjudication. We used the MAGICapp platform to generate the GRADE summary of findings table.

Data synthesis and statistical methods

For continuous outcomes, we calculated the mean difference and its corresponding 95% confidence interval. For dichotomous outcomes, we calculated the relative risk and its corresponding 95% confidence interval and determined the absolute effect by multiplying the relative risk and its confidence interval with the estimated baseline risk. The median of the placebo group of included randomised controlled trials provided the baseline risk.

Statistical heterogeneity was determined with the Q statistic and I^2. We used the DerSimonian-Laird random effects model for the meta-analysis of all outcomes. Regardless of the observed statistical heterogeneity, we conducted the following prespecified subgroup analyses when each subgroup was represented by at least two studies: age (children *v* adults), postulating a larger effect in adults; route of administration of corticosteroids (oral *v* parenteral), postulating a larger effect for parenteral; presence or absence of positive results on culture for a bacterial pathogen or direct antigen test for group A β haemolytic streptococcus, postulating a larger effect in patients with positive test results; initial setting (emergency departments *v* family practice), postulating a larger effect in patients consulting the emergency department; and place of subsequent care (admitted to hospital *v* outpatient), postulating a larger effect among the patients admitted. For subgroup analysis, we tested for interaction using a χ^2 significance test.[21] We planned to examine publication bias using funnel plots for outcomes for which data from 10 or more studies were available.[22] Data were analysed with STATA software (version 14.2, TX, USA).

Patient involvement

Five patient representatives were full members of the guideline panel, and contributed to the selection and prioritisation of outcomes, values and preferences assessments, and critical feedback to the protocol for the systematic review and the *BMJ* Rapid Recommendations manuscript.

Results

Description of included studies

We identified 2349 titles and abstracts through our literature search, of which 46 were potentially eligible and 36 were excluded (19 were not randomised trials; 14 had no patients with sore throat/acute pharyngitis; in three corticosteroids were not among the interventions or were not compared with a placebo/usual care). Figure 1 shows the details of study selection process.

The 10 randomised controlled trials that proved eligible enrolled 1426 individuals. Eight studies recruited patients from hospital emergency departments[23-30] and two from primary care.[16 31] Three studies enrolled children,[27-29] six studies enrolled adults,[16 24-26 30 31] and one study included both children and adults.[23] Oral dexamethasone (single dose of 10 mg for adults and 0.6 mg/kg, maximum 10 mg for children) was the most common intervention (five studies) followed by single dose intramuscular injection of dexamethasone (three studies). All patients in three trials received both antibiotics and analgesics as the usual care[25 26 30]; in two trials, all patients received antibiotics, while analgesics were prescribed at the physician's discretion.[23 24] In the five remaining trials, patients in usual care group received antibiotics or analgesics at the physician's discretion.[16 27-29 31] Table 1 presents study details.

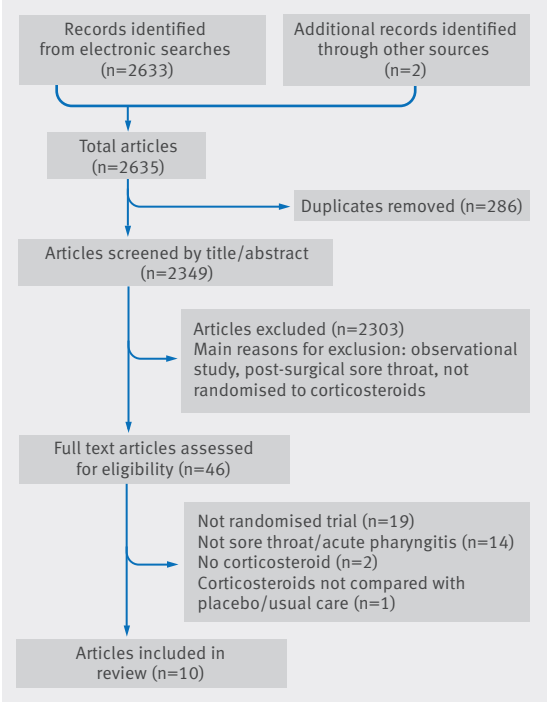

Fig 1 | Selection of studies in review of corticosteroids for treatment of sore throat

Table 1 | Characteristics of studies included in systematic review of corticosteroids for treatment of sore throat

Study	Setting	Population	Mean age (years)	No randomised (intervention/control)	Pathogen positive* (%)	Type of steroid	Dose and duration	Antibiotic use (%)		Analgesic use (%)	
								Intervention	Control	Intervention	Control
Hayward, 2017[16]	Primary care	Adults	34.0	293/283	14.9	Dexamethasone (oral)	10 mg, single dose	39.9	39.0	77.1	78.9
Tasar, 2008[30]	ED	Adults	31.3	31/42	NR	Dexamethasone (IM)	8 mg, single dose	100	100	100	100
Niland, 2006[29]	ED	Children	7.7†	30/30	100.0	Dexamethasone (oral)	0.6 mg/kg, max 10 mg, single dose	NR	NR	NR	NR
Olympia, 2005[28]	ED	Children	11.9	75/75	55.2	Dexamethasone (oral)	0.6 mg/kg, max 10 mg, single dose	47.1	63.0	35.1	41.2
Kiderman, 2005[31]	Primary care	Adults	33.9	40/39	57.5	Prednisone (oral)	60 mg, single dose (100%) or for 2 days (50%)	51.4	63.2	NR	NR
Bulloch, 2003[27]	ED	Children	9.7	92/92	46.2	Dexamethasone (oral)	0.6 mg/kg, max 10 mg, single dose	48.9	43.5	NR	NR
Ahn, 2003[26]	ED	Adults	35.3	36/36	45.0	Dexamethasone (oral)	5 mg for 2 days	100	100	100	100
Wei, 2002[25]	ED	Adults	28.1	42/38	39.0	Dexamethasone (oral and IM)	10 mg, single dose	100	100	100	100
Marvez-Valls, 1998[24]	ED	Adults	29.2	46/46	53.26	Betamethasone (IM)	8 mg/2 mL injection‡, single dose	100	100	NR	NR
O'Brien, 1993[23]	ED	Both	26.4	31/27	NR	Dexamethasone (IM)	10 mg, single dose	100	100	NR	NR

ED=emergency department; NR=not reported.
*Positive result on culture or rapid test for group A β haemolytic streptococcus (GABHS).
†Median (interquartile range 6-12).
‡Dose is best guess from US formularies.

Among the included studies, four randomised controlled trials were at high risk of bias.[23 24 26 28] One study had issues in more than one category of risk.[26] The three remaining studies had issues in concealment of the treatment allocation, incomplete outcome reporting, and blinding of outcome assessors. Appendix 2 summarises the risk of bias assessments.

Table 2 shows findings for all outcomes. Interactive tables summarising findings are available at https://www.magicapp.org/goto/guideline/JjXYAL/section/j79pvn

Pain

In the five randomised controlled trials that reported complete resolution of symptoms at 24 hours,[16 25 29-31] patients who received a single dose of corticosteroids were twice as likely to experience complete symptom resolution than placebo patients (relative risk 2.24, 95% confidence interval 1.17 to 4.29; I^2=69%, 22.4% *v* 10.0%; moderate quality evidence; fig 2, table 2). All studies reporting this outcome were at low risk of bias. Tests of interaction showed no evidence of any subgroup effect (table A in appendix 3).

In the four trials that reported complete resolution of pain at 48 hours,[16 29-31] patients treated with corticosteroids were 50% more likely to experience complete resolution (relative risk 1.48, 95% confidence interval 1.26 to 1.75; I^2=3%, 60.8% *v* 42.5%; high quality; fig 3, table 2). These four studies were all at low risk of bias, and tests of interaction showed no evidence of any subgroup effect (table A in appendix 3).

In the eight studies that reported mean time to onset of pain relief,[16 23-28 30] patients who received corticosteroids experienced onset of pain relief on average 4.8 hours earlier than those who received placebo (95% confidence interval −1.9 to −7.8; I^2=78%; moderate quality; fig 4, table 2). We found no evidence of subgroup effect for this outcome (table A in appendix 3).

Time to complete resolution of pain was reported in six studies.[16 23 24 27 28 30] On average, patients receiving a single dose corticosteroid experienced complete resolution 11.1 hours earlier (95% confidence interval −0.4 to −21.8; I^2=85%; low quality; fig 5, table 2). In our subgroup analysis, we found a significantly larger effect among those treated with intramuscular corticosteroids (mean difference −22.4 (95% confidence interval −27.3 to −17.5) and −1.5 (−12.6 to 9.5), for intramuscular and oral corticosteroids, respectively; P=0.001 for interaction); however, the effect modification is suggested by comparison between rather than within studies. We found no other subgroup effect (table B in appendix 3).

Meta-analysis from eight studies that assessed pain with a visual analogue scale (0=no pain, 10=maximum pain) at baseline and after 24 hours[16 23-28 31] showed a 1.3 points lower pain score among patients treated with corticosteroids compared with those treated with placebo at 24 hours (95% confidence interval 0.7 to 1.9; I^2=65%; moderate quality; fig 6, table 2). We

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Table 2 | GRADE summary of findings for corticosteroids (intervention) versus no corticosteroids (control) in patients with sore throat

Outcome and timeframe	Study results (95% CI) and measurements	Absolute effect estimates			Quality of evidence	Summary
		No corticosteroids	Corticosteroids	Difference (95% CI)		
Complete resolution of pain at 24 hours	Relative risk: 2.24 (1.17 to 4.29). 1049 patients in 5 studies	100/1000	224/1000	124 more (17 more to 329 more	Moderate (inconsistency and imprecision)* † ‡	Corticosteroids probably increase chance of complete resolution of pain at 24 hours
Complete resolution of pain at 48 hours	Relative risk: 1.48 (1.26 to 1.75). 1076 patients in 4 studies	425/1000	629/1000	204 more (111 more to 319 more)	High‡	Corticosteroids increase chance of complete resolution of pain at 48 hours
Recurrence/relapse of symptoms	Relative risk: 0.52 (0.16 to 1.73). 372 patients in 3 studies	65/1000	34/1000	31 fewer (55 fewer to 47 more)	Moderate (serious imprecision)‡ § ¶	Corticosteroids probably have no important effect on chance that symptoms recur
Antibiotics prescription	Relative risk: 0.83 (0.61 to 1.13). 342 patients in 1 study. Follow-up 28 days	564/1000	468/1000	96 fewer (220 fewer to 73 more)	Low (very serious imprecision)**	Corticosteroids might decrease chance of taking antibiotics in patients given prescription with instructions to take antibiotic if unimproved or worse
Mean time to onset of pain relief (hours)	907 patients in 8 studies	12.3 hours	7.4 hours	4.8 fewer (7.8 fewer to 1.9 fewer)	Moderate (inconsistency and imprecision)‡ †† ‡‡ §§	Corticosteroids probably shorten the time until pain starts to improve.
Mean time to complete resolution of pain (hours)	720 patients in 6 studies	44.0 hours	33.0 hours	11.1 fewer (21.8 fewer to 0.4 fewer)	Low (serious imprecision and inconsistency)‡ †† ‡‡ ¶¶	Corticosteroids might shorten duration of pain
Pain reduction 24 hours	Scale: high better. 1247 patients in 8 studies	Mean 3.3 hours	Mean 4.6 hours	1.3 higher (0.7 higher to 1.9 higher)	Moderate (inconsistency and imprecision)‡ †† ‡‡ ***	Corticosteroids probably reduce severity of pain at 24 hours
Duration of bad/non-tolerable symptoms	—	—	—	0 (0 to 0)	—	No studies provided information on this outcome
Days missed from work or school	181 patients in 2 studies. Follow-up to 14 days	Two trials reported days missed from work/school. In Kiderman et al, 22/40 (55%) in steroids group and 27/39 (69%) in placebo group took time off work (relative risk 0.79, 95% CI 0.56 to 1.13). Marvez-Valls et al reported average time patients in each arm missed from work/school: average 0.4 (SD 1.4) days in intervention group adults *v* and 0.7 (SD 1.4) days in placebo group adults; mean difference 0.30 days, −0.28 to 0.88)			Moderate (serious imprecision and some concerns of risk of bias)††† ‡‡‡	Corticosteroids probably have no important effect on days missed from work or school
Serious adverse events	808 patients in 3 studies. Follow-up to 10 days	Few adverse effects reported in trials, mostly disease related complications, and occurred with similar frequency in intervention and control groups (see table 3)			Moderate§§§	Corticosteroids probably do not increase risk of adverse events

*Considerable heterogeneity (I^2=69%). Not rated down because clinical inconsistency was deemed not important as all results of included studies have similar clinical implication.
†Limits of confidence interval suggest small benefit in one extreme and benefit important to patients in other. Because imprecision is linked to inconsistency, certainty of evidence rated down by only one level.
‡Publication bias not tested because of small number of studies.
§Not rated down for risk of bias as one of three trials judged to be at high risk of bias from missing participant data.
¶Confidence interval suggests that corticosteroids increase chance of recurrence of symptoms in one extreme but decrease this chance in other extreme.
**Confidence interval suggest that corticosteroids could largely reduce chance of taking antibiotics in one extreme but could slightly increase this chance in other extreme.
††Not rated down for risk of bias as equal number of trials judged to be at high and low risk of bias, but P value for test of interaction showed no difference between two estimates.
‡‡Large unexplained clinical and statistical inconsistency.
§§Confidence interval suggests small benefit in one extreme and benefit that some patients might consider important in other extreme. As this imprecision was result of inconsistency, certainty of evidence rated down by only one level.
¶¶Confidence interval suggests trivial benefit in one extreme and benefit that would be considered important by most patients in other extreme.
***Confidence interval suggests small benefit in one extreme and benefit important to patients in other. As this imprecision was related to inconsistency, rated down by only one level.
†††One study was at high risk of bias from concerns with regards to allocate concealment.
‡‡‡Studies showed that corticosteroids could increase days missed from school or work in one extreme but decrease them in other extreme.
§§§High risk of bias studies showed similar results as low risk of bias studies; however, high risk of selective outcome reporting was possible.

found no evidence of subgroup effect for this outcome (table B in appendix 3).

To assess the possibility that there was selective reporting, we examined the magnitude of effect on the time to onset of pain relief, time to complete resolution of pain, and absolute pain reduction in studies that did and did not report resolution of pain at 24 and 48 hours. The magnitude of effect on the other pain outcomes was similar in both sets of studies, making selective reporting less likely (table C in appendix 3).

Other outcomes

The authors of one study reported a possible decrease in the likelihood of receipt of antibiotics in patients treated with corticosteroids (relative risk 0.83, 95% confidence interval 0.61 to 1.13; moderate quality).[16] Three studies[27 28 31] suggested a possible lower risk of recurrence/relapse of the symptoms (0.52, 0.16to 1.73; I^2=23%; moderate quality, table D in appendix 3, table 2).

Kiderman and colleagues reported that 22/40 (55%) patients treated with corticosteroids and 27/39 (69%) taking placebo took time off work because of sore throat (relative risk 0.8, 95% confidence interval 0.6 to 1.1).[31] Marvez-Valls and colleagues reported that adult patients treated with corticosteroids missed an average of 0.4 (SD 1.4) days, whereas patients in the placebo arm missed an average of 0.7 (SD 1.4) days (mean

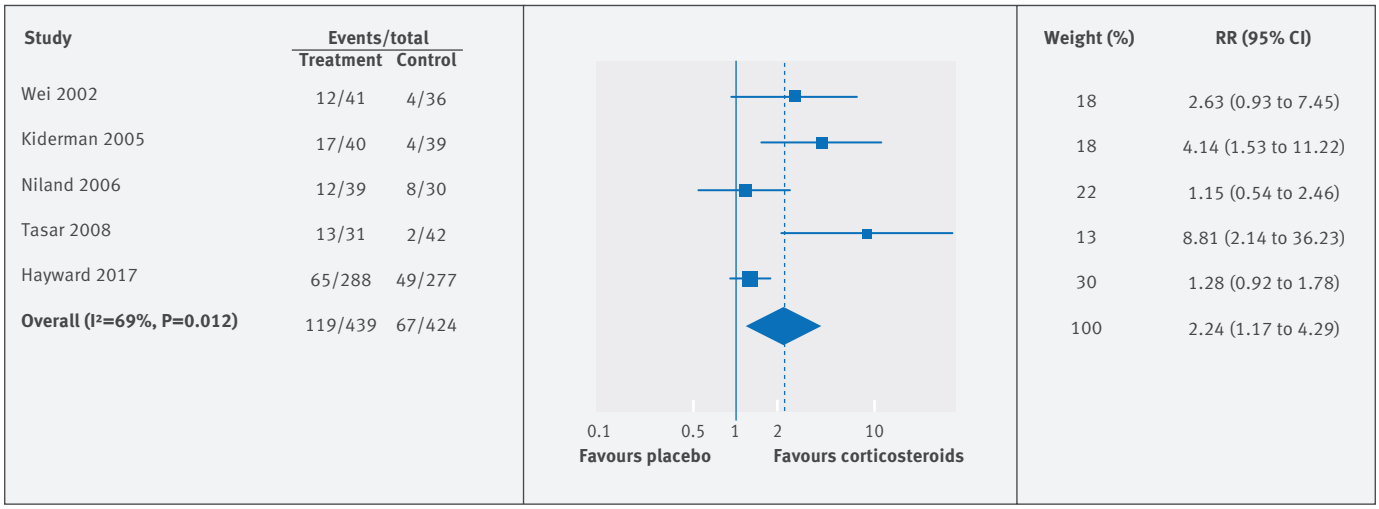

Fig 2 | Relative risk for complete resolution of pain at 24 hours for corticosteroid *v* placebo groups in review of treatment of sore throat. Pooled relative risk calculated by DerSimonian-Laird random effects model

difference −0.3 days, 95% confidence interval −0.87 to 0.27).[24] None of the trials reported duration of bad/non-tolerable symptoms.

All studies except one sought information on adverse effects using different methods including standardised questionnaire (two studies), open ended questions or diaries to capture self reported adverse events (five studies), or a checklist of complications (two studies). Table 3 provides details of adverse effects assessed and methods used for capturing them. Six studies reported no adverse effects, and three studies reported adverse events, in both steroids and comparator arms, which were mostly complications related to disease and occurred with similar frequency in the intervention and control groups (table 3). Hayward and colleagues reported two serious adverse events (admission to hospital for pharyngeal or peritonsillar abscess, tonsillitis, and pneumonia) in the corticosteroids group (0.7%) and three in the placebo group (1.1%).[16] Olympia and colleagues reported one out of the 57 (1.8%) children in the corticosteroids group and two out of the 68 (2.9%) children in the placebo group developed a peritonsillar abscess (moderate quality, table 2 and table 3).[28]

Discussion

In patients with acute sore throat, there is primarily moderate to high quality evidence that one or two low doses of corticosteroids reduces the intensity and duration of pain—pain scores at 24 hours, complete resolution of pain at 24 and at 48 hours, time to onset of pain relief, and time to complete pain relief. In this review, results were consistent across studies and across all pain outcomes (table 2). The reduction in pain achieved was modest—for example, mean time to complete resolution of pain was about 11 hours shorter, and about 18% more patients had complete pain relief at 48 hours. At 24 hours, the mean improvement in

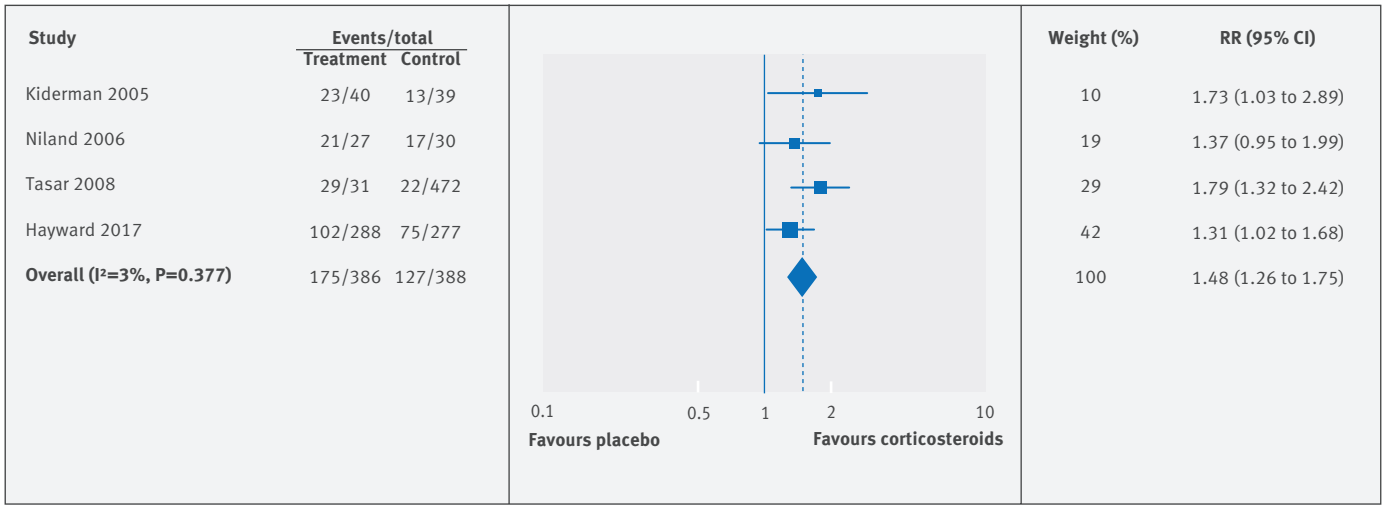

Fig 3 | Relative risk for complete resolution of pain at 48 hours for corticosteroid *v* placebo groups in review of treatment of sore throat. Pooled relative risk calculated by DerSimonian-Laird random effects model

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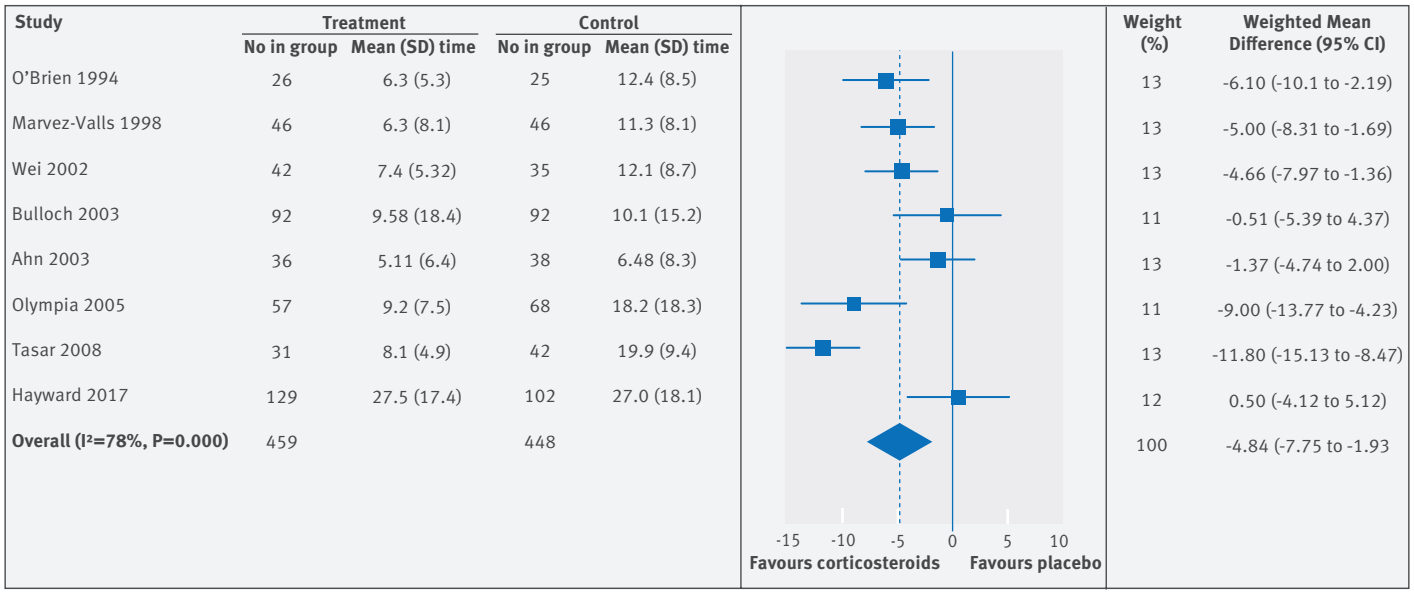

Fig 4 | Weighted mean difference in mean time to onset of pain relief (hours) between corticosteroids and placebo groups in review of treatment of sore throat. Pooled mean difference was calculated by DerSimonian-Laird random effects model

pain scores was about 13 mm on a visual analogue scale from 0 to 100 mm (with the minimal important difference being about 10 mm).[32] The relative effects were similar across severities, though patients with less severe sore throat had less absolute benefit from corticosteroids. The balance of benefits and harms therefore almost certainly depends on the severity of the patient's sore throat.

Whether corticosteroids reduce recurrence/relapse of symptoms, number of days missed from school or work, duration of bad/intolerable symptoms, or antibiotic use remains uncertain. Regarding the safety of the short courses and low doses of corticosteroids, studies reported few adverse effects, with no apparent increase in events in patients treated with corticosteroid.

Strengths and limitations of study

Strengths of this review include explicit eligibility criteria; a comprehensive search developed with a research librarian; duplicate assessment of eligibility, risk of bias, and data abstraction; consideration of all outcomes important to patients; consideration of selective reporting bias; consideration of possible subgroup effects; and rigorous use of the GRADE approach to rate quality of evidence. The limitations of our review have to do with the underlying evidence. Only three trials explicitly reported adverse events, and they did so inconsistently.[16 25 28] We observed substantial statistical heterogeneity in some of the outcomes. We explored the source(s) of heterogeneity by subgroup analysis and rated down for inconsistency in GRADE assessments for outcomes with unexplained heterogeneity.

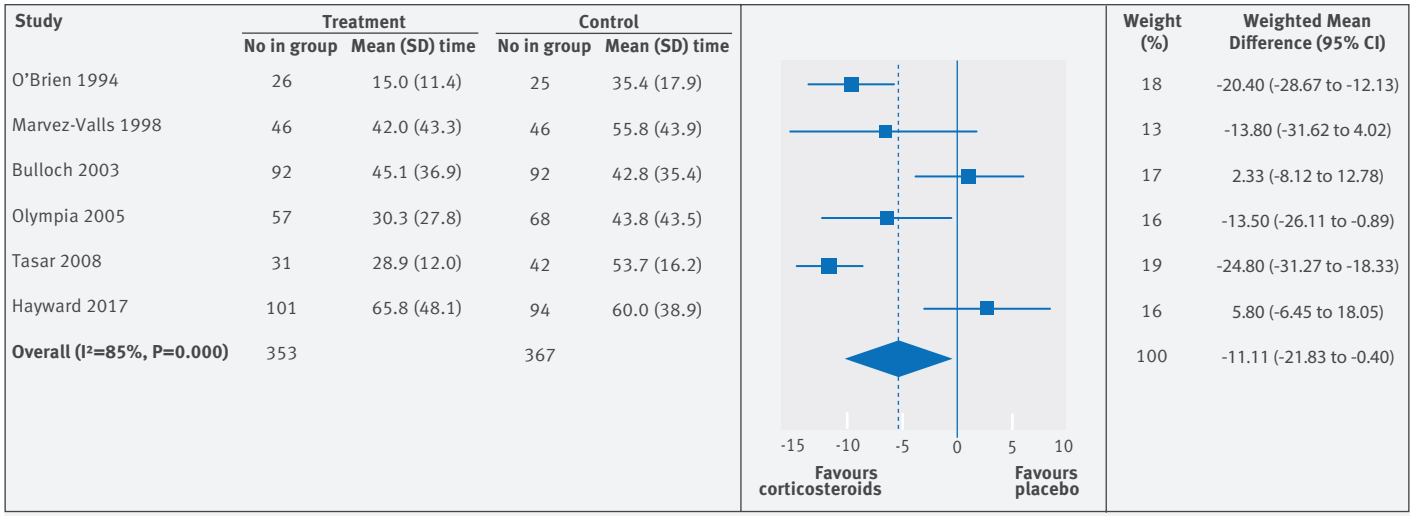

Fig 5 | Weighted mean difference in mean time to complete resolution of pain (hours) between corticosteroids and placebo groups in review of treatment of sore throat. Pooled mean difference calculated by DerSimonian-Laird random effects model

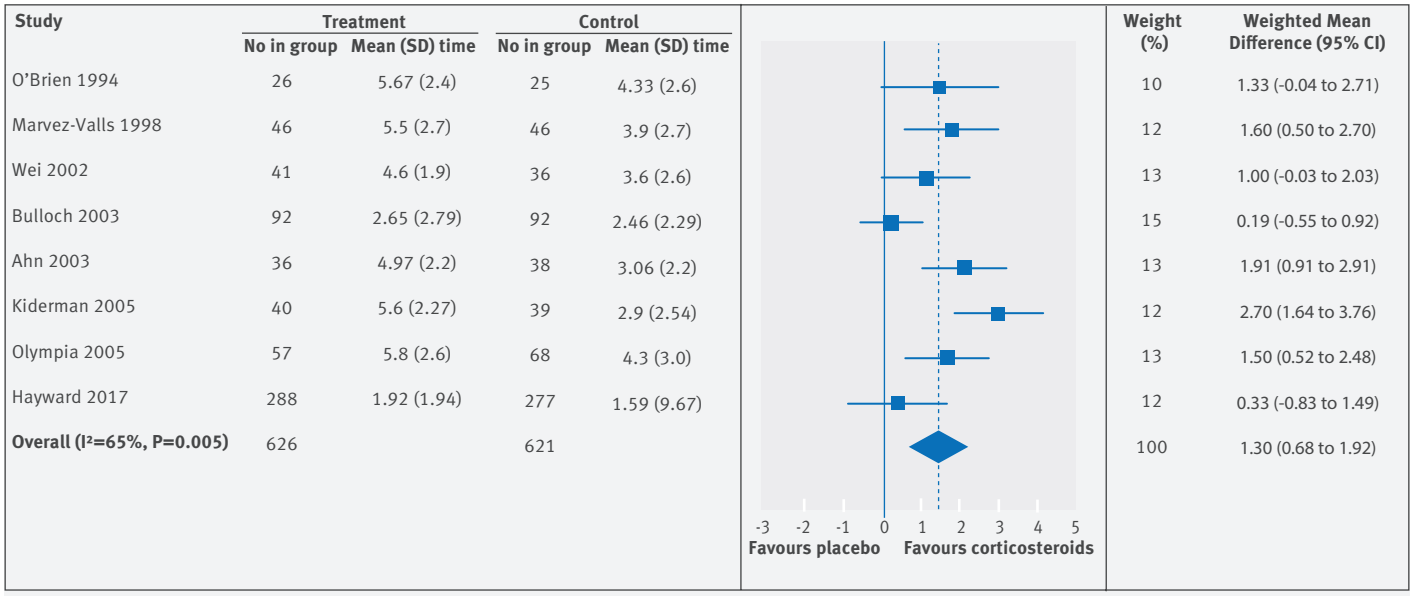

Fig 6 | Weighted mean difference in absolute reduction of pain at 24 hours (0-10; 0=no pain, 10=maximum pain) between corticosteroids and placebo groups in review of treatment of sore throat. Pooled mean difference calculated by DerSimonian-Laird random effects model

In comparison with previous systematic reviews,[11 12] we included two additional randomised controlled trials,[16 26] which almost doubled the number of participants. Results from our meta-analysis are consistent with previous findings that corticosteroids reduce pain at 48 hours and probably reduce other pain outcomes. In addition to enhanced precision with the additional studies, our meta-analysis adds to the existing evidence in that we considered absolute in addition to relative effect measures, providing a clear picture of the magnitude of effect.[33] In part because of input from the guideline panel, we considered additional outcomes that participating patients considered important, including risk of recurrence of symptoms, duration of bad/non-tolerable symptoms, need for antibiotics, and days missed from school or

Table 3 | Summary of adverse event assessments among trials included in systematic review of corticosteroids for treatment of sore throat

Study	Methods used to assess adverse effects	Adverse effects assessed*	Adverse effects reported
O'Brien, 1993	Standardised questionnaire	Nausea, vomiting, or diarrhoea	None reported
Marvez-Valls, 1998	Self reported side effects at follow-up call	Any adverse event	None reported
Wei, 2002	Self reported side effects at follow-up call	Any adverse event	1 patient who received corticosteroids (3%) reported hiccups
Ahn, 2003	Not reported	Not reported	None reported
Bulloch, 2003	Checklist of complication at follow-up call	Rash, joint pain, movement disorder, persistent fever, or blood in urine or "cola coloured" urine in past month, peritonsillar abscess	None reported
Kiderman, 2005	Not reported	Any adverse event	None reported
Olympia, 2005	Checklist of complication at daily follow-up calls	Headache, nausea or vomiting, abdominal pain, myalgia, mood changes, dizziness, and swollen legs, peritonsillar abscess	1/57 (1.8%) children in corticosteroids group and 2/68 (2.9%) in control group developed peritonsillar abscess. 3/57 (5.3%) children in corticosteroid group and 2/68 (2.9%) in placebo group were admitted for dehydration
Niland, 2006	Patient completed diaries and by structured telephone interviews	Headache, abdominal pain (Wong-Baker FACES scale), fever, vomiting, and information sought regarding additional medical care	Steroid treatment did not result in additional patient adverse effects, symptom relapses, or complications related to disease
Tasar, 2008	Self reported side effects at follow-up call	Complications related to dexamethasone and azithromycin	None reported
Hayward, 2017	Attendance or telephone contact at any healthcare facility (including GP clinic, urgent care clinic, emergency department, or hospital admission) with symptoms or complications associated with sore throat (defined as direct suppurative complications or presentation with sore throat symptoms)	Any adverse event	2 serious adverse events (admissions for pharyngeal or peritonsillar abscess, tonsillitis, and pneumonia) in corticosteroids group (0.7%) and 3 in placebo group (1.1%)

*Reflect investigators' attempts not only to detect adverse effect attributable to steroids, but also treatment failures, relapses, and complications related to disease.

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work. An important additional contribution of the new evidence is that it extends the applicability beyond patients with severe sore throat treated with antibiotics for group A β haemolytic streptococcus pharyngitis in the emergency department, to a broader range of patients not treated with antibiotics.

We explored and were able to dismiss subgroup effects, with one exception: the reduction in mean time to complete resolution of pain was greater with intramuscular than with oral corticosteroids. The subgroup effect and its direction was specified a priori, the difference between subgroups was relatively large (about 21 hours), and chance seems an unlikely explanation (P<0.001). Credibility of the effect, however, is undermined[34] as the effect modification is suggested by comparison between rather than within studies, and we found no similar difference in any other outcome. In addition, the only randomised controlled trial that compared oral and intramuscular treatment with dexamethasone reported no significant difference in any outcome.[25]

The few serious adverse effects in the included trials occurred with similar frequency in the intervention and control groups, although some minor adverse effects reported by patients might not always have been noted. Potential adverse effects that appear later are more likely to occur after repeated use or are rare would not have been captured in the trials. Recent observational studies have raised the possibility of extremely rare but serious adverse effects after short courses of corticosteroids.[35] The quality of this evidence is, for several reasons, low with respect to the current question. The studies used observational designs from large databases with suboptimal verification of diagnoses; serious confounding by indication raises the possibility that the association is a result of the underlying disease process (such as acute inflammation or exacerbation) rather than the corticosteroids themselves; and indirectness in that the doses used in the trials were lower and the duration of treatment was considerably shorter than the duration in the observational studies. Among children, a recent overview of reviews looked at evidence from 44 randomised controlled trials on conditions that required a short course of steroids (such as asthma, bronchiolitis, croup, wheeze, and pharyngitis/tonsillitis) and reported no major adverse events.[36]

Despite previous evidence that corticosteroids might be beneficial, several groups and guidelines currently recommend against their routine use on the basis that evidence was applicable only to patients with severe pharyngitis who were also prescribed antibiotics in an emergency department.[1 37 38] The body of evidence now includes a broader representation of patients. The largest and most recent randomised controlled trial included 565 patients presenting to their general practitioner rather than an emergency department, and none of the patients initially received antibiotics.[16] We found no subgroup differences with respect to patient group: the evidence seems to apply equally to patients who did and did not receive antibiotics. The evidence also seems to apply equally to patients with sore throat from group A β haemolytic streptococcus pharyngitis and some with sore throat negative for group A β haemolytic streptococcus.

In the five trials that reported co-interventions, about 80% of the participants received additional analgesics such as paracetamol and NSAIDs. Therefore, a single dose of corticosteroids seems to further reduce pain when used in combination with other analgesics. Although the benefits are relatively small, many patients are likely to consider them important. Patients with less severe sore throat, however, will obtain less absolute benefit from corticosteroids. Thus, the balance of benefits and harms almost certainly depends on the severity of the patient's sore throat. With available evidence suggesting that serious adverse effects are rare or absent, the addition of one or two doses of steroids to the symptomatic management of sore throat is likely to appeal to many patients. More high quality data would be helpful to fully understand the net balance of benefits and harms according to severity of symptoms, particularly in primary care settings.

Linked articles in this *BMJ* Rapid Recommendations cluster

- Aertgeerts B, Agoritsas T, Siemieniuk RAC, et al. Corticosteroids for sore throat: a clinical practice guideline. *BMJ* 2017;358:j4090 doi:10.1136/bmj.j4090
  summary of the results from the Rapid Recommendation process
- Magic App (www.magicapp.org)
  expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

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Contributors: BS and RACS contributed equally to this work. TA, RACS, POV, and GHG conceived the study idea. BS, RACS, RB-P, TA coordinated the systematic review. BS, RACS, and TA wrote the first draft of the manuscript. BS and LL designed the search strategy. BS, RACS, LL, DP, and RB-P screened abstracts and full texts. BS, RACS, RB-P, and DP acquired the data and judged risk of bias in the studies. BS performed the data analysis and is guarantor. All authors interpreted the data analysis and critically revised the manuscript.

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Ethical approval: Not required.

Data sharing: All data are freely available within the appendices. No additional data available.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

1 Pelucchi C, Grigoryan L, Galeone CESCMID Sore Throat Guideline Group. Guideline for the management of acute sore throat. *Clin Microbiol Infect* 2012;18(Suppl 1):1-28. doi:10.1111/j.1469-0691.2012.03766.x.
2 Principi N, Bianchini S, Baggi E, Esposito S. No evidence for the effectiveness of systemic corticosteroids in acute pharyngitis, community-acquired pneumonia and acute otitis media. *Eur J Clin Microbiol Infect Dis* 2013;32:151-60. doi:10.1007/s10096-012-1747-y.
3 Shaikh N, Leonard E, Martin JM. Prevalence of streptococcal pharyngitis and streptococcal carriage in children: a meta-analysis. *Pediatrics* 2010;126:e557-64. doi:10.1542/peds.2009-2648.
4 Herath VC, Carapetis J. Sore throat: Is it such a big deal anymore?*J Infect* 2015;71(Suppl 1):S101-5. doi:10.1016/j.jinf.2015.04.010.
5 Kenealy T. Sore throat. *BMJ Clin Evid* 2011;2011:1509.
6 Bally M, Dendukuri N, Rich B. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ* 2017;357:j1909. doi:10.1136/bmj.j1909.
7 Thomas M, Del Mar C, Glasziou P. How effective are treatments other than antibiotics for acute sore throat?*Br J Gen Pract* 2000;50:817-20.
8 Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010;340:c2096. doi:10.1136/bmj.c2096.
9 Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. *Cochrane Database Syst Rev* 2013;(11):CD000023. doi:10.1002/14651858.CD000023.pub4.
10 van Driel ML, De Sutter A, Deveugele M. Are sore throat patients who hope for antibiotics actually asking for pain relief?*Ann Fam Med* 2006;4:494-9. doi:10.1370/afm.609.
11 Hayward G, Thompson M, Heneghan C, Perera R, Del Mar C, Glasziou P. Corticosteroids for pain relief in sore throat: systematic review and meta-analysis. *BMJ* 2009;339:b2976. doi:10.1136/bmj.b2976.
12 Hayward G, Thompson MJ, Perera R, Glasziou PP, Del Mar CB, Heneghan CJ. Corticosteroids as standalone or add-on treatment for sore throat. *Cochrane Database Syst Rev* 2012;10:CD008268. doi:10.1002/14651858.CD008268.pub2.
13 Korb K, Scherer M, Chenot JF. Steroids as adjuvant therapy for acute pharyngitis in ambulatory patients: a systematic review. *Ann Fam Med* 2010;8:58-63. doi:10.1370/afm.1038.
14 Wing A, Villa-Roel C, Yeh B, Eskin B, Buckingham J, Rowe BH. Effectiveness of corticosteroid treatment in acute pharyngitis: a systematic review of the literature. *Acad Emerg Med* 2010;17:476-83. doi:10.1111/j.1553-2712.2010.00723.x.
15 Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:i5191. doi:10.1136/bmj.i5191.
16 Hayward GN, Hay AD, Moore MV. Effect of Oral Dexamethasone Without Immediate Antibiotics vs Placebo on Acute Sore Throat in Adults: A Randomized Clinical Trial. *JAMA* 2017;317:1535-43. doi:10.1001/jama.2017.3417.
17 Aertgeerts B, Agoritsas T, Siemieniuk RAC. Corticosteroids for sore throat: a clinical practice guideline. *BMJ* 2017;358:j4090.
18 Higgins JPT, Altman DG, Gøtzsche PCCochrane Bias Methods GroupCochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928. doi:10.1136/bmj.d5928.
19 Akl EA, Sun X, Busse JW. Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. *J Clin Epidemiol* 2012;65:262-7. doi:10.1016/j.jclinepi.2011.04.015.
20 Guyatt GH, Oxman AD, Vist GEGRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. doi:10.1136/bmj.39489.470347.AD.
21 Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003;326:219. doi:10.1136/bmj.326.7382.219
22 Sterne JA, Sutton AJ, Ioannidis JP. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002. doi:10.1136/bmj.d4002
23 O'Brien JF, Meade JL, Falk JL. Dexamethasone as adjuvant therapy for severe acute pharyngitis. *Ann Emerg Med* 1993;22:212-5. doi:10.1016/S0196-0644(05)80205-7
24 Marvez-Valls EG, Ernst AA, Gray J, Johnson WD. The role of betamethasone in the treatment of acute exudative pharyngitis. *Acad Emerg Med* 1998;5:567-72. doi:10.1111/j.1553-2712.1998.tb02462.x
25 Wei JL, Kasperbauer JL, Weaver AL, Boggust AJ. Efficacy of single-dose dexamethasone as adjuvant therapy for acute pharyngitis. *Laryngoscope* 2002;112:87-93. doi:10.1097/00005537-200201000-00016.
26 Ahn JH, Woo WK, Kim YS. Efficacy of adjuvant short term oral steroid therapy for acute pharyngitis. *Korean J Otolaryngol Head Neck Surg* 2003;46:971-4.
27 Bulloch B, Kabani A, Tenenbein M. Oral dexamethasone for the treatment of pain in children with acute pharyngitis: a randomized, double-blind, placebo-controlled trial. *Ann Emerg Med* 2003;41:601-8. doi:10.1067/mem.2003.136.
28 Olympia RP, Khine H, Avner JR. Effectiveness of oral dexamethasone in the treatment of moderate to severe pharyngitis in children. *Arch Pediatr Adolesc Med* 2005;159:278-82. doi:10.1001/archpedi.159.3.278.
29 Niland ML, Bonsu BK, Nuss KE, Goodman DG. A pilot study of 1 versus 3 days of dexamethasone as add-on therapy in children with streptococcal pharyngitis. *Pediatr Infect Dis J* 2006;25:477-81. doi:10.1097/01.inf.0000219469.95772.3f.
30 Tasar A, Yanturali S, Topacoglu H, Ersoy G, Unverir P, Sarikaya S. Clinical efficacy of dexamethasone for acute exudative pharyngitis. *J Emerg Med* 2008;35:363-7. doi:10.1016/j.jemermed.2007.11.029.
31 Kiderman A, Yaphe J, Bregman J, Zemel T, Furst AL. Adjuvant prednisone therapy in pharyngitis: a randomised controlled trial from general practice. *Br J Gen Pract* 2005;55:218-21.
32 Powell CV, Kelly AM, Williams A. Determining the minimum clinically significant difference in visual analog pain score for children. *Ann Emerg Med* 2001;37:28-31. doi:10.1067/mem.2001.111517.
33 Alonso-Coello P, Carrasco-Labra A, Brignardello-Petersen R. Systematic reviews experience major limitations in reporting absolute effects. *J Clin Epidemiol* 2016;72:16-26. doi:10.1016/j.jclinepi.2015.11.002.
34 Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010;340:c117. doi:10.1136/bmj.c117.
35 Waljee AK, Rogers MA, Lin P. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ* 2017;357:j1415. doi:10.1136/bmj.j1415.
36 Fernandes RM, Oleszczuk M, Woods CR, Rowe BH, Cates CJ, Hartling L. The Cochrane Library and safety of systemic corticosteroids for acute respiratory conditions in children: an overview of reviews. *Evid Based Child Health* 2014;9:733-47. doi:10.1002/ebch.1980.
37 Management of sore throat and indications for tonsillectomy. A national clinical guideline. Scottish Intercollegiate Guideline Network (SIGN), April 2010. http://www.sign.ac.uk/assets/sign117.pdf
38 Shulman ST, Bisno AL, Clegg HW. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2012;55:1279-82. doi:10.1093/cid/cis847.

Appendix 1: Search terms and strategies
Appendix 2: Summary of risk of bias assessments among the included trials
Appendix 3: Supplementary tables and figure

CHAPTER 9: Antibiotics after incision and drainage for uncomplicated skin abscesses: a clinical practice guideline

The *Rapid Recommendations* panel recommends clindamycin or trimethoprim-sulfamethoxazole for patients with skin abscesses, with a preference for trimethoprim-sulfamethoxazole if both are options based on local risk of antibiotic resistance. The balance of desirable and undesirable consequences was close, and we therefore include a detailed description of what the shared-decision making process should look like.

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RAPID RECOMMENDATIONS

Antibiotics after incision and drainage for uncomplicated skin abscesses: a clinical practice guideline

Mieke Vermandere,[1] Bert Aertgeerts,[1 2] Thomas Agoritsas,[3 4] Catherine Liu,[5] Jako Burgers,[6 7] Arnaud Merglen,[8] Patrick Mbah Okwen,[9] Lyubov Lytvyn,[3 10] Shunjie Chua,[11] Per O Vandvik,[12 13] Gordon H Guyatt,[3] Claudia Beltran-Arroyave,[14] Valéry Lavergne,[15] Reinhart Speeckaert,[16] Finn E Steen,[17] Victoria Arteaga,[18] Rachelle Sender,[19] Shelley McLeod,[20] Xin Sun,[21] Wen Wang,[21] Reed A C Siemieniuk[3 22]

Full author details can be found at the end of the article

Correspondence to: R Siemieniuk
reed.siemieniuk@medportal.ca

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This *BMJ* Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (www.magicproject.org) and *The BMJ*. A summary is offered here and the full version including decision aids is on the MAGICapp (www.magicapp.org), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualisation of our recommendations to local or other contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact *The BMJ* for permission to reuse content in this article.

What role do antibiotics have in the treatment of uncomplicated skin abscesses after incision and drainage? A recent study suggested that, for small uncomplicated skin abscesses, antibiotics after incision and drainageimprove the chance of short term cure compared with placebo. Triggered by this trial, the Rapid Recommendation team produced a new systematic review. Relying on this review and using the GRADE framework according to the BMJ Rapid Recommendation process, an expert panel makes a weak recommendation in favour of trimethoprim-sulfamethoxazole (TMP-SMX, co-trimoxazole) or clindamycin in addition to incision and drainage over incision and drainage alone. For patients who have chosen to initiate antibiotics, the panel issues a strong recommendation for TMP-SMX or clindamycin rather than a cephalosporin and a weak recommendation for TMP-SMX rather than clindamycin. The box overleaf shows the articles and evidence linked to this Rapid Recommendation. The infographic presents the recommendations together with other pertinent information, including an overview of the absolute benefits and harms of candidate antibiotics in the standard GRADE format. The panel emphasises shared decision making in the choice of whether to initiate antibiotics and in which antibiotic to use, because the desirable and undesirable consequences are closely balanced: clinicians using MAGICapp (http://magicapp.org/goto/guideline/jlRvQn/section/ER5RAn) will find decision aids to support the discussion with patients. Table 2 below shows any evidence that has emerged since the publication of this article.

WHAT YOU NEED TO KNOW

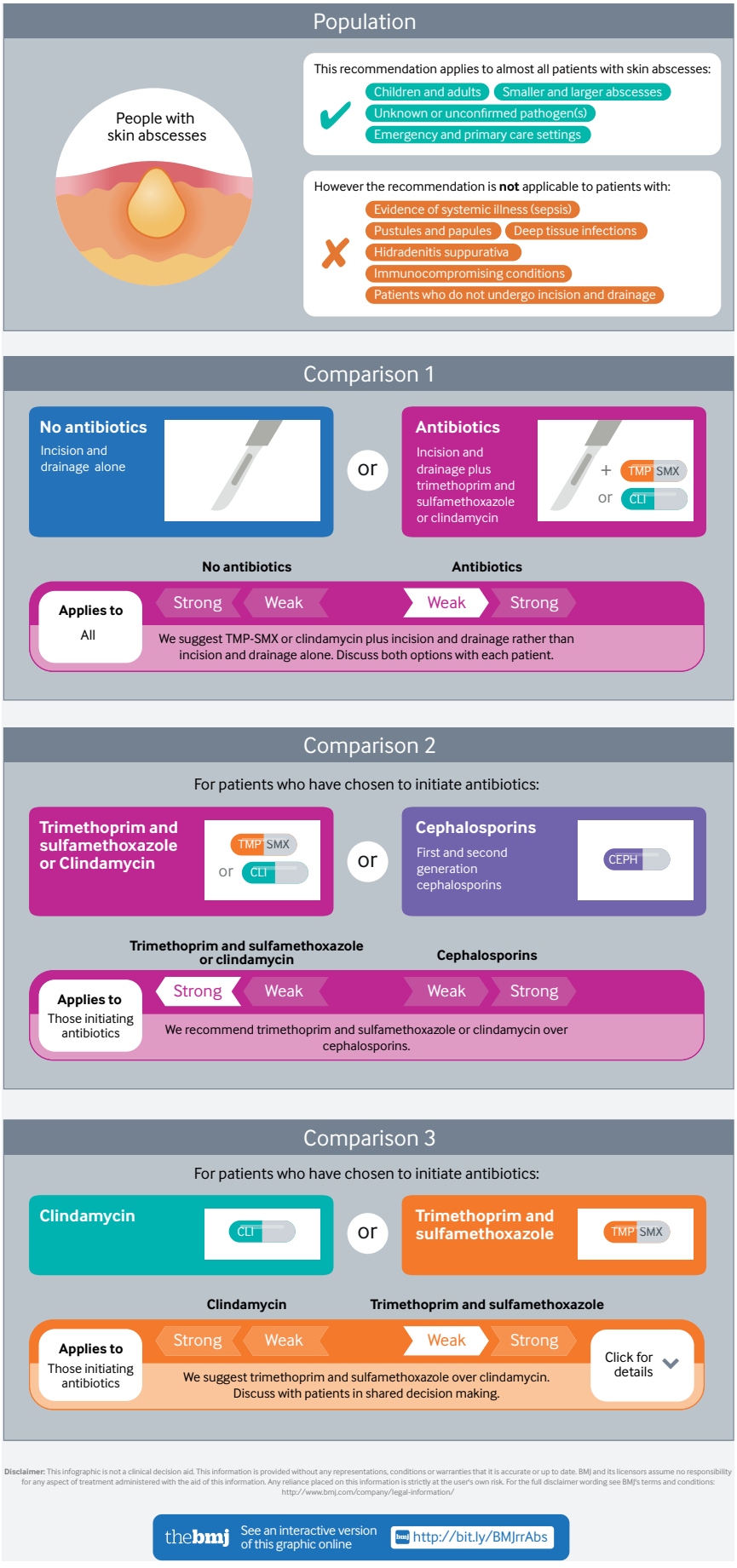
- For bacterial skin infections, we suggest using trimethoprim-sulfamethoxazole (TMP-SMX) or clindamycin in addition to incision and drainage rather than incision and drainage alone, but we emphasise the need for shared decision making because the modest benefits of TMP-SMX or clindamycin will be outweighed by the side effects and burdens for many patients
- TMP-SMX or clindamycin modestly reduces pain and treatment failure and probably reduces abscess recurrence, but increase the risk of adverse effects including nausea and diarrhoea
- We suggest TMP-SMX rather than clindamycin because TMP-SMX has a lower risk of diarrhoea
- Cephalosporins in addition to incision and drainage are probably not more effective than incision and drainage alone in preventing treatment failure in most settings
- We take an individual patient perspective in creating our recommendations. From a societal perspective, the modest benefits from adjuvant antibiotics may not outweigh the risk of antimicrobial resistance in the community

Current understanding

A skin abscess is an isolated collection of pus within the dermis and deeper skin tissues. Uncomplicated skin abscesses are collections of pus within the skin structures and are usually caused by bacterial infections. Careful history and clinical examination are usually sufficient to diagnose a skin abscess.[1-3] Skin abscesses present as single or multiple tender, erythematous, indurated nodules, often surrounded by an area of erythema or swelling.[1] Fluctuance beneath the skin often indicates a fluid filled cavity. There may be a pustule at the area where the abscess is closest to the skin or spontaneous drainage of pus.[3] The use of point-of-care ultrasonography can help differentiate an abscess from other soft tissue infections in the emergency department.[4]

Skin infections are common. More than 4% of people seek treatment for skin infections annually in the United States.[5] In European countries, it may be less common: in Belgium and the Netherlands about 0.5-0.6% visit their general practitioner with bacterial skin infections each year.[6-8]

Identifying the infecting pathogen may not be necessary for treating uncomplicated skin abscesses, but cultures can provide helpful information in patients with recurrent abscesses or systemic illness.[1 3] The most



Linked articles in this BMJ Rapid Recommendation cluster

- Vermandere M, Aertgeerts B, Agoritsas T, et al. Antibiotics after incision and drainage for uncomplicated skin abscesses: a clinical practice guideline. *BMJ* 2018;360:k243
  - Summary of the results from the Rapid Recommendation process
- Wang W, Chen W, Liu Y, et al. Antibiotics for uncomplicated skin abscesses: systematic review and network meta-analysis. *BMJ Open* 2018;8:e020991
  - Review of all available randomised trials that assessed antibiotics for uncomplicated skin abscesses
- MAGICapp (http://magicapp.org/goto/guideline/jlRvQn/section/ER5RAn)
  - Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

common pathogens are *Staphylococcus aureus*, most often methicillin-resistant (MRSA), and several other bacteria, most originating from the skin flora.[1 9] MRSA accounts for a substantial number of visits by patients with skin and soft tissue infections.[10-12]

Table 1 summarises current management guidelines, which do not recommend antibiotics for uncomplicated skin abscesses.

The evidence

To inform the recommendations, the guideline panel requested a systematic review of randomised controlled trials (RCTs) on the effects of adjuvant antibiotic therapy compared with no antibiotic therapy in addition to incision and drainage in patients with uncomplicated skin abscesses.[15]

A large RCT published in March 2016 suggested that TMP-SMX treatment resulted in a higher cure rate than placebo among patients with a drained cutaneous abscess.[16] Another RCT published in June 2017 found that, compared with incision and drainage alone, clindamycin or TMP-SMX in addition to incision and drainage improved short term outcomes in patients who had an uncomplicated skin abscess.[5] The Rapid Recommendations team believed these two trials, in addition to the existing body of evidence, might change practice.[17]

Figure 1 gives an overview of the characteristics of patients and trials included in the systematic review of the effects of antibiotics on uncomplicated skin abscesses. There were 14 RCTs: eight included a comparison of antibiotics versus no antibiotics, and seven included a comparison of two different antibiotics.

Table 1 | Current recommendations for antibiotics in patients with skin abscesses*

	Recommendation	Situations where antibiotics are recommended
IDSA[2]	Against	Systemic illness
EBM Guidelines[13]	Against	Systemic illness, extensive tissue damage, nasal region, immunocompromising conditions, artificial joint
NHG[14]	Against	1 dose in patients with immunocompromising conditions, artificial joint, or at high risk of endocarditis
ESCMID	No recommendation available	N/A

*These guidelines have not taken account of the new evidence captured in our Rapid Recommendations.
IDSA=Infectious Diseases Society of America; EBM=Evidence-Based Medicine; NHG=Nederlands Huisartsen Genootschap; ESCMID=European Society for Clinical Microbiology and Infectious Diseases.

HOW THE RECOMMENDATION WAS CREATED

The scope of the recommendation and the outcomes important to patients were defined by an international guideline panel consisting of two adults with lived experience of skin abscesses, one adult with lived experience as a carer for a child with skin abscess, five general practitioners, three paediatric or adult infectious disease physicians, four general internists, a general paediatrician, a dermatologist, and several health research methodologists. They requested a systematic review on the benefits and harms of different antibiotics to inform the recommendation.[15] The panel then met online to discuss the evidence and to formulate specific recommendations. As with all *BMJ* Rapid Recommendations, no panel member had financial conflicts of interest; intellectual and professional conflicts were minimised and managed (see appendix 1 on bmj.com).[17]

The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation, including using the GRADE approach to critically appraise the evidence and to move from evidence to recommendations (appendix 2 on bmj.com).[17 31-33] The panel initially identified patient-important outcomes and subgroup hypotheses needed to inform the recommendation. When creating the recommendation, the panel considered the balance of benefits, harms, costs, burdens of the treatments, the quality of evidence for each outcome, typical patient values and preferences and their expected variations, as well as acceptability.[34] Recommendations can be strong or weak, for or against a course of action. The recommendations take a patient-centred perspective which de-emphasises public health, societal, and health payer point of view.

Explicit descriptions of abscess definitions, for each trial, were summarised in the accompanying systematic review (table C of appendix 2).[15] The largest trial specifically focused on small abscesses (all <5 cm diameter and about half ≤2 cm) in patients who had no signs of systemic infection.[5] The RCTs included participants with skin abscesses anywhere on the body.

Eleven trials reported study setting, of which nine were conducted in emergency departments,[5 16 18-23] one in outpatient dermatology clinics,[24] and one in an Integrated Soft Tissue Infection Services (ISIS) clinic involving patients with high rates of comorbidity, such as infection with hepatitis C, hepatitis B, or HIV.[25] The RCTs included children and adults. Almost all patients underwent incision and drainage for their skin abscess. The most common pathogen was MRSA (49-88%) followed by methicillin-sensitive *Staphylococcus aureus* (MSSA, 9-18%).

Understanding the recommendation

Absolute benefits and harms

The infographic provides an overview of the recommendations and the absolute benefits and harms of different antibiotics. Estimates of the baseline risk for side effects are derived from the control groups of the trials in the systematic review. Detailed information can also be viewed through MAGICapp, including consultation decision aids designed to support shared decision making with patients.[26]

This clinical practice guideline is applicable to patients with uncomplicated skin abscesses, which means that it is not applicable to patients with evidence of systemic

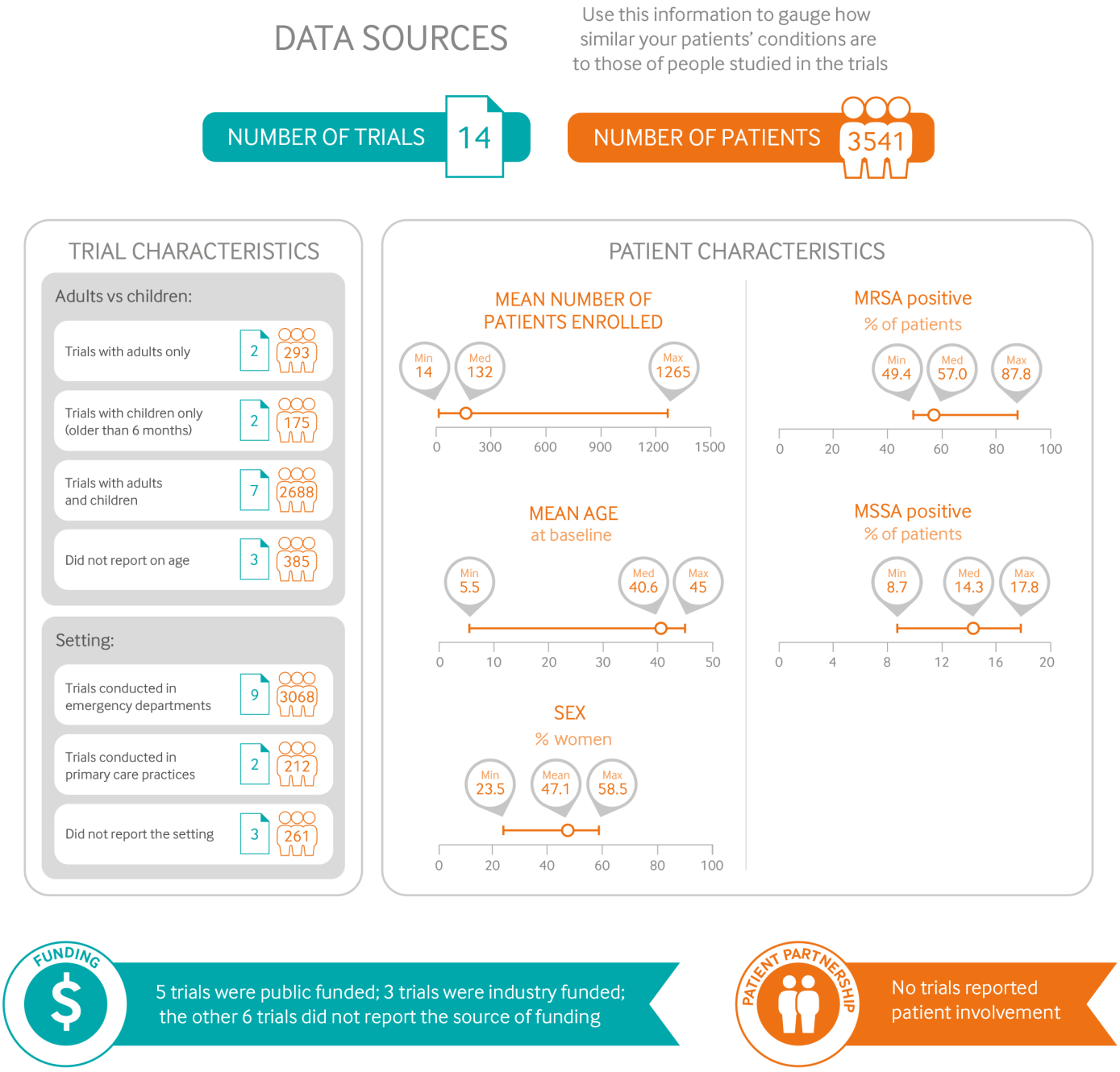


Fig 1 | Characteristics of patients and trials included in systematic review of the effects of antibiotics on uncomplicated skin abscesses. (MRSA=meticillin resistant *Staphylococcus aureus*; MSSA=meticillin susceptible *S aureus*)

illness (such as sepsis), deep tissue infections, superficial infections (such as pustules and papules), hidradenitis suppurativa, or immunocompromising conditions, and patients who do not undergo incision and drainage.

The first recommendation relates to the usefulness of adjuvant TMP-SMX or clindamycin compared with no antibiotics in addition to incision and drainage. The effects of other antibiotics are speculative, except for cephalosporins, which are probably less effective or not effective (see evidence summary for recommendation No 2). Compared with no antibiotics, TMP-SMX or clindamycin reduces the absolute risk of treatment failure by approximately 5% at one month (high quality evidence). In patients who were cured, these antibiotics reduced the absolute risk of recurrence at three months by approximately 8% (high quality evidence). When considering both treatment failure and abscess recurrence, antibiotic therapy thus provides an approximate 13% reduction (high quality evidence). TMP-SMX or clindamycin probably provides a modest reduction in pain (tenderness) during treatment (7% fewer), and a small reduction in hospitalisation (2% fewer) and in similar infections among household contacts (2% fewer) (all moderate quality evidence). Considering the characteristics of involved patients and medical conditions may differ between emergency departments and general

practices, antibiotics may confer an even smaller benefit in patients who present to their GP. Antibiotics probably do not reduce the risk of serious or invasive infections or death (moderate quality evidence).

The occurrence of adverse effects depends on the antibiotic. With clindamycin, the risk of gastrointestinal side effects (predominately diarrhoea) is approximately 10% higher than with no antibiotics (high quality evidence). TMP-SMX probably increases the risk of gastrointestinal side effects by a smaller amount (approximately 2%; moderate quality evidence), and it is predominately nausea rather than diarrhoea. The severity of antibiotic-associated diarrhoea was not described, but is likely to range from mild to severe. Two large trials monitored for *Clostridium difficile* infection with routine clinical monitoring and no such infection occurred in any treatment arm.[15]

Overall, there is no important difference in treatment failure between TMP-SMX and clindamycin (high quality evidence). In patients who were initially cured, one study suggested that clindamycin may reduce the risk of early recurrence at one month by approximately 7% (low quality evidence),[5] but the confidence interval was wide and this result is inconsistent with indirect evidence from other RCTs, which suggests that the reduction in risk of abscess recurrence compared with placebo is similar for both TMP-SMX and clindamycin. Whether clindamycin reduces abscess recurrence more than TMP-SMX is therefore uncertain (low quality evidence). Local resistance patterns may affect the relative effectiveness of each antibiotic option.[27-30] Clindamycin has a 10% higher risk of antibiotic-associated diarrhoea than TMP-SMX (high quality evidence).

The panel also considered evidence for cephalosporins compared with TMP-SMX and clindamycin used for uncomplicated skin abscesses. The network meta-analysis suggested that, at least in settings with a substantial prevalence of MRSA, cephalosporins in addition to incision and drainage probably do not reduce treatment failure compared with incision and drainage alone (moderate quality evidence). Both early and later generation cephalosporins probably confer a higher risk of treatment failure compared with either TMP-SMX or clindamycin (moderate quality evidence). The RCTs investigating cephalosporins did not report sufficient information to directly compare other outcomes. However, the panel felt that cephalosporins were unlikely to provide any other benefits if they do not reduce the risk of treatment failure compared with placebo (low quality evidence). This evidence directly applies to almost all settings where the prevalence of MRSA is more than 10%.[1 2]

The panel is confident that the evidence applies to almost all patients with uncomplicated skin abscesses treated with incision and drainage: adults and children, patients presenting to emergency departments and to primary care practices, smaller and larger abscesses, first abscess occurrences and recurrences, and abscesses with unknown infection pathogens. The systematic review and meta-analyses contained adequate representation from such groups and settings, and results were consistent between pre-specified subgroups.[15]

Values and preferences

The panel believes that there is a high degree of variability between patients and carers weighing the expected desirable and undesirable consequences of antibiotic therapy compared with no antibiotic therapy. This variation is reflected in the weak recommendation, which warrants shared decision making to ensure that each individual's decision is in line with what they consider most important. The expected benefit of antibiotic therapy in reducing pain, risk of treatment failure, and recurrence is modest, but large enough that the panel anticipates that most fully informed patients would value these benefits sufficiently to choose antibiotic treatment. This might particularly be the case when, for example, the abscess is very painful, perhaps because of location in sensitive places (such as groin, axillae, etc).

For patients who decide to initiate antibiotic treatment, reasonable choices include either TMP-SMX or clindamycin. In some settings, cephalosporins or other antibiotics are often prescribed for skin abscesses. Given that, in most circumstances, cephalosporins probably do not provide any additional benefit beyond incision and drainage alone, the panel felt that all or almost all patients would choose to use antibiotic options with proven efficacy (TMP-SMX or clindamycin), hence the strong recommendation against cephalosporins.

People who place a higher value on the possibility of avoiding abscess recurrence may choose clindamycin, while those who place a higher value on avoiding diarrhoea and on minimising costs are likely to prefer TMP-SMX.

Person-centred versus societal perspective (impact on antibiotic resistance)

The recommendations explicitly take a person-centred perspective rather than a public health or societal perspective. The use of antibiotics is associated with the emergence of antibiotic resistance within the community and may increase the risk of antibiotic resistant infections in community members. The increasing rates of antimicrobial resistance are a public health priority. From a societal perspective, it is possible that the modest benefits from adjuvant antibiotics in this scenario would not outweigh the risk of increased antimicrobial resistance in the community. However, the impact of an individual course of antibiotics on community resistance rates is unknown. Therefore, whether antibiotics in this situation provide a net benefit or harm to society is highly speculative. Clinicians engaging in shared decision making can also address the issue of antibiotic resistance or the local prevalence of other pathogens (such as Panton-Valentine leukocidin (PVL) positive *Staphylococcus aureus*) with patients facing this decision.

Practical issues and other considerations

Figure 2 outlines the key practical issues for patients and clinicians discussing initiating antibiotics for uncomplicated skin abscesses after incision and drainage, which are also accessible as decision aids along with the evidence in an expanded format to support shared decision making in MAGICapp. The antibiotic course was typically

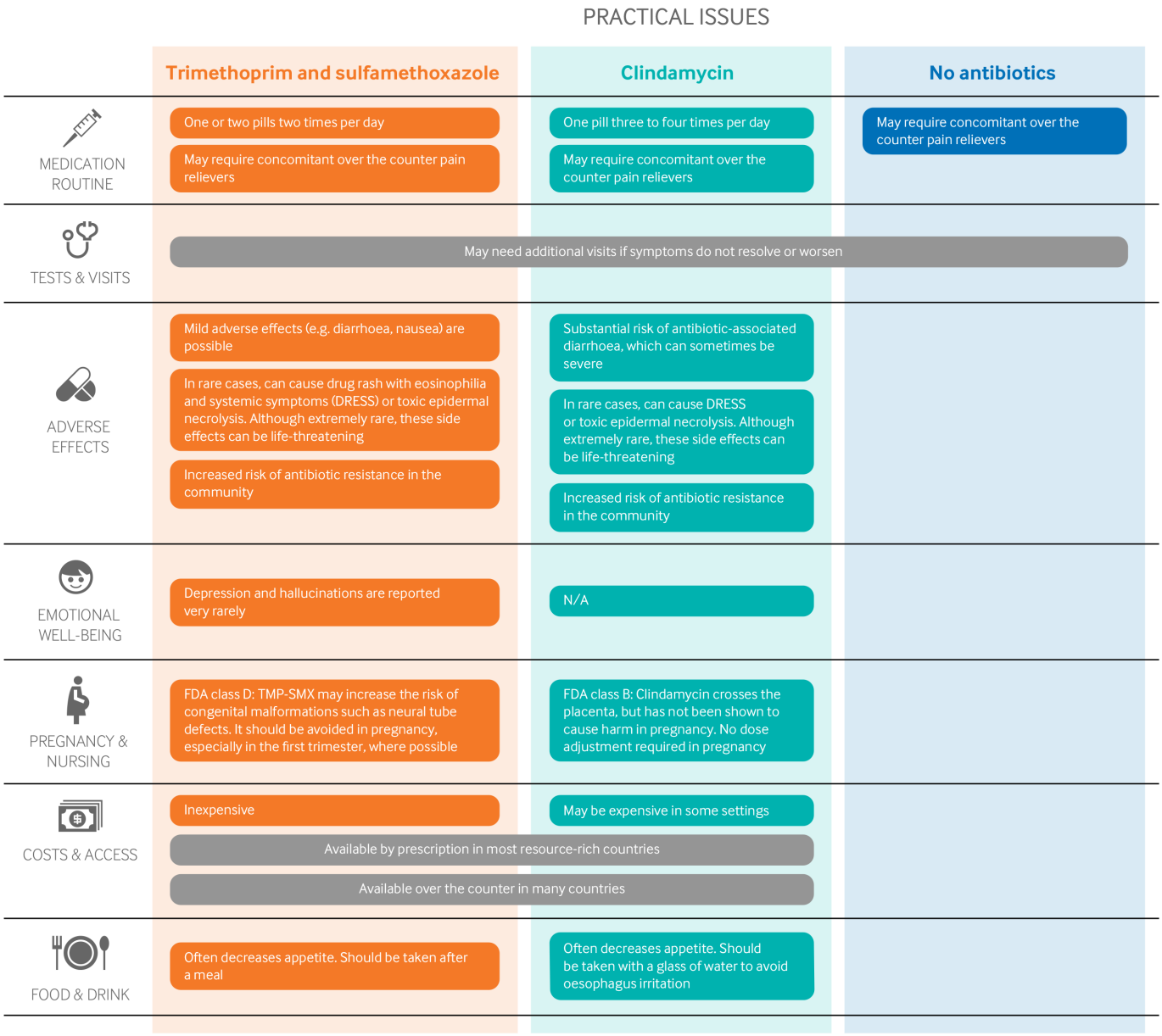


Fig 2| Practical issues about use of antibiotics after incision and drainage of uncomplicated skin abscesses. (FDA=US Food and Drug Administration)

five to 10 days in the RCTs, and dosing varied. TMP-SMX may slightly increase the risk of congenital malformations, including neural tube defects, when prescribed to pregnant women.

Costs and resources

TMP-SMX is inexpensive; clindamycin is probably more expensive in most places. However, the overall impact on costs to the individual and the healthcare payer are uncertain when the consequences of each option are considered.

Future research

Key research questions to inform decision makers and future guidelines are:

- What is the impact of different types of antibiotics in settings where MRSA is rare (prevalence <10%)?
- Do antibiotics have different effects in different populations, such as people who are immunocompromised or in people with recurrent skin abscesses?
- What are the long term effects (such as >6 months) of antibiotics on abscess recurrence, *Clostridium difficile* infection, and MRSA resistance to TMP-SMX or clindamycin?
- Is a shorter course of antibiotics (such as 5 days) as effective as a longer course (10 days)?
- Is topical therapy (such as iodine, honey, silver, other antimicrobials) effective for treating uncomplicated skin abscesses compared with systemic therapy? Do other adjunctive measures, such as nasal decontamination or antisepsis for the body, reduce the risk that skin abscesses will recur?

Table 2 | New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article.				

EDUCATION INTO PRACTICE

- Do you currently consider antibiotics for patients with uncomplicated skin abscesses after surgical treatment?
- What information could you share with your patient to help reach a decision together?
- Would you consider using online decision aid tools (such as the one available on MAGICapp) to facilitate shared decision making?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Three people with lived experience of skin abscesses were full panel members: two had previously experienced skin abscesses before (one with recurrent abscesses), and one person is a parent of a child who experienced a skin abscess. These panel members identified patient-important outcomes, and led the discussion on values and preferences. These patient partners agreed that, although pain reduction was the most important outcome to them, these values may not be shared by all patients. The close balance between desirable and undesirable consequences made it difficult for them (and the panel) to decide which options most individuals would choose.

Updates to this article

Table 2 shows evidence which has emerged since the publication of this article. As new evidence is published, a group will assess the new evidence and make a judgment on to what extent it is expected to alter the recommendation.

Competing interests: All authors have completed the *BMJ* Rapid Recommendations interests disclosure form and a detailed, contextualised description of all disclosures is reported in appendix 2 on bmj.com. As with all *BMJ* Rapid Recommendations, the executive team and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions.

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Transparency: B Aertgeerts affirms that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

1 Stevens DL, Bisno AL, Chambers HF, et al. Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2014;59:e10-52. doi:10.1093/cid/ciu296. pmid:24973422.
2 Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. *Clin Infect Dis* 2011;52:285-92. doi:10.1093/cid/cir034. pmid:21217178.
3 Mistry RD. Skin and soft tissue infections. *Pediatr Clin North Am* 2013;60:1063-82. doi:10.1016/j.pcl.2013.06.011. pmid:24093896.
4 Barbic D, Chenkin J, Cho DD, Jelic T, Scheuermeyer FX. In patients presenting to the emergency department with skin and soft tissue infections what is the diagnostic accuracy of point-of-care ultrasonography for the diagnosis of abscess compared to the current standard of care? A systematic review and meta-analysis. *BMJ Open* 2017;7:e013688. doi:10.1136/bmjopen-2016-013688. pmid:28073795.
5 Daum RS, Miller LG, Immergluck L, et al. DMID 07-0051 Team. A placebo-controlled trial of antibiotics for smaller skin abscesses. *N Engl J Med* 2017;376:2545-55. doi:10.1056/NEJMoa1607033 pmid:28657870.
6 NIVEL Primary care database: Netherlands Institute for Health Services Research. 2016. www.nivel.nl/en/dossier/nivel-primary-care-database
7 FaMe-net. 2014. www.transhis.nl/language/nl/.
8 Truyers C, Goderis G, Dewitte H, Akker Mv, Buntinx F. The Intego database: background, methods and basic results of a Flemish general practice-based continuous morbidity registration project. *BMC Med Inform Decis Mak* 2014;14:48. doi:10.1186/1472-6947-14-48 pmid:24906941.
9 Moran GJ, Krishnadasan A, Gorwitz RJ, et al. EMERGEncy ID Net Study Group. Methicillin-resistant S. aureus infections among patients in the emergency department. *N Engl J Med* 2006;355:666-74. doi:10.1056/NEJMoa055356. pmid:16914702.
10 Ray GT, Suaya JA, Baxter R. Microbiology of skin and soft tissue infections in the age of community-acquired methicillin-resistant Staphylococcus aureus. *Diagn Microbiol Infect Dis* 2013;76:24-30. doi:10.1016/j.diagmicrobio.2013.02.020 pmid:23537783.
11 Hersh AL, Chambers HF, Maselli JH, Gonzales R. National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. *Arch Intern Med* 2008;168:1585-91. doi:10.1001/archinte.168.14.1585. pmid:18663172.
12 Karamatsu ML, Thorp AW, Brown L. Changes in community-associated methicillin-resistant Staphylococcus aureus skin and soft tissue infections presenting to the pediatric emergency department: comparing 2003 to 2008. *Pediatr Emerg Care* 2012;28:131-5. doi:10.1097/PEC.0b013e318243fa36. pmid:22270497.
13 Salava A. Skin abscess and folliculitis. *Evidence-Based Med Guideline*. 2017. www.ebm-guidelines.com/dtk/ebmg/home.
14 Bons S, Bouma M, Draijer L, et al. NHG-standaard bacteriële huidinfecties (tweede herziening). 2017. www.nhg.org/standaarden/volledig/nhg-standaard-bacteriele-huidinfecties.
15 Wang W. Antibiotics for uncomplicated skin abscesses: systematic review and network meta-analysis. *BMJ Open* 2018;8:e020991.
16 Talan DA, Mower WR, Krishnadasan A, et al. Trimethoprim-sulfamethoxazole versus placebo for uncomplicated skin abscess. *N Engl J Med* 2016;374:823-32. doi:10.1056/NEJMoa1507476. pmid:26962903.
17 Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:i5191. doi:10.1136/bmj.i5191 pmid:27680768.
18 Duong M, Markwell S, Peter J, Barenkamp S. Randomized, controlled trial of antibiotics in the management of community-acquired skin abscesses in the pediatric patient. *Ann Emerg Med* 2010;55:401-7. doi:10.1016/j.annemergmed.2009.03.014. pmid:19409657.
19 Llera JL, Levy RC. Treatment of cutaneous abscess: a double-blind clinical study. *Ann Emerg Med* 1985;14:15-9. doi:10.1016/S0196-0644(85)80727-7 pmid:3880635.
20 Schmitz GR, Bruner D, Pitotti R, et al. Randomized controlled trial of trimethoprim-sulfamethoxazole for uncomplicated skin abscesses in patients at risk for community-associated methicillin-resistant Staphylococcus aureus infection. *Ann Emerg Med* 2010;56:283-7. doi:10.1016/j.annemergmed.2010.03.002. pmid:20346539.
21 Macfie J, Harvey J. The treatment of acute superficial abscesses: a prospective clinical trial. *Br J Surg* 1977;64:264-6. doi:10.1002/bjs.1800640410 pmid:322789.
22 Giordano PA, Elston D, Akinlade BK, et al. Cefdinir vs. cephalexin for mild to moderate uncomplicated skin and skin structure infections in adolescents and adults. *Curr Med Res Opin* 2006;22:2419-28. doi:10.1185/030079906X148355. pmid:17257456.
23 Miller LG, Daum RS, Creech CB, et al. DMID 07-0051 Team. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. *N Engl J Med* 2015;372:1093-103. doi:10.1056/NEJMoa1403789. pmid:25785967.
24 Keiichi F, Eiichiro N, Hisashi T. Clinical evaluation of cefadroxil in the treatment of superficial suppurativve skin and soft tissue infections - a double-blind study comparing to L-cephalexin. *Clin Eval* 1982;10:175-200.
25 Rajendran PM, Young D, Maurer T, et al. Randomized, double-blind, placebo-controlled trial of cephalexin for treatment of uncomplicated skin abscesses in a population at risk for community-acquired methicillin-resistant Staphylococcus aureus infection. *Antimicrob Agents Chemother* 2007;51:4044-8. doi:10.1128/AAC.00377-07. pmid:17846141.
26 Agoritsas T, Heen AF, Brandt L, et al. Decision aids that really promote shared decision making: the pace quickens. *BMJ* 2015;350:g7624. doi:10.1136/bmj.g7624 pmid:25670178.
27 Stein M, Komerska J, Prizade M, Sheinberg B, Tasher D, Somekh E. Clindamycin resistance among Staphylococcus aureus strains in Israel: implications for empirical treatment of skin and soft tissue infections. *Int J Infect Dis* 2016;46:18-21. doi:10.1016/j.ijid.2016.02.016. pmid:26987479.
28 Macmorran E, Harch S, Athan E, et al. The rise of methicillin resistant Staphylococcus aureus: now the dominant cause of skin and soft tissue infection in central Australia. *Epidemiol Infect* 2017;145:2817-26. doi:10.1017/S0950268817001716. pmid:28803587.
29 Nurjadi D, Friedrich-Jänicke B, Schäfer J, et al. Skin and soft tissue infections in intercontinental travellers and the import of multi-resistant Staphylococcus aureus to Europe. *Clin Microbiol Infect* 2015;21:567.e1-10. doi:10.1016/j.cmi.2015.01.016. pmid:25753191.

30 Nurjadi D, Olalekan AO, Layer F, et al. Emergence of trimethoprim resistance gene dfrG in Staphylococcus aureus causing human infection and colonization in sub-Saharan Africa and its import to Europe. *J Antimicrob Chemother* 2014;69:2361-8. doi:10.1093/jac/dku174. pmid:24855123.

31 Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ* 2016;354:i5085. doi:10.1136/bmj.i5085 pmid:27680583.

32 Aertgeerts B, Agoritsas T, Siemieniuk RAC, et al. Corticosteroids for sore throat: a clinical practice guideline. *BMJ* 2017;358:j4090. doi:10.1136/bmj.j4090 pmid:28931507.

33 Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. doi:10.1136/bmj.39489.470347.AD pmid:18436948.

34 Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;66:726-35. doi:10.1016/j.jclinepi.2013.02.003. pmid:23570745.

[1]Academic Centre for General Practice, Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium
[2]CEBAM, Belgian Centre for Evidence-Based Medicine, Cochrane Belgium, Leuven, Belgium
[3]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada L8S 4L8
[4]Division General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, CH-1211, Geneva, Switzerland
[5]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center; Division of Allergy and Infectious Diseases, University of Washington
[6]Dutch College of General Practitioners, Utrecht, The Netherlands
[7]Care and Public Health Research Institute, Department Family Medicine, Maastricht, The Netherlands
[8]Division of General Pediatrics, University Hospitals of Geneva & Faculty of Medicine, University of Geneva, Geneva, Switzerland
[9]Bali District Hospital, Bali, and Centre for Development of Best Practices in Health, Yaounde, Cameroon
[10]Oslo University Hospital, Blindern 0317 Oslo, Norway
[11]MOH Holdings, Singapore, Singapore 099253
[12]Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[13]Norwegian Institute of Public Health, Oslo, Norway
[14]Department of Paediatrics, Universidad de Antioquia, Medellín, Colombia
[15]Department of medical microbiology and infectious diseases, Sacré-Coeur Hospital, University of Montreal, Montreal, Quebec, Canada
[16]Department of Dermatology, Ghent University Hospital, Ghent, Belgium
[17]BI Norwegian Business School, Oslo, Norway
[18]Medellín, Colombia
[19]Department of Family Medicine, McMaster University Medical School, Hamilton, Ontario, Canada
[20]Schwartz/Reisman Emergency Medicine Institute, Sinai Health System; Department of Family & Community Medicine, University of Toronto, Ontario, Canada
[21]Chinese Evidence-based Medicine Center and CREAT Group, West China Hospital, Sichuan University, Chengdu 610041, China
[22]Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Appendix 1. Rapid Recommendation panel members
Antibiotics for skin abscess: a clinical practice guideline

Chair:

Bert Aertgeerts, MD, PhD
General practitioner
Academic Centre for General Practice, Department of Public Health and Primary Care, KU Leuven, Belgium
CEBAM, Belgian Centre for Evidence-Based Medicine, Cochrane Belgium, Leuven, Belgium

Methods editor:

Reed A.C. Siemieniuk, MD
General internal medicine
PhD student
Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Clinical experts:

Jako Burgers, MD, PhD
General practitioner
Dutch College of General Practitioners, Utrecht, The Netherlands
Care and Public Health Research Institute, Department Family Medicine, Maastricht, The Netherlands

Patrick Mbah Okwen, MD
General practitioner
Bali District Hospital, Bali and Centre for Development of Best practices in Health Yaounde, Cameroon

Rachelle Sender, MD
General practitioner
Department of Family Medicine, McMaster University Medical School, Hamilton, Ontario, Canada

Mieke Vermandere, MD, PhD
General practitioner
Academic Centre for General Practice, Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium

Reinhart Speeckaert, MD
Dermatologist
Department of Dermatology, Univeristy of Ghent, Ghent, Belgium

Claudia Beltrán, MD
Paediatric infectious diseases physician
Department of Paediatrics, Universidad de Antioquia, Medellín, Colombia

Arnaud Merglen, MD, MSc
Paediatrician
Division of General Pediatrics, University Hospitals of Geneva & Faculty of Medicine, University of Geneva, Geneva, Switzerland

Valéry Lavergne, MD
Medical microbiologist and infectious disease physician
Infectious Disease Society of America
Department of medical microbiology and infectious diseases, Sacré-Coeur Hospital, University of Montreal, Montreal, Quebec, Canada

Catherine Liu, MD
Infectious disease physician
Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center and Division of Allergy and Infectious Diseases, University of Washington, Washington, DC, USA

Shelley McLeod, MD
Emergency medicine research director
PhD student
Schwartz/Reisman Emergency Medicine Institute, Sinai Health System, Toronto, Ontario, Canada
Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada
Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

Thomas Agoritsas, MD, PhD
General internal medicine
Expert in shared decision making research
Division General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland
Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada

Per Olav Vandvik, MD, PhD
General internal medicine
Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway
Department of Medicine, Innlandet Hospital Trust-division, Gjøvik, Norway
Norwegian Institute of Public Health, Oslo, Norway

<u>Patient/carer partners:</u>

Victoria Arteaga
Mother of a patient
Medellín, Colombia

Shunjie Chua
Cochrane Consumer Group
MOH Holdings, 1 Maritime Square, Singapore, Singapore 099253

Finn E. Steen
BI Norwegian Business School, Oslo, Norway

Methodology and research content experts:

Gordon H. Guyatt, MD, MSc
General internal medicine
Guideline expert, methodologist
Department of Medicine and Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

Lyubov Lytvyn, MSc
Patient partnership expert, methodologist
PhD student
Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada

Appendix 2: Full list of authors' declarations of interests

Pre-screening

All panel members were pre-screened for conflicts of interest prior to the guideline process that resulted in the *BMJ* Rapid Recommendations. The pre-screening was performed by the RapidRecs Executive team from the non-profit organisation MAGIC (www.magicproject.org) with support and approval from at least two unconflicted *BMJ* editors. No financial conflicts of interest were allowed (specifically, no financial ties to pharmaceutical companies with any stake in steroids or antibiotics) and intellectual and professional conflicts of interest were managed appropriately (see appendix 3: Methods for *BMJ* Rapid Recommendations). Panel members could not have a conflict for the past three years and do not anticipate a conflict arising in the foreseeable future, which we defined as at least one year.

Disclosures

Financial disclosures: No panel members had any financial conflicts of interest to disclose related to this clinical question. Catherine Liu was a paid contributor an Independent Efficacy Adjudication Committee for a study funded by Theravance (drug company). This company does not make any oral antibiotics or medications considered in this guideline. It does make an antibiotic (Telavancin), which is an intravenous antibiotic used exclusively for serious infections in hospitalised patients. Serious infections after an uncomplicated abscess are extremely rare.

Professional disclosures: The majority of the physician panel members routinely see patients with uncomplicated skin abscesses, but their practice and renumeration will be unaffected by these recommendations.

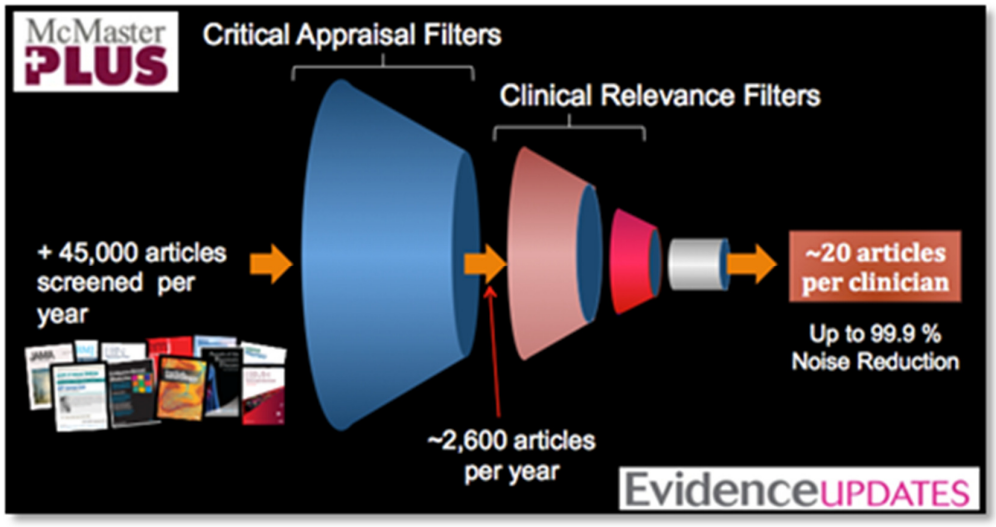
Intellectual disclosures: Valéry Laverge works as a guideline methodologist for the Infectious Diseases Society of America, but has not made recommendations about skin abscesses. Catherine Liu chaired a guideline panel on management of methicillin-resistant *Staphyloccus aureus* (MRSA) by the Infectious Diseases Society of America, which made a previous recommendation (against antibiotics) in patients with MRSA-abscesses; this was judged to be a potential conflict of interest. Jako Burgers co-authored a guideline on skin infections, but did not make recommendations about this issue. Wang Wen, Xin Sun, Reed Siemieniuk, Thomas Agoritsas, and Gordon Guyatt, participated in the writing the complementary systematic review that formed the evidence base for this guideline. Reed Siemieniuk, Arnaud Merglen, Thomas Agoritsas, Per Vandvik, Lyubov Lytvyn, and Gordon Guyatt are members of the GRADE Working Group: BMJ Rapid Recommendations adheres to GRADE methods. No panel member had any other intellectual conflict to disclose.

About *BMJ* Rapid Recommendations

Translating research to clinical practice is challenging. Trustworthy clinical practice recommendations are one useful knowledge translation strategy. Organisations creating systematic reviews and guidelines often struggle to deliver timely and trustworthy recommendations in response to potentially practice-changing evidence. *BMJ* Rapid Recommendations aims to create trustworthy clinical practice recommendations based on the highest quality evidence in record time. The project is supported by an international network of systematic review and guideline methodologists, people with lived experience of the diseases or conditions, clinical specialists, and front-line clinicians. This overview is one of a package that includes recommendations and one or more systematic reviews published by the *BMJ* group and in MAGICapp (http://www.magicapp.org). The goal is to translate evidence into recommendations for clinical practice in a timely and transparent way, minimizing bias and centred around the experience of patients. *BMJ* Rapid Recommendations will consider both new and old evidence that might alter established clinical practice.

Process overview

1. On a daily basis, we monitor the literature for practice-changing evidence:
    a. Formal monitoring through McMaster Premium LiteratUre Service (PLUS)



b. Informal monitoring the literature by *BMJ* Rapid Recommendations expert groups, including clinician specialists and patients

2. The *RapidRecs* executive team and editors at *The BMJ* choose which clinical questions to pursue among the identified potentially-practice changing evidence, based on relevance to a wide audience, widespread interest, and likelihood to change practice.

3. We incorporate the evidence into the existing body of evidence and broader context of clinical practice via:

a. a rapid and high-quality systematic review and meta-analysis on the benefits and harms with a focus on the outcomes that matter to patients

b. parallel rapid recommendations that meet the standards for trustworthy guidelines[1] by an international panel of people with relevant lived experience, front-line clinicians, clinical content experts, and methodologists.

c. The systematic review and the recommendation panel will apply standards for trustworthy guidelines.[1,2] They use the GRADE approach, which has developed a transparent process to rate the quality (or certainty) of evidence and grade the strength of recommendations.[3,4]

d. Further research may be conducted including:

i. A systematic review of observational studies to identify baseline risk estimates that most closely represent the population at the heart of the

clinical question, a key component when calculating the estimates of absolute effects of the intervention

ii. A systematic review on the preferences and values of patients on the topic.

4. Disseminate the rapid recommendations through
   a. publication of the research in *BMJ* journals
   b. short summary of recommendations for clinicians published in *The BMJ*
   c. press release and/or marketing to media outlets and relevant parties such as patient groups
   d. Links to BMJ Group's *Best Practice* point of care resource
   e. MAGICapp which provides recommendations and all underlying content in digitally structured multilayered formats for clinicians and others who wish to re-examine or consider national or local adaptation of the recommendations.

Who is involved?

Researchers, systematic review and guideline authors, clinicians, and patients often work in silos. Academic journals may publish work from any one or combinations of these groups of people and findings may also be published in the media. But it is rare that these groups work together to produce a comprehensive package. *BMJ-RapidRecs* circumvents organisational barriers in order to provide clinicians with guidance for potentially practice-changing evidence.

Our collaboration involves

a. The *RapidRecs* group with a designated Executive team responsible for recruiting and coordinating the network of researchers who perform the systematic reviews and the recommendation panels.. The *RapidRecs* group is part of MAGIC (www.magicproject.org), a non for profit organization that provides MAGICapp (www.magicapp.org) an authoring and publication

platform for evidence summaries, guidelines and decision aids, which are disseminated online for all devices.[5]

b. *The BMJ* helps identifiying practice-changing evidence on key clinical questions, coordinates the editorial process and publishes the package of content linking to the MAGICapp that is presented in a user friendly way.

METHODS FOR THE RAPID RECOMMENDATIONS

The formation of these recommendations adheres to standards for trustworthy guidelines with an emphasis on patient involvement, strict management of conflicts of interests, as well as transparent and systematic processes for assessing the quality of evidence and for moving from evidence to recommendations.[1,2,6]

Guidance on how the panel is picked and how they contribute

Panel members are sought and screened through an informal process.

The following panel members are important

- At least one author of the individual systematic reviews
- At least one patient representative with lived experience of the disease or condition. This person receives patient-oriented documents to explain the process and is allocated a linked panel member to empower their contribution.
- A full spectrum of practicing clinicians involved in the management of the clinical problem and patients it affects, including front-line clinicians with generalist experience and those with deep content clinical and research expertise in the particular topic.
- Methodological experts in health research methodology and guideline development

Any potential conflicts of interest are managed with extreme prudence:

  - No panel member can have a financial interest – as assessed by the panel chair, the *Rapidrecs* executive team or *The BMJ* editors as relevant to the topic
  - No more than two panel members with an intellectual interest on the topic (typically having published statements favouring one of the interventions).

Illustrative example: For the BMJ Rapid Recommendations on antibiotics for skin abscesses, no person was allowed to have received funding from any company that makes skin oral antibiotics.

How the panel meets and works

The international panel communicates via teleconferences and e-mail exchange of written documents throughout the process. Minutes from teleconferences are audiorecorded, transcribed, and stored for later documentation (available for peer-reviewers on request).

Teleconferences typically occur at three timepoints, with circulated documents by e-mail in advance:

1. At the initiation of the process to provide feedback on the systematic review protocol (for example, on selection of patient-important outcomes and appropriate prespecified analysis of results) before it is performed.
2. At the evidence summary stage with discussion, feedback and agreement on draft evidence (GRADE evidence profile) prepared by the Chair and the methods editor based on the systematic review.
3. At the recommendation formulation phase with discussion, feedback and agreement on draft recommendations and other content underlying the recommendation (e.g. GRADE SoF-table, key information, rationale, practical advice)

Following the last teleconference the final version of the recommendations is circulated by e-mail specifically requesting feedback from all panel members to document agreement before submission to *The BMJ*. Additional teleconferences are arranged as needed.

How we move from research findings to recommendations

What information is considered?

The panel considers best current evidence from available research. Beyond systematic reviews - performed in the context of the *BMJ* Rapid Recommendations - the panel may also include a number of other research papers to further inform the recommendations.

How is a trustworthy guideline made?

The Institute of Medicine (IOM)'s guidance on out how trustworthy guidelines should be developed and articulated key standards as outlined in the table below.[1] The standards are similar to those developed by the Guideline International Network (G-I-N).[2] These standards have been widely adopted by the international guideline community. Peer reviewers of the recommendation article are asked whether they found the guideline trustworthy (in accordance with IOM standards). The table below lays out how we hope to meet the standards for our rapid recommendations:

1. Establishing transparency **"The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible"***
● This method is available and published as a supplementary file as well as in MAGICapp where all recommendations and underlying content is available. ● We ask the peer-reviewers to judge whether the guidance is trustworthy and will respond to concerns raised.
2. Managing conflicts of interest **"Prior to selection of the guideline development group, individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity….",**

- Interests of each panel member are declared prior to involvement and published with the rapid recommendations
- No one with any potential financial interests in the past three years, or forthcoming 12 months will participate - as judged by the panel chair and *The BMJ*
- No more than two panel members have declared an intellectual conflict of interest. Such conflicts include having taken a position on the issue for example by a written an editorial, commentary, or conflicts related to performing a primary research study or written a prior systematic review on the topic.
- The Chair must have methods expertise, a clinical background and no financial or intellectual interests.
- Funders and pharmaceutical companies have no role in these recommendations.

3. Guideline Development Group Composition

"The guideline development group should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG"

- *The RapidRecs* group will aim to include representation from most or every major geographic region in the world, with specific efforts made to achieve gender-balance.
- We will facilitate patient and public involvement by including patient experience, via patient-representatives and systematic reviews addressing values and preferences to guide outcome choices and relative weights of each outcome, where available

● Patient-representatives will be given priority during panel meetings and will have an explicit role in vetting the panel's judgements of values and preferences.
4. Clinical Practice Guideline–Systematic Review Intersection **"CPG developers should use systematic reviews that meet standards set by the IOM. Guideline development group and systematic review team should interact regarding the scope, approach, and output of both processes".**
● Each rapid recommendation will be based on one or more high-quality SRs either developed and published in parallel with our *BMJ* Rapid Recommendations or produced by other authors and available at the time of making the recommendaiton. ● The recommendation panel and SR teams will interact, with up to three members participating in both teams to facilitate communication and continuity in the process
5. Establishing Evidence Foundations for and Rating Strength of Recommendations **"For each recommendation: explain underlying reasoning, including a clear description of potential benefits and harms, a summary of relevant available evidence and description of the quality., explain the part played by values, opinion, theory, and clinical experience in deriving the recommendation, "provide rating of strength of recommendations"**
● The GRADE approach will provide the framework for establishing evidence foundations and rating strength of recommendations.[6] For each recommendation systematic and transparent assessments are made across the

following key factors:

- Absolute benefit and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE Summary of Findings tables)[4]
- Quality of the evidence[7]
- Values and preferences of patients
- Resources and other considerations (e.g. feasibility, applicability, equity)

- Each outcome will - if data are available through systematic reviews - include an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in Summary of Findings tables. If such data are not available narrative summaries will be provided.
- A summary of the underlying reasoning and all additional information (e.g. key factors, practical advice, references) will be available online in an interactive format at www.magicapp.org. This summary will include descriptions of how theory (e.g. patophysiology) and clinical experience played into the evidence assessment and recommendation development.
- Recommendations will be rated either weak or strong, as defined by GRADE.[8]
- If the panel members disagree regarding evidence assessment or strength of recommendations, we will follow a structured consensus process customized to the GRADE system and report any final differences in opinion, with their rationale, in the online supplement and online at www.magicapp.org.

6. Articulation of recommendations

"Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed, and so that compliance with the recommendation(s) can be evaluated"

- Each recommendation will appear at the top of the guideline infographic, published in *The BMJ*, and will be available in standardised formats in MAGICapp, articulated to be actionable based on best current evidence on presentation formats of guidelines.[9]
- There will be a statement included in each summary article in *The BMJ* and in the MAGICapp that these are recommendations to provide clinicians with guidance. They do not form a mandate of action and should be contextualised in the healthcare system a clinician's works in, and or with an individual patient.

7. External review

"External reviewers should comprise a full spectrum of relevant stakeholders…., authorship should be kept confidential….., all reviewer comments should be considered….a rationale for modifying or not should be recorded in writing…. a draft of the recommendation should be made available to general public for comment.."

- At least two external peer-reviewers and one patient reviewer will review the article for *The BMJ* and provide open peer review. Each will have access to all the information in the package. They will be asked for general feedback as well as to make an overall judgement on whether they view the guidelines as trustworthy
- A *BMJ* series adviser with methodological and/or statistical expertise will review the *BMJ* Rapid Recommendations publication and the systematic reviews.
- The *Rapidrecs* panel will be asked to read and respond to the peer review comments and make amendments where they judge reasonable

- *The BMJ* and *RapidRecs* executive team may, on a case-by-case basis, choose to invite key organizations, agencies, or patient/public representatives to provide and submit public peer-review.
- There will be post-publication public review process through which people can provide comments and feedback through MAGICapp (or through *The BMJ*). The Chair will, on behalf of panel authors, aim to respond to each publicly-available peer-review within 30 days, for a period of six months after publication.

8. Updating

"The date for publication, systematic review and proposed date for future review should be documented, the literature should be monitored regularly and the recommendation should be updated when warranted by new evidence"

- The *Rapidrecs* panel will, through monitoring of new research evidence for published *BMJ* Rapid Recommendations, aim to provide updates of the recommendations in situations in which the evidence suggests a change in practice. These updates will be initially performed in MAGICapp and submitted to *The BMJ* for consideration of publication of a new Rapid Recommendation.

References:

1. Laine C, Taichman DB, Mulrow C. Trustworthy clinical guidelines. *Annals of internal medicine.* 2011;154(11):774-775.
2. Qaseem A, Forland F, Macbeth F, et al. Guidelines International Network: toward international standards for clinical practice guidelines. *Annals of internal medicine.* 2012;156(7):525-531.
3. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *Bmj.* 2008;336(7652):1049-1051.

4. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of clinical epidemiology.* 2011;64(4):383-394.
5. Vandvik PO, Brandt L, Alonso-Coello P, et al. Creating clinical practice guidelines we can trust, use, and share: a new era is imminent. *Chest.* 2013;144(2):381-389.
6. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Bmj.* 2008;336(7650):924-926.
7. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of clinical epidemiology.* 2011;64(4):401-406.
8. Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *Journal of clinical epidemiology.* 2013;66(7):726-735.
9. Kristiansen A, Brandt L, Alonso-Coello P, et al. Development of a novel, multilayered presentation format for clinical practice guidelines. *Chest.* 2015;147(3):754-763.

CHAPTER 10: Corticosteroid therapy for sepsis: a clinical practice guideline

Our guideline panel made a weak recommendation in favour of corticosteroids in patients with all severities of sepsis, based on moderate certainty evidence that corticosteroids result in a modest reduction in death.

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RAPID RECOMMENDATIONS

Corticosteroid therapy for sepsis: a clinical practice guideline

Francois Lamontagne,[1 2] Bram Rochwerg,[3 4] Lyubov Lytvyn,[4] Gordon H Guyatt,[4] Morten Hylander Møller,[5] Djillali Annane,[6] Michelle E Kho,[7] Neill K J Adhikari,[8 9] Flavia Machado,[10 11] Per O Vandvik,[12 13] Peter Dodek,[14] Rebecca Leboeuf,[15] Matthias Briel,[4 16] Madiha Hashmi,[17] Julie Camsooksai,[18] Manu Shankar-Hari,[19 20] Mahder Kinfe Baraki,[21] Karie Fugate,[22] Shunjie Chua,[23] Christophe Marti,[24] Dian Cohen,[25] Edouard Botton,[26] Thomas Agoritsas,[4 27] Reed A C Siemieniuk[4]

Full author details can be found at the end of the article

Correspondence to:
R A C Siemieniuk
reed.siemieniuk@medportal.ca

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Do corticosteroids reduce death or improve recovery in people with sepsis or septic shock? Our panel make a weak recommendation to give corticosteroids to people with all types and severity of sepsis, based on new evidence. Because we are not certain that they are beneficial, it is also reasonable not to prescribe them. Patients' values and preferences may guide this decision-making process.

This rapid recommendation was triggered by two trials, with differing conclusions whose results might change practice:

- **ADRENAL (3658 patients who had septic shock) found no statistically significant difference in 90 day mortality between the hydrocortisone and placebo groups.[1]**
- **APROCCHSS (1241 patients who had septic shock) found that hydrocortisone plus fludrocortisone reduced 90 day mortality.[2]**

The trials are incorporated into a linked systematic review comparing corticosteroids with placebo.[3] This BMJ Rapid Recommendation promptly and transparently translates this evidence using GRADE methodology for trustworthy guidelines. Sepsis is a life threatening organ dysfunction from infection. Currently most guidelines advise against giving corticosteroids in sepsis in the absence of refractory shock, but these guidelines have not taken into account the new evidence. We do not anticipate that new clinical trials will substantively alter the evidence suggesting a small but uncertain mortality reduction. The box below shows publications linked in this Rapid Recommendation package. The main infographic provides an overview of the absolute benefits and harms. The table at the end of the article shows any evidence that has emerged since the publication of this guideline.

WHAT YOU NEED TO KNOW

- Sepsis is a syndrome of life threatening infection with organ dysfunction, and most guidelines do not advise use of corticosteroids to treat it in the absence of refractory shock
- Two new trials of corticosteroid treatment for sepsis came to differing conclusions
- Corticosteroids may reduce the risk of death by a small amount and increase neuromuscular weakness by a small amount, but the evidence is not definitive
- This guideline makes a weak recommendation for corticosteroids in patients with sepsis; both steroids and no steroids are reasonable management options
- Fully informed patients who value avoiding death over quality of life and function would likely choose corticosteroids

Current understanding

Sepsis is life threatening organ dysfunction caused by a dysregulated host response to infection.[4] In practice, a sepsis-related organ failure assessment (SOFA) score of ≥2 in patients with infections is sepsis (table 1).[4 5] Worldwide, about 30 million people are hospitalised with sepsis every year and up to six million of them die.[6]

Clinicians typically manage sepsis with early, broad spectrum antibiotics. They may provide supportive treatment such as vasoactive drugs and mechanical ventilation. They track and adjust treatment based on clinical signs and laboratory data.[7] Septic shock is the most severe form of sepsis. These patients experience profound circulatory, metabolic, and cellular abnormalities.[4 8] They require vasopressors to maintain perfusion pressure and have elevated serum lactate concentrations despite adequate fluid repletion.

Linked articles in the BMJ Rapid Recommendation cluster

- Lamontagne F, Rochwerg B, Lytvyn L, et al. Corticosteroid therapy for sepsis: a clinical practice guideline. *BMJ* 2018;362:k3284
  - Summary of the results from the Rapid Recommendation process
- Rochwerg B, Oczkowski SJ, Siemieniuk RAC, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. *Crit Care Med* 2018. doi:10.1097/CCM.0000000000003262[3]
  - Review and meta-analysis of all available randomised trials that assessed corticosteroid therapy for sepsis
- MAGICapp (https://app.magicapp.org/public/guideline/EZ1w8n)
  - Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

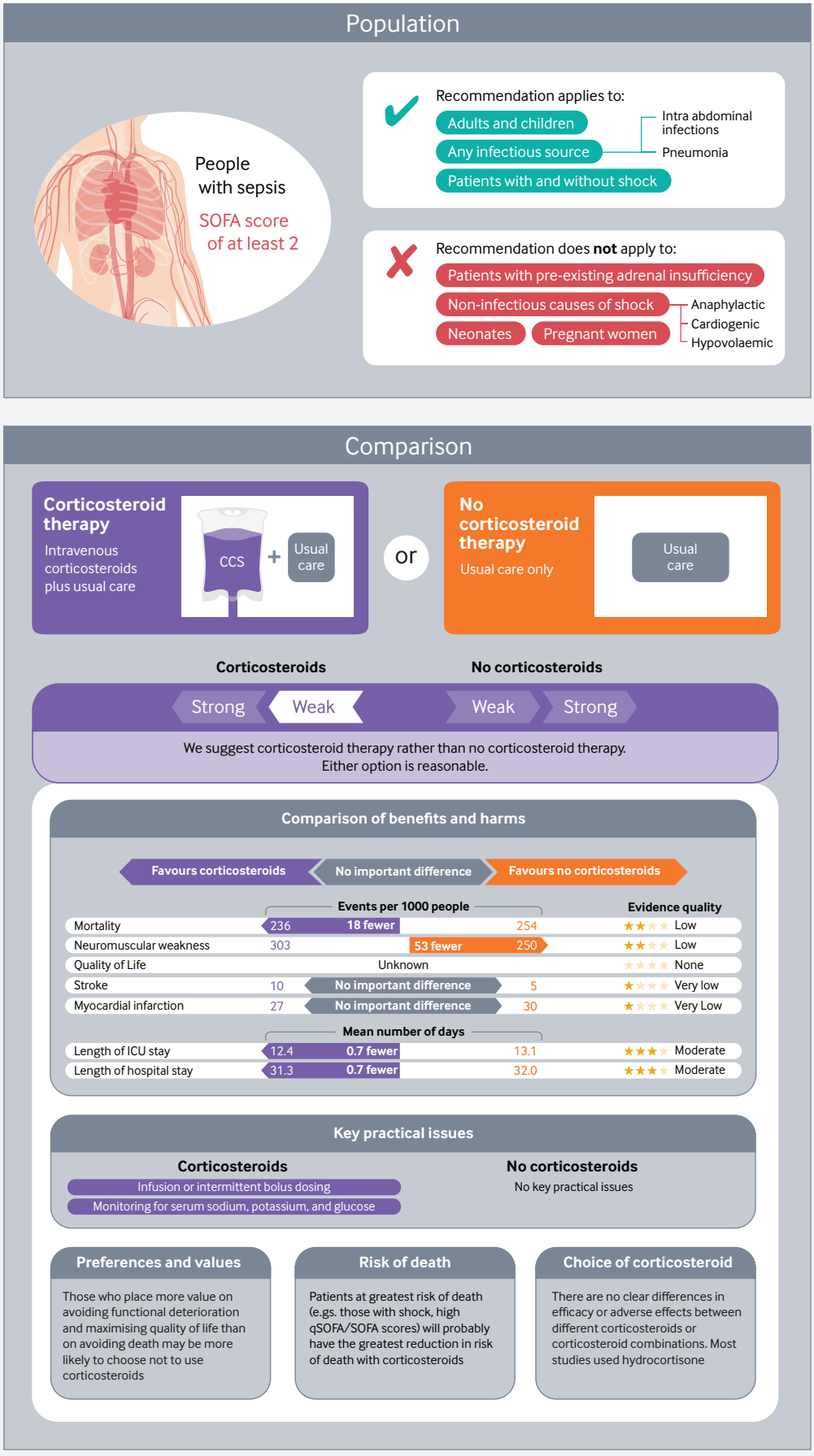

Table 1 | Sepsis-related organ failure assessment (SOFA) score to help diagnose sepsis (adapted from Vincent et al[5])*

System or organ and measure	SOFA score				
	0	1	2	3	4
Respiratory:					
P_aO_2/FiO_2, mm Hg	≥400	300-399	200-299	100-199 with respiratory support	<100 with respiratory support
Coagulation:					
Platelets, × 10^3/μL	≥150	100-149	50-99	20-49	<20
Liver:					
Bilirubin, μmol/L (mg/dL)	<20 (1.2)	20-32 (1.2-1.9)	33-101 (2.0-5.9)	102-204 (6.0-11.9)	>204 (12.0)
Circulatory:					
Mean arterial pressure, mm Hg	≥70	<70	Low dose dopamine or any dose dobutamine	Low-medium dose noradrenalin or adrenalin; medium dose dopamine	High dose noradrenalin, adrenalin, or dopamine
Central nervous system:					
Glasgow Coma Scale score	15	13-14	10-12	6-9	<6
Renal:					
Creatinine, μmol/L (mg/dL)	<110 (1.2)	110-170 (1.2-1.9)	171-299 (2.0-3.4)	300-440 (3.5-4.9)	>440 (5.0)
Urine output, mL/day	–	–	–	<500	<200

*Our recommendation applies to patients with an infection and a SOFA score of ≥2.
P_aO_2 = partial pressure of oxygen (arterial). F_iO_2 = fraction of inspired oxygen.

Table 2 | Current recommendations for corticosteroid therapy in patients with sepsis

Society	Recommendation regarding corticosteroid use		
	In sepsis	In septic shock	Other situations
"Surviving Sepsis" for SCCM and ESICM, 2016[7]	Against	In favour for hypotension refractory to fluid resuscitation and vasopressor	History of adrenal insufficiency or corticosteroid use
CIRCI guidelines for SCCM and ESICM, 2018[12 13]	Against	In favour for shock not responsive to fluid and at least moderate dose vasopressor	Acute respiratory distress syndrome Community acquired pneumonia Bacterial meningitis History of adrenal insufficiency or corticosteroid use
CAEP, 2008[14]	Against	In favour for haemodynamically unstable patients not responsive to fluid resuscitation and vasopressor	
NICE, 2017[15]	Not mentioned	Not mentioned	Not mentioned
JSICM, 2018[16]	Against	In favour for shock not responsive to initial fluid resuscitation and vasoactive drugs	

SCCM = Society of Critical Care Medicine. ESICM = European Society for Intensive Care Medicine. CIRCI = critical illness-related corticosteroid insufficiency. CAEP = Canadian Association of Emergency Physicians. NICE = National Institute for Health and Care Excellence (UK). JSICM = Japanese Society for Intensive Care Medicine.

It is possible that corticosteroids help improve the dysregulated immune response caused by sepsis[9] and increase blood pressure if it is low.[10] Some clinicians have found this biological rationale, and results of early studies, compelling. Others disagree and do not use corticosteroids.[11]

Most professional organisations recommend against corticosteroid use in the absence of refractory shock.[12] Table 2 summarises current professional society guidelines.

The evidence

The linked systematic review identified 42 randomised controlled trials (RCTs) comparing corticosteroids with no corticosteroids (typically placebo).[3] Figure 2 provides an overview of the trials and participants.

The systematic review includes total of 10 194 patients who had sepsis. Of the 42 trials included, 24 restricted enrolment to patients who had septic shock. The typical patient was critically ill—a median of 32% of participants died within the first month. The most common sources of sepsis were pulmonary infections (median 44%) and abdominal infections (median 17%). Most of the RCTs used hydrocortisone alone (n=26), others used hydrocortisone plus fludrocortisone (n=2), methylprednisolone (n=6), prednisolone (n=3), or dexamethasone (n=3) (see fig 2). Although most of the clinical trials included patients who had septic shock, many included patients who did not (16 trials, 2241 patients). The linked systematic review provides detailed trial descriptions, including risk of bias assessments and patient characteristics.[3]

Subgroups of patients

Corticosteroids did not seem to be more or less effective in particular clinical subgroups, for example:

- Septic shock
- Pneumonia
- Acute respiratory distress syndrome (ARDS)
- Higher baseline risk of death
- Different corticosteroid drugs (such as hydrocortisone, methylprednisolone)
- Different corticosteroid doses
- Different corticosteroid regimens (such as single agents or corticosteroid combinations such as hydrocortisone plus fludrocortisone)
- More recent *v* older trials
- Trials with higher *v* lower risk of bias.

Older studies tended to use much higher doses of corticosteroids for a shorter time than are typically used now; the pooled evidence from these older studies is imprecise (few events), and the linked meta-analysis was underpowered to detect important subgroup differences such as by dose. All tests for relative subgroup effects may be underpowered to detect true differences because the effect sizes are small, especially for mortality. Therefore, we cannot be certain that a true subgroup effect does not exist. Future meta-analyses of individual patient data may help to identify populations that benefit more or less from corticosteroids. Until such time, we can only conclude that the evidence applies to all subgroups.

Understanding the recommendation

The main infographic provides an overview including the benefits and harms, and our certainty in the evidence for each outcome.

Absolute benefits and harms

There was better survival in the group taking corticosteroids, but this was not certain. This drives the weak rather than strong recommendation.

Mortality

Corticosteroids may reduce mortality in the first month after admission to an intensive care unit (ICU) by approximately 2%. However, the panel had low certainty that this is true. The confidence interval crosses the line of no difference, and the results were inconsistent, with some RCTs showing a mortality reduction and others showing none.

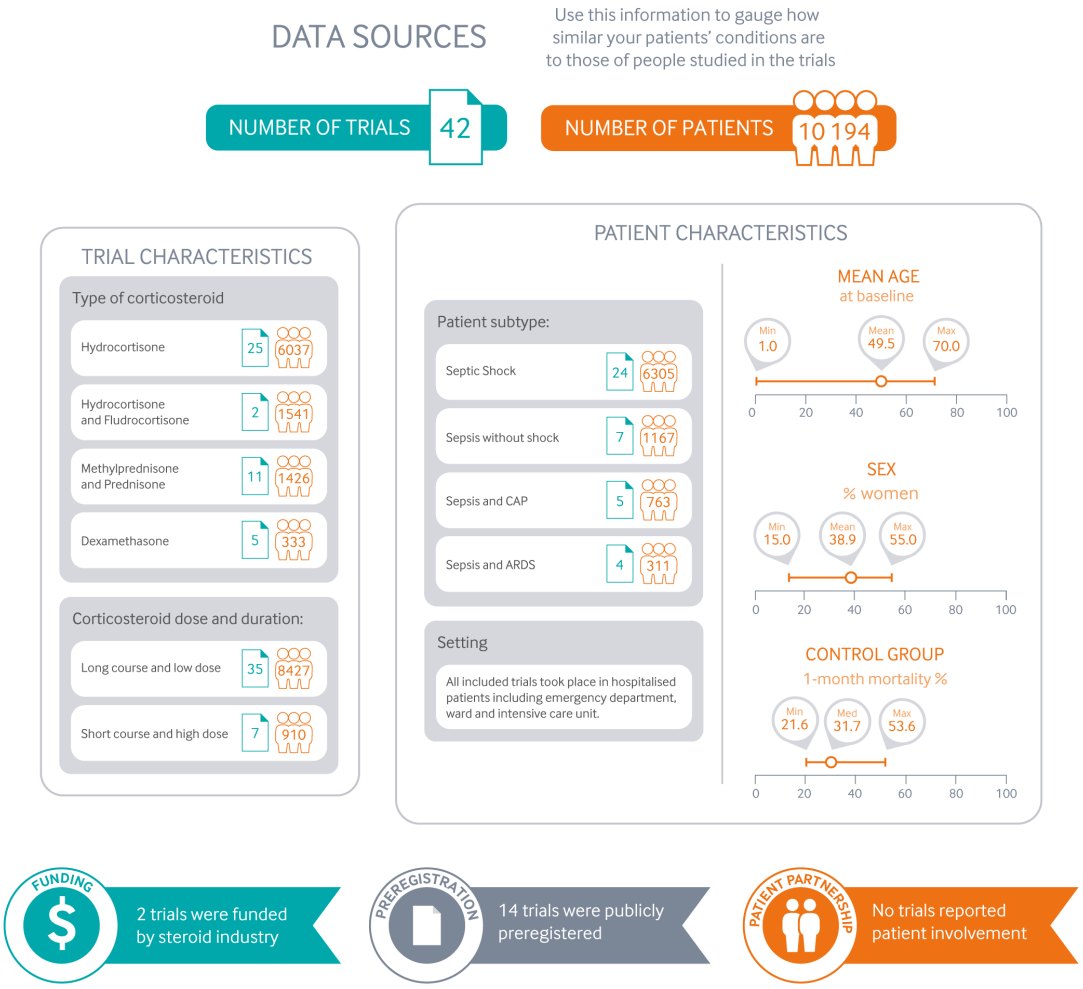

Fig 2| Characteristics of patients and trials included in systematic review of the use of corticosteroids for treating sepsis[3]
CAP=community acquired pneumonia. ARDS=acute respiratory distress syndrome.

The effect on longer term mortality (from 60 days to 1 year) was similar. Fewer studies reported this outcome, so, although the results were consistent in the RCTs that did report this outcome, the panel also had low certainty that corticosteroids reduce longer term mortality.

Quality of life

No RCT reported quality of life outcomes at any time point. The ADRENAL study investigators are collecting quality of life data at six months, but these data have not been published.[17]

Outcomes of some interest

Corticosteroids may reduce the length of ICU and hospital stay by less than a day each (moderate quality evidence). The impact of corticosteroids on other patient-important outcomes such as stroke and myocardial infarction was extremely uncertain. They may increase the risk of neuromuscular weakness by a small amount (low quality evidence from seven RCTs). Possible explanations include the toxic effects on nerve and muscle cells, and hyperglycaemia from corticosteroid use.[18] Weakness may compromise patients' ability to function independently[19] and delay recovery.[20]

In two of the seven RCTs evaluating weakness, it was prospectively evaluated one month after enrolment.[2 21] Evaluations of neuromuscular weakness, especially in RCTs that relied on investigator identification, were unreliable. The panel therefore believed that the RCTs probably underestimated the risk of neuromuscular weakness.

Outcomes of less importance

Corticosteroids probably increase the risk of hyperglycaemia and hypernatraemia. Corticosteroids probably improve organ function at day 7 and the chance of shock reversal at day 7.

Patient subgroups

Our recommendation applies to all patients with sepsis. There was no meaningful difference in the efficacy of corticosteroids in different groups of patients including those with septic shock, pneumonia, acute respiratory distress syndrome, or other sources of sepsis, or those who were sicker. However, the absolute reduction in mortality from corticosteroids will be greater in patients with a higher risk of death. The absolute harm (such as neuromuscular weakness) will also be greater in sicker patients.

The analysis of a subgroup effect showed no convincing evidence of such an effect. Based on published criteria for credible subgroup effects,[22] in the absence of a subgroup

HOW THIS RECOMMENDATION WAS CREATED

Our international panel included sepsis survivors, family caregivers of patients who had sepsis, intensivists, internists, nurses, an endocrinologist, physiotherapists, trialists, and methodologists (see appendix 1 on bmj.com). They decided on the scope of the recommendation and the outcomes that are most important to patients. The panel judged death and quality of life to be the most important outcomes. Myocardial infarction, stroke, duration of stay in hospital and in the intensive care unit (ICU), superinfections, and neuromuscular weakness (such as ICU-acquired weakness) were also identified as important outcomes for patients.

Surrogate outcomes such as time to shock reversal, organ dysfunction measured by the sepsis-related organ failure assessment (SOFA) score, hyperglycaemia, and hypernatraemia were less important to the panel. This view is consistent with GRADE recommendations to focus on patient-important outcomes rather than surrogates.[29]

Subgroups of interest—The panel wanted to know whether the effect of corticosteroids differed in people with sepsis, compared with people who had septic shock, pneumonia, acute respiratory distress syndrome, or were at higher risk of death.[3 30] They also wanted to know whether the type of corticosteroid or its dose influenced outcomes.

The panel met by videoconference to discuss the evidence and formulate a recommendation. No panel member had financial conflicts of interest; intellectual and professional conflicts were minimised and managed (see appendix 2 on bmj.com).

The panel requested a systematic review of randomised controlled trials on the impact of corticosteroid therapy for patients who have sepsis, including those who have septic shock.[3] This review examines the two latest, as well as previous studies, on corticosteroids in sepsis. The aim was to resolve apparently conflicting evidence.

The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation,[31] including using the GRADE approach to critically appraise the evidence and create recommendations (see appendix 3 on bmj.com).[32] The panel considered the balance of benefits, harms, and burdens of corticosteroids, the quality of the evidence for each outcome, expected variations in patient values and preferences, and acceptability of corticosteroids.[33] Determining patient values and preferences occurred before the panel received the results of the meta-analysis to reduce the risk that opinions regarding outcome importance will be data driven. According to the GRADE approach, recommendations can be strong or weak and for or against a course of action.[33] High quality evidence of an effect on surrogate outcomes do not trigger strong recommendations.

effect, the interpretation of the effect of corticosteroids in any particular subgroup should be guided by the effect in the overall population of septic patients.

Several trials of corticosteroids for pneumonia or acute respiratory distress syndrome have enrolled patients who did not have sepsis; we did not consider these trials. Therefore, clinicians treating these conditions should also consider evidence[23 24] and guidelines[12] applicable to patients who have pneumonia and acute respiratory distress syndrome.

Patient values and preferences

Fully informed patients who place a higher value on avoiding death than on quality of life and function would be more likely to choose to receive corticosteroids. We heard from our patient partners that most patients will want to reduce their risk of death, even if this reduction is small and uncertain. This view is consistent with the experiences of the rest of the panel. Most patients will likely be willing to accept a small increased risk of weakness.

Patients (or their care givers and surrogate decision-makers) will probably vary in how they would weigh the balance of expected desirable and undesirable consequences from corticosteroids. We assume that most patients want to avoid death and will value even a small, uncertain reduction in mortality. We judge that they will be less concerned about the possible increase in weakness among survivors. There is also likely to be a sizeable minority of patients who would place a large value on avoiding a very uncertain but possible decline in quality of life and functional abilities even at the cost of a small increase in risk of death.[25] Shared decision making conversations about specific interventions in patients with sepsis may not always be feasible, and could delay care. However, clinicians should do their best to elicit each patient's values and preferences. For example, they could talk about the patient's goals of care with the patient, their family, and friends.

Practical considerations

Figure 3 outlines the key practical issues for patients and clinicians discussing corticosteroid treatment for sepsis.

The optimal corticosteroid drug, dose, and duration of treatment are uncertain. Hydrocortisone was the most commonly used corticosteroid in the RCTs and is therefore a reasonable choice. Differences among corticosteroids, if they do exist, are probably small; dexamethasone, methylprednisolone, and prednisolone were also studied and produced similar results. Adding an agent that has additional mineralocorticoid activity, such as fludrocortisone, could be helpful, but that is highly speculative.

The typical hydrocortisone dose for an adult in the RCTs was 200-300 mg/day, given either as an infusion or as boluses every six hours.[26] If an infusion is chosen, a bolus of 50-100 mg can be given before the infusion. In the RCTs the duration of treatment was typically 7-14 days, or less for those who were rapidly improving.

Inflammation may recur after discontinuing corticosteroid therapy,[27] especially when it is stopped abruptly.[28] Clinicians should carefully monitor all patients after discontinuing corticosteroids. In patients who deteriorate after stopping corticosteroids (such as development of shock or need for mechanical ventilation), reinitiating corticosteroid therapy could be helpful, although this is highly speculative. Whether corticosteroids should be tapered rather than stopped abruptly is unclear. Corticosteroid induced adrenal suppression is probably duration dependent, and so patients who receive longer courses of corticosteroids (such as >14 days) might be particularly likely to benefit from a taper before discontinuing and an evaluation of hypothalamo-pituitary-adrenal axis function if in doubt.[12]

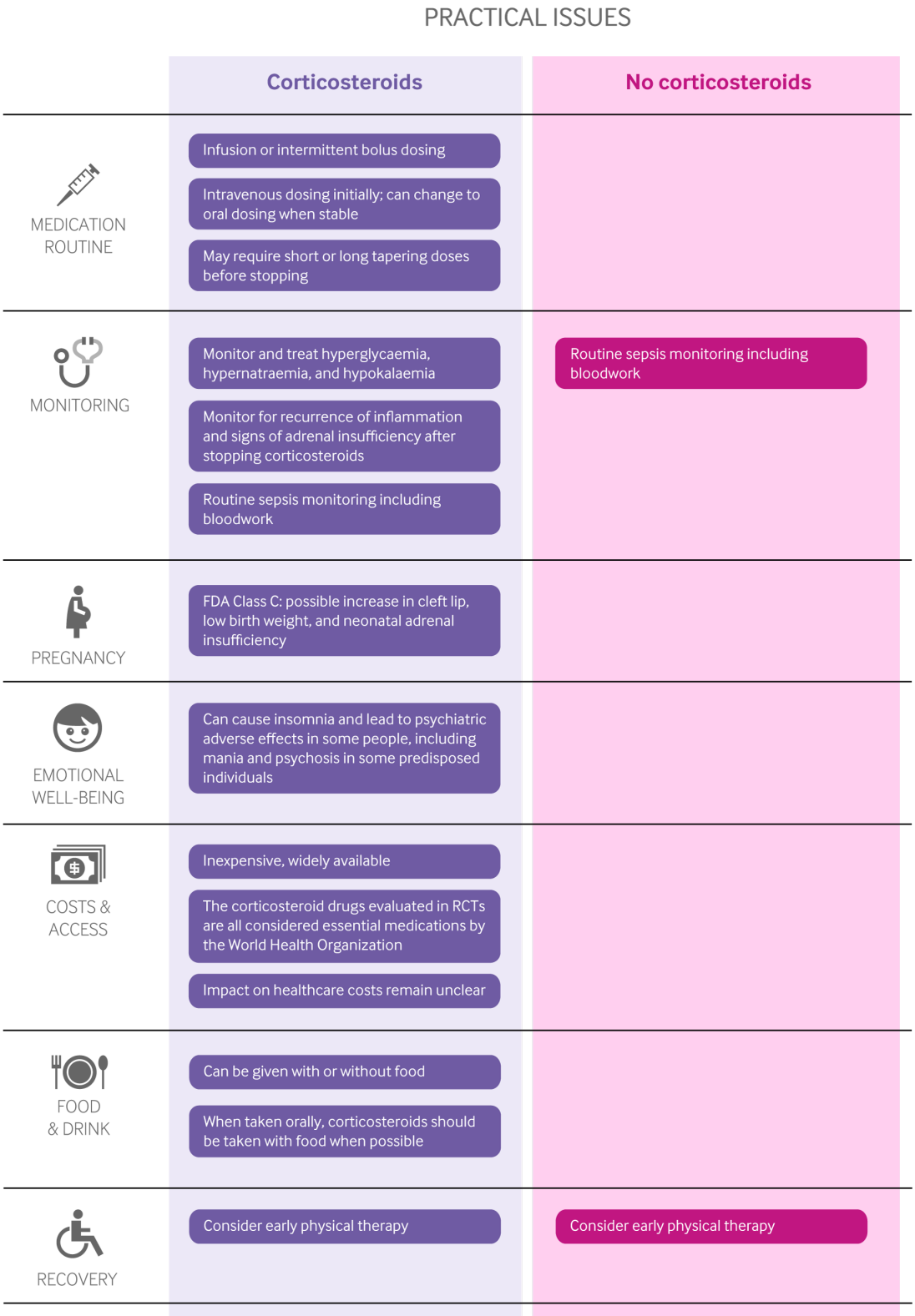

Fig 3| Practical issues about use of corticosteroids for treatment of sepsis

Costs

Corticosteroids are typically inexpensive and widely available. The impact of corticosteroids on the overall costs to patients and to health systems is uncertain and would be driven mostly by ICU and hospital lengths of stay or prolonged periods of rehabilitation.

Future research

With the exception of the awaited analysis of quality of life in the ADRENAL trial, there are currently no planned or ongoing RCTs in patients who have sepsis that are likely to substantively change the overall effect estimates for the key outcomes. Given remaining uncertainty regarding the

New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article.				

effect of corticosteroids in different subgroups, additional analyses of existing data to explore heterogeneity of treatment effects are logical next steps before more patients are enrolled in similar trials. Such work mandates individual patient-data meta-analyses that rely on investigators sharing the data from their RCTs and cooperation among research networks.

It is possible that additional adaptive RCTs could help to resolve remaining uncertainty. Key research questions to inform decision makers and future guidelines are:

- What is the impact of corticosteroid therapy on quality of life in the short and long term?
- What is the impact of corticosteroid therapy on functional recovery?
- What is the impact of corticosteroid therapy on healthcare costs?
- Are there subgroups of patients with sepsis who benefit more or less from corticosteroid therapy?
- Are there differences between bolus and infusion dosing?
- Does the addition of fludrocortisone improve outcomes?

Updates to this article

The final table shows evidence that has emerged since the publication of this article. As new evidence is published, a group will assess the new evidence and make a judgment on to what extent it is expected to alter the recommendation.

Competing interests: All authors have completed the *BMJ* Rapid Recommendations interests disclosure form, and a detailed description of all disclosures is reported in appendix 2 on bmj.com. As with all *BMJ* Rapid Recommendations, the executive team and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions.

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Transparency: R A C Siemieniuk affirms that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

1 Venkatesh B, Finfer S, Cohen J, et al. ADRENAL Trial Investigators and the Australian-New Zealand Intensive Care Society Clinical Trials Group. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018;378:797-808. 10.1056/NEJMoa1705835 pmid:29347874.
2 Annane D, Renault A, Brun-Buisson C, et al. CRICS-TRIGGERSEP Network. Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 2018;378:809-18. 10.1056/NEJMoa1705716 pmid:29490185.
3 Rochwerg B, Oczkowski SJ, Siemieniuk RAC, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. *Crit Care Med* 2018. 10.1097/CCM.0000000000003262 pmid:29979221.
4 Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:801-10. 10.1001/jama.2016.0287 pmid:26903338.
5 Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707-10. 10.1007/BF01709751 pmid:8844239.
6 Fleischmann C, Scherag A, Adhikari NK, et al. International Forum of Acute Care Trialists. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *Am J Respir Crit Care Med* 2016;193:259-72. 10.1164/rccm.201504-07810C pmid:26414292.
7 Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017;43:304-77. 10.1007/s00134-017-4683-6 pmid:28101605.
8 Shankar-Hari M, Phillips GS, Levy ML, et al. Sepsis Definitions Task Force. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:775-87. 10.1001/jama.2016.0289 pmid:26903336.
9 Franchimont D, Kino T, Galon J, Meduri GU, Chrousos G. Glucocorticoids and inflammation revisited: the state of the art. NIH clinical staff conference. *Neuroimmunomodulation* 2002-2003;10:247-60. . 10.1159/000069969 pmid:12759562.
10 Hylands M, Moller MH, Asfar P, et al. A systematic review of vasopressor blood pressure targets in critically ill adults with hypotension. *Can J Anaesth* 2017;64:703-15. 10.1007/s12630-017-0877-1 pmid:28497426.
11 Bruno JJ, Dee BM, Anderegg BA, Hernandez M, Pravinkumar SE. US practitioner opinions and prescribing practices regarding corticosteroid therapy for severe sepsis and septic shock. *J Crit Care* 2012;27:351-61. 10.1016/j.jcrc.2011.12.011 pmid:22341726.
12 Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med* 2017;43:1751-63. 10.1007/s00134-017-4919-5 pmid:28940011.
13 Pastores SM, Annane D, Rochwerg B. Corticosteroid Guideline Task Force of SCCM and ESICM. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (part II): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med* 2018;46:146-8. 10.1097/CCM.0000000000002840 pmid:29095205.
14 Green RS, Djogovic D, Gray S, et al. CAEP Critical Care Interest Group. Canadian Association of Emergency Physicians Sepsis Guidelines: the optimal management of severe sepsis in Canadian emergency departments. *CJEM* 2008;10:443-59. 10.1017/S148180350001054X pmid:18826733.
15 Tavaré A, O'Flynn N. Recognition, diagnosis, and early management of sepsis: NICE guideline. *Br J Gen Pract* 2017;67:185-6. 10.3399/bjgp17X690401 pmid:28360070.
16 Nishida O, Ogura H, Egi M, et al. The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016 (J-SSCG 2016). *J Intensive Care* 2018;6:7. 10.1186/s40560-017-0270-8 pmid:29435330.
17 Venkatesh B, Myburgh J, Finfer S, et al. ANZICS CTG investigators. The ADRENAL study protocol: adjunctive corticosteroid treatment in critically ill patients with septic shock. *Crit Care Resusc* 2013;15:83-8.pmid:23931038.
18 Wilcox SR. Corticosteroids and neuromuscular blockers in development of critical illness neuromuscular abnormalities: A historical review. *J Crit Care* 2017;37:149-55. 10.1016/j.jcrc.2016.09.018 pmid:27736708.
19 Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009;373:1874-82. 10.1016/S0140-6736(09)60658-9 pmid:19446324.
20 Herridge MS, Chu LM, Matte A, et al. RECOVER Program Investigators (Phase 1: towards RECOVER) Canadian Critical Care Trials Group. The RECOVER Program: disability risk groups and 1-year outcome after 7 or more days of mechanical ventilation. *Am J Respir Crit Care Med* 2016;194:831-44. 10.1164/rccm.201512-2343OC pmid:26974173.
21 Keh D, Trips E, Marx G, et al. SepNet–Critical Care Trials Group. Effect of hydrocortisone on development of shock among patients with severe sepsis: the HYPRESS randomized clinical trial. *JAMA* 2016;316:1775-85. 10.1001/jama.2016.14799 pmid:27695824.
22 Sun X, Ioannidis JP, Agoritsas T, Alba AC, Guyatt G. How to use a subgroup analysis: users' guide to the medical literature. *JAMA* 2014;311:405-11. 10.1001/jama.2013.285063 pmid:24449319.
23 Siemieniuk RA, Meade MO, Alonso-Coello P, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. *Ann Intern Med* 2015;163:519-28. 10.7326/M15-0715 pmid:26258555.
24 Meduri GU, Bridges L, Shih MC, Marik PE, Siemieniuk RAC, Kocak M. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. *Intensive Care Med* 2016;42:829-40. 10.1007/s00134-015-4095-4 pmid:26508525.
25 Lamontagne F, Cohen D, Herridge M. Understanding patient-centredness: contrasting expert versus patient perspectives on vasopressor therapy for shock. *Intensive Care Med* 2017;43:1052-4. 10.1007/s00134-016-4518-x pmid:27624068.
26 Loisa P, Parviainen I, Tenhunen J, Hovilehto S, Ruokonen E. Effect of mode of hydrocortisone administration on glycemic control in patients with septic shock: a prospective randomized trial. *Crit Care* 2007;11:R21. 10.1186/cc5696 pmid:17306016.
27 Briel M, Spoorenberg SMC, Snijders D, et al. Ovidius Study Group Capisce Study Group STEP Study Group. Corticosteroids in patients hospitalized with community-acquired pneumonia: systematic review and individual patient data metaanalysis. *Clin Infect Dis* 2018;66:346-54. 10.1093/cid/cix801 pmid:29020323.

28 Meduri GU, Bridges L, Siemieniuk RAC, Kocak M. An exploratory reanalysis of the randomized trial on efficacy of corticosteroids as rescue therapy for the late phase of acute respiratory distress syndrome. *Crit Care Med* 2018;46:884-91. . 10.1097/CCM.0000000000003021 pmid:29432350.
29 Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. *J Clin Epidemiol* 2013;66:158-72. 10.1016/j.jclinepi.2012.01.012 pmid:22609141.
30 Rochwerg B, Oczkowski S, Siemieniuk RA, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis (protocol). *BMJ Open* 2017;7:e016847. 10.1136/bmjopen-2017-016847 pmid:28667229.
31 Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:i5191. 10.1136/bmj.i5191 pmid:27680768.
32 Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. 10.1136/bmj.39489.470347.AD pmid:18436948.
33 Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;66:726-35. 10.1016/j.jclinepi.2013.02.003 pmid:23570745.

[1]Department of Medicine, Université de Sherbrooke, Sherbrooke, Canada
[2]Centre de recherche du CHU de Sherbrooke, Centre intégré universitaire de santé et de services sociaux - Estrie, Sherbrooke, Canada
[3]Department of Medicine, McMaster University, Hamilton, Canada
[4]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
[5]Department of Intensive Care, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[6]Service de Médecine Intensive et Réanimation, Hôpital Raymond Poincaré, Garches, France
[7]School of Rehabilitation Science, McMaster University, Hamilton, Canada
[8]Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, Toronto Canada
[9]Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada
[10]Federal University of Sao Paulo, Sao Paulo, Brazil
[11]Latin America Sepsis Institute, Sao Paulo, Brazil
[12]Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway
[13]Department of Medicine, Innlandet Hospital Trust-division, Gjøvik, Norway
[14]Center for Health Evaluation and Outcome Sciences and Division of Critical Care Medicine, St Paul's Hospital and University of British Columbia, Vancouver, Canada
[15]Department of Medicine, Centre Hospitalier de l'Université de Montréal, Montréal, Canada
[16]Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland
[17]Department of Anaesthesiology, Aga Khan University, Karachi, Pakistan
[18]Poole Hospital NHS Foundation Trust, Dorset, United Kingdom
[19]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
[20]NIHR Clinician Scientist, School of Immunology & Microbial Sciences, Kings College London, United Kingdom
[21]Department of Anesthesiology, Addis Ababa University, Addis Ababa, Ethiopia
[22]Renton, USA
[23]Carevise Mexico, Mexico City, Mexico
[24]Division of General Internal Medicine, Rehabilitation and Geriatrics, University Hospitals of Geneva, Geneva, Switzerland
[25]Centre de santé de la vallée Massawippi, Ayer's Cliff, Canada
[26]Comité stratégique patient-partenaire, Centre de recherche du CHU de Sherbrooke, Centre intégré universitaire de santé et de services sociaux - Estrie, Sherbrooke, Canada
[27]Division General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland

CHAPTER 11: Oxygen therapy for acutely ill medical patients: a clinical practice guideline

Based on evidence that too much oxygen can be harmful, we were able to make recommendations for both when to initiate (or titrate up) and when to stop (or titrate down) oxygen therapy. We did this based on subsets of patients enrolled in the trials at the upper and lower ends of the oxygen saturation.

Citation:
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RAPID RECOMMENDATIONS

Oxygen therapy for acutely ill medical patients: a clinical practice guideline

Reed A C Siemieniuk,[1] Derek K Chu,[2] Lisa Ha-Yeon Kim,[2] Maria-Rosa Güell-Rous,[3] Waleed Alhazzani,[1 2] Paola M Soccal,[4 5] Paul J Karanicolas,[6] Pauline D Farhoumand,[7] Jillian L K Siemieniuk,[8] Imran Satia,[2] Elvis M Irusen,[9] Marwan M. Refaat,[10] J. Stephen Mikita,[11] Maureen Smith,[12] Dian N Cohen,[13] Per O Vandvik,[14] Thomas Agoritsas,[1 7 15] Lyubov Lytvyn,[1] Gordon H Guyatt[1 2]

Full author details can be found at the end of the article

Correspondence to:
R A C Siemieniuk
reed.siemieniuk@medportal.ca

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This *BMJ* Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (http://magicproject.org/) and *The BMJ*. A summary is offered here and the full version including decision aids is on the MAGICapp (https://app.magicapp.org), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualisation of our recommendations to local or other contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact *The BMJ* for permission to reuse content in this article. Series adviser Rafael Perera-Salazar.

What is the best way to use oxygen therapy for patients with an acute medical illness? A systematic review published in the *Lancet* in April 2018 found that supplemental oxygen in inpatients with normal oxygen saturation increases mortality.[1] Its authors concluded that oxygen should be administered conservatively, but they did not make specific recommendations on how to do it. An international expert panel used that review to inform this guideline. It aims to promptly and transparently translate potentially practice-changing evidence to usable recommendations for clinicians and patients.[2] The panel used the GRADE framework and following standards for trustworthy guidelines.[3]

The panel asked;

- In acutely ill patients, when should oxygen therapy be started? (What is the lower limit of peripheral capillary oxygen saturation (SpO_2)?)
- In acutely ill patients receiving oxygen therapy, how much oxygen should be given? (What is the upper limit of SpO_2?)

The panel makes a strong recommendation for maintaining an oxygen saturation of no more than 96% in acutely ill medical patients (upper limit). The panel did not make a recommendation on when to start (the lower limit) for all medical patients because there was not enough evidence. Instead, the panel suggests that patients with acute stroke or myocardial infarction and a SpO_2 ≥90% not receive supplemental oxygen (a weak recommendation if SpO_2 is 90-92% and a strong recommendation if 93-100%). Box 1 shows the article and evidence linked to this Rapid Recommendation. The infographic provides an overview of the key absolute benefits and harms, as well as the quality of evidence that informed each of the recommendations.

The panel was confident that the recommendation against letting oxygen saturation rise above 96% applies to almost all patients in hospital with a medical problem. The recommendation also applies to pre-hospital care. The evidence may apply to surgical and obstetric patients, but the panel did not review the evidence on postoperative healing and infections and therefore decided not to comment on these patients. Similarly, the panel did not review the evidence on oxygen therapy in neonates and infants.

WHAT YOU NEED TO KNOW

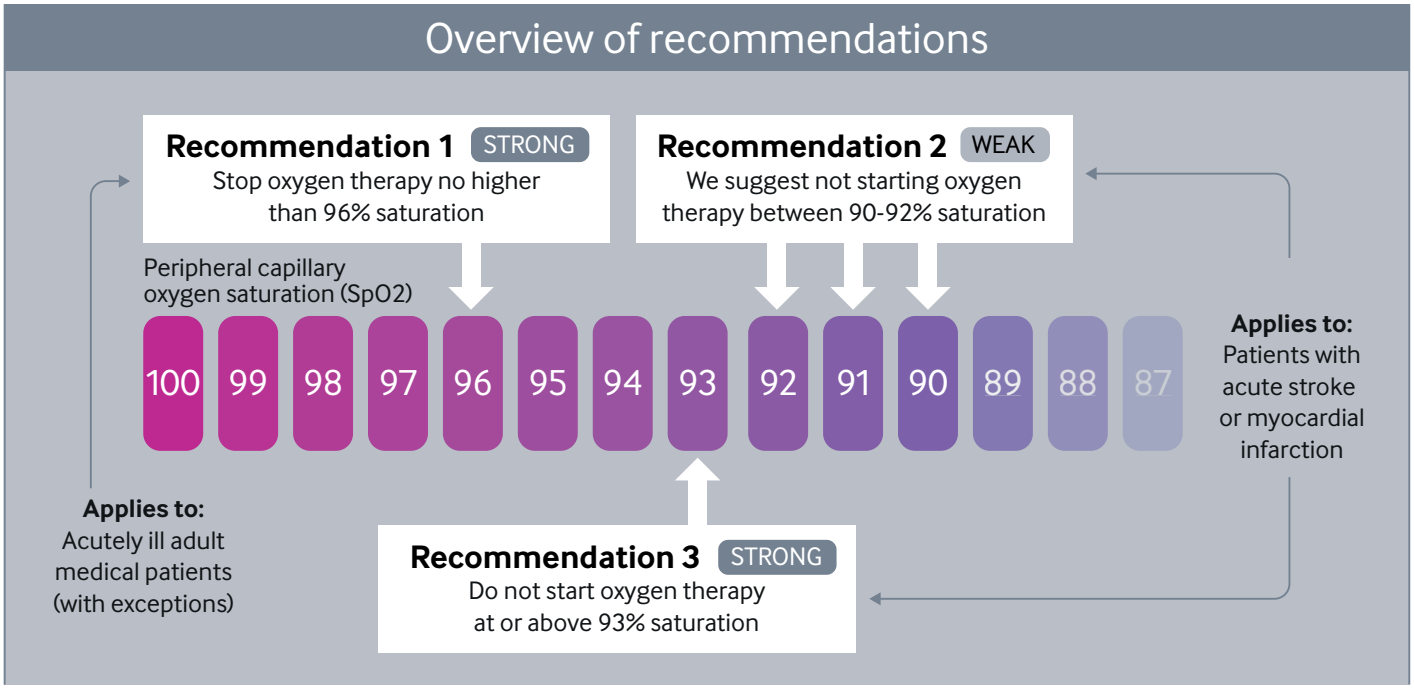
- It is a longstanding cultural norm to provide supplemental oxygen to sick patients regardless of their blood oxygen saturation
- A recent systematic review and meta-analysis has shown that too much supplemental oxygen increases mortality for medical patients in hospital
- For patients receiving oxygen therapy, aim for peripheral capillary oxygen saturation (SpO_2) of ≤96% (strong recommendation)
- For patients with acute myocardial infarction or stroke, do not initiate oxygen therapy in patients with SpO_2 ≥90% (for ≥93% strong recommendation, for 90-92% weak recommendation)
- A target SpO_2 range of 90-94% seems reasonable for most patients and 88-92% for patients at risk of hypercapnic respiratory failure; use the minimum amount of oxygen necessary

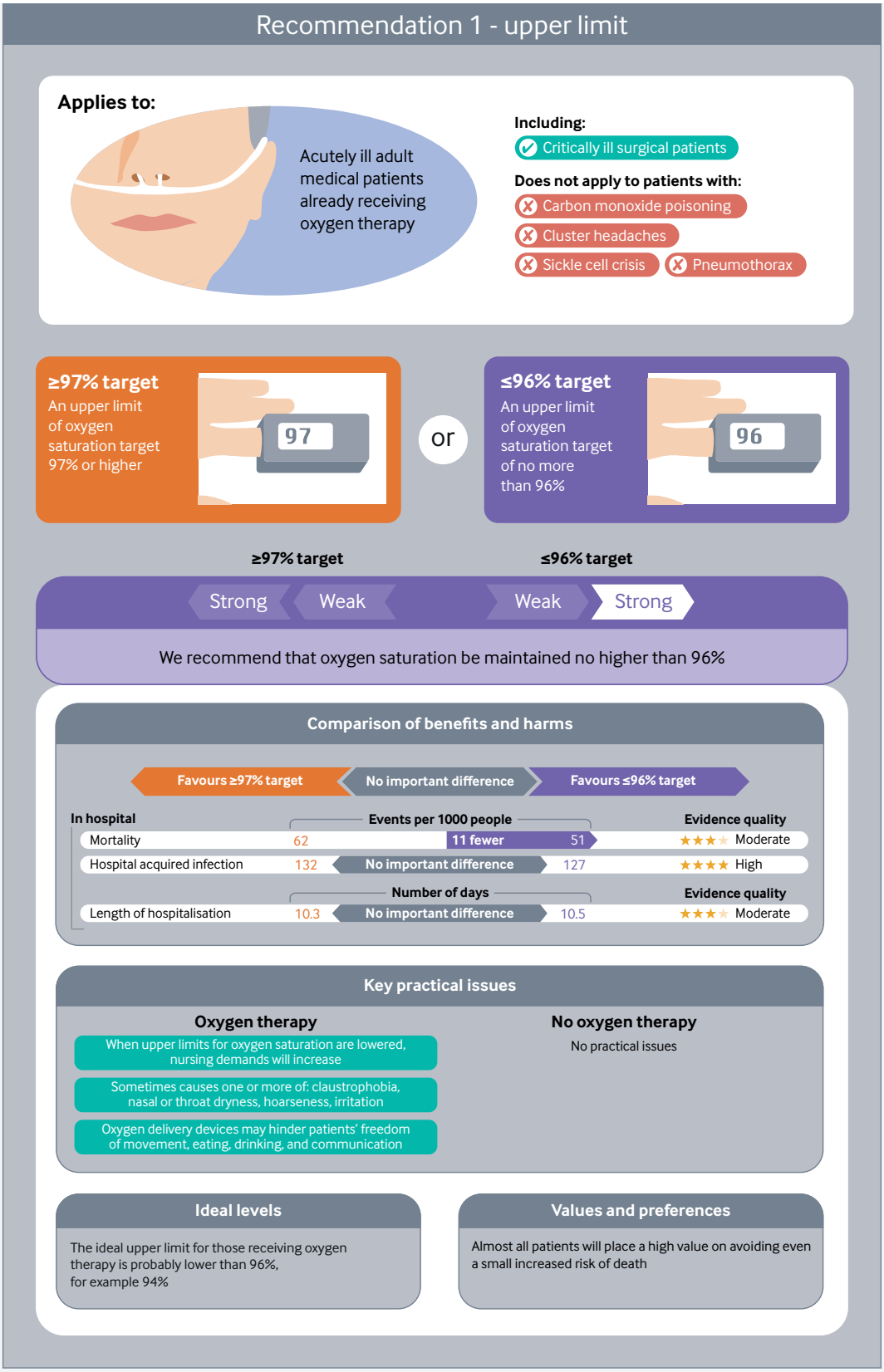
Current practice

Supplemental oxygen therapy is widely used in hospitals: 25% or more of patients who visit the emergency department receive oxygen.[4] Clinicians often give oxygen to many patients presenting with stroke without hypoxaemia, and to almost all patients presenting with myocardial infarction.[5] Until recently, many healthcare professionals believed that oxygen had little or no harm

Box 1 | Linked resources in this *BMJ* Rapid Recommendations cluster

- Siemieniuk RAC, Chu DK, Kim LH-Y, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. *BMJ* 2018;363:k4169
  - Summary of the results from the Rapid Recommendation process
- Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018;391:1693-705.
  - Review and meta-analysis of all available randomised trials that assessed oxygen therapy for acute illnesses
- MAGICapp (https://app.magicapp.org/public/guideline/jxQ7OL)
  - Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices





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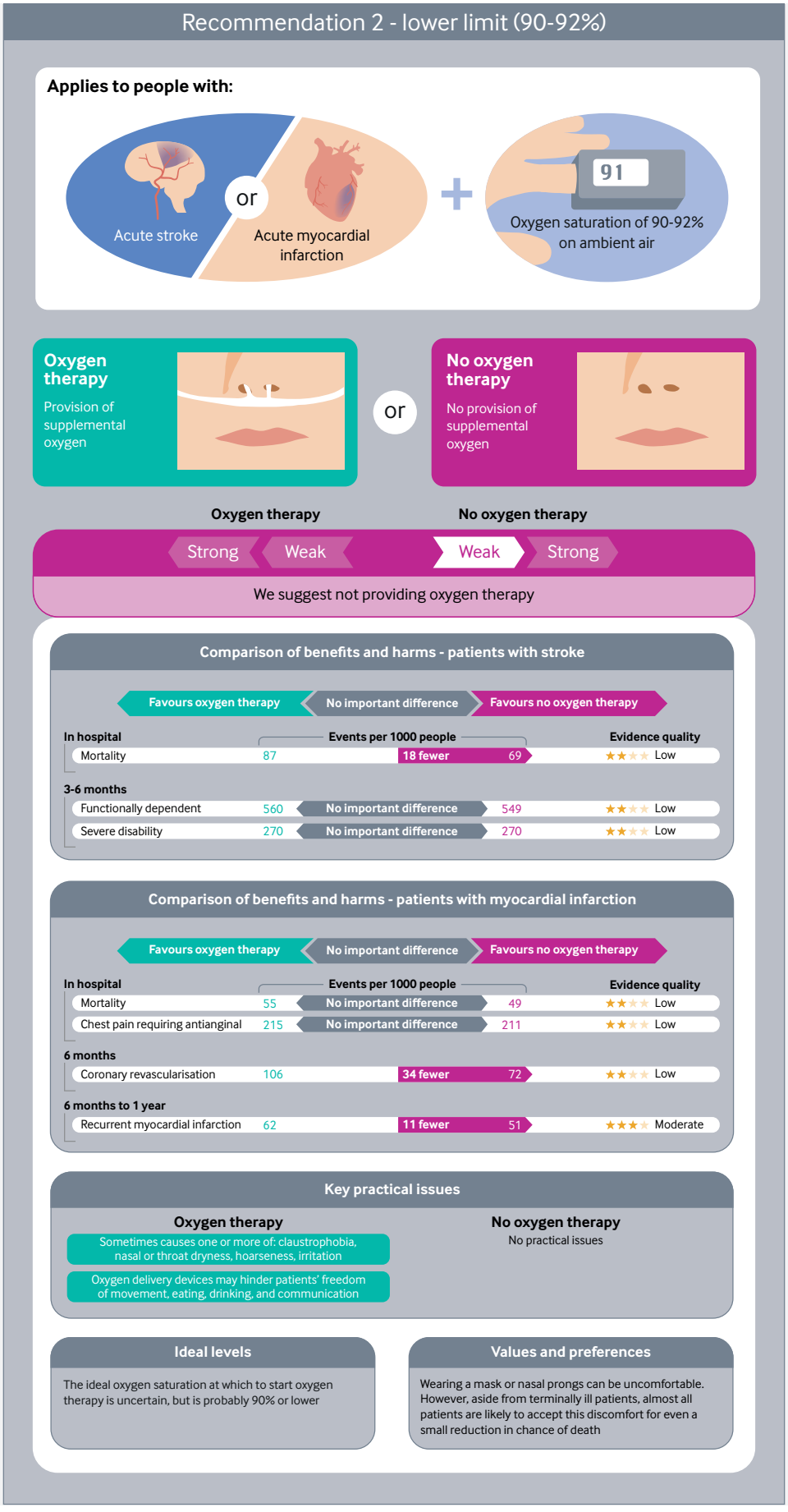

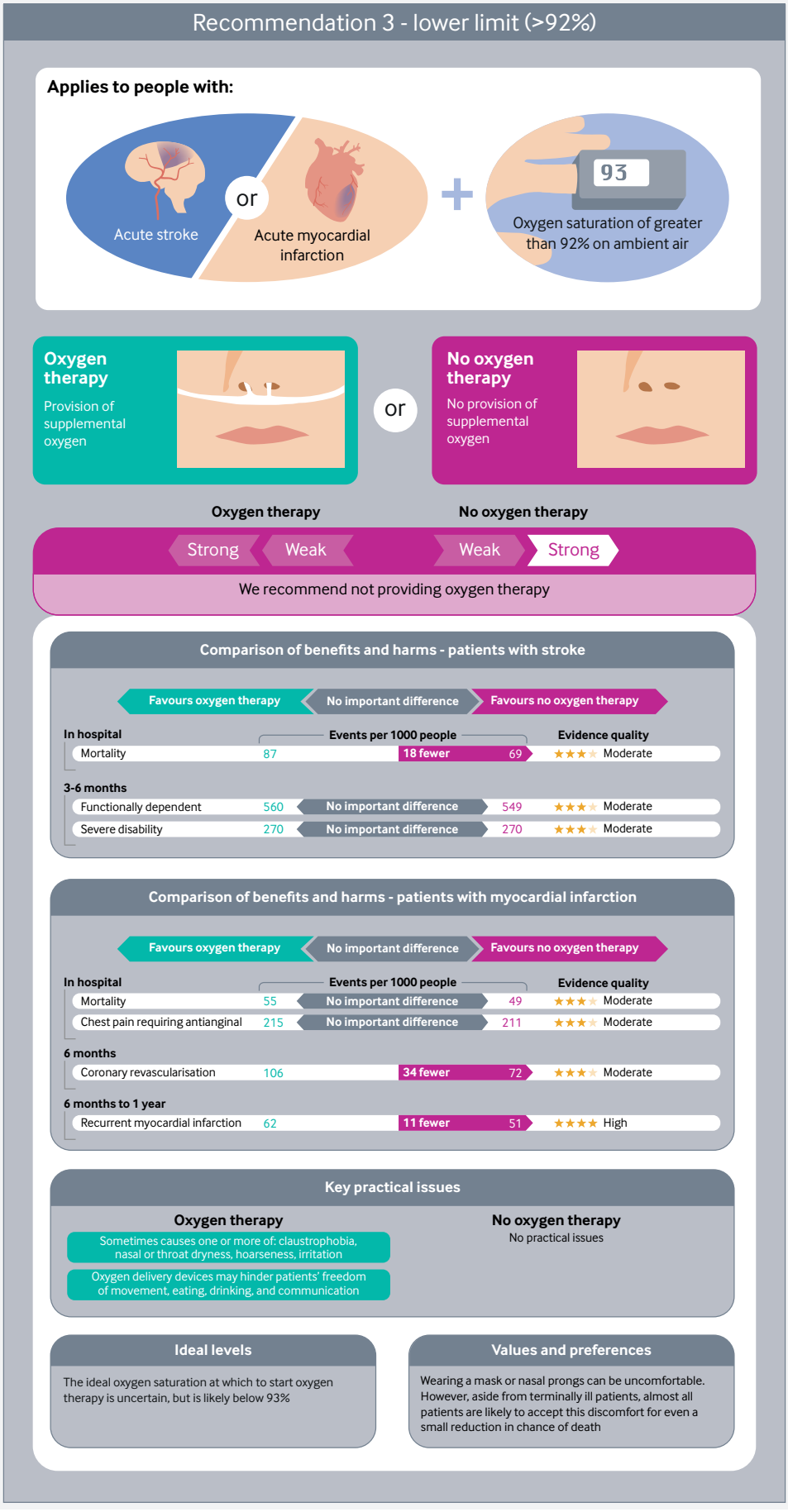

Table 1 | Current guidance on supplemental oxygen therapy

		Recommendations	
Organisation	Condition	Lower limit	Upper limit
AARC, 2002[8]	All patients in acute care facility	Provide oxygen if SaO_2 <90%	No upper limit
AHA/ASA, 2018[9]	Ischaemic stroke	Provide oxygen to maintain SaO_2 >94%	No upper limit
EAN, 2018[10]	Ischaemic stroke	Provide oxygen to maintain normoxia in patients with SaO_2 <95%. Routine use of O_2 is not recommended	None mentioned
AHA, 2013[11]	Myocardial infarction with ST elevation	Provide oxygen in patients with SaO_2 <90%, heart failure, or dyspnoea	No upper limit
ESC, 2017[12]	Myocardial infarction with ST elevation	Provide oxygen in patients with hypoxaemia (SaO_2 <90% or PaO_2 <60 mm Hg). Routine oxygen not recommended if SaO_2 ≥90%	No upper limit
ESC, 2015[13]	Myocardial infarction without ST elevation	Provide oxygen blood oxygen saturation <90% or respiratory distress.	No upper limit
BTS, 2017[14]	Acute medical conditions	Provide oxygen if SaO_2 <94% for most acutely ill patients; <88% for patients with hypercapnia	98% for most patients, 92% for patients with hypercapnia
TSANZ[15]	Acute medical conditions	Provide oxygen if SpO2 <92%	96% for most patients

AARC=American Association for Respiratory Care; AHA=American Heart Association; ASA=American Stroke Association; EAN=European Academy of Neurology; ESC=European Society of Cardiology; BTS=British Thoracic Society; TSANZ=Thoracic Society of Australia and New Zealand.
SaO_2=oxygen saturation; PaO_2=partial pressure of oxygen; SpO_2=peripheral capillary oxygen saturation

for acutely ill adults. In addition to mortality, other difficulties caused by oxygen can include nasal or throat irritation and hampered mobility. Doctors first used oxygen for medical purposes in the 19th century,[6] and its use became routine in the early 20th century.[7] Modern guidelines vary in their advice on when to give oxygen for acute medical conditions and how much to give (see table 1).

HOW THIS RECOMMENDATION WAS CREATED

Our international panel included methodologists, a respiratory therapist/technician, a nurse, patient partners who have been hospitalised for an acute medical condition, pulmonologists, intensivists, internists, an anaesthesiologist, a cardiologist, emergency physicians, and a surgeon (see appendix 1 on bmj.com for details of panel members). They decided on the scope of the recommendation and the outcomes most important to patients. The panel identified three key patient-important outcomes: mortality, hospital acquired infections, and length of hospitalisation. For two specific populations for which there was substantial randomised evidence available, the panel noted additional key outcomes: for patients with stroke, disability; and for patients with acute myocardial infarction, recurrent myocardial infarction, revascularisation, and chest pain.

The panel met to discuss the evidence and formulate a recommendation. No member had financial conflicts of interest; intellectual and professional conflicts were minimised and are transparently described (appendix 2 on bmj.com). The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation,[2] including using the GRADE approach to critically appraise the evidence and create recommendations (appendix 3 on bmj.com).[3] The panel considered the benefits, as well as any harms and burdens, of oxygen therapy, the certainty (quality) of the evidence for each outcome, typical and expected variations in patient values and preferences, acceptability, and feasibility.[22] Within the GRADE framework, recommendations can be either strong or weak (also known as conditional), and for or against a specific course of action.[23]

The panel considered several key practical issues: psychological comfort from oxygen, discomfort (such as nasal irritation), and feasibility (such as impact on nursing resources). The panel was interested in knowing whether the impacts of oxygen were different in different medical conditions or study populations.

When to start oxygen—Peripheral capillary oxygen saturation (SpO_2) thresholds typically trigger the use of oxygen treatment. Thresholds range from SpO_2 <90% to <95% in guidelines. Recommendations for starting oxygen in specific groups vary: patients with stroke with SpO_2 <95%,[9] and, regardless of SpO_2, those experiencing an acute myocardial infarction who feel breathless, are offered oxygen.[11]

When to stop oxygen—Many guidelines do not say how much is too much. Healthcare workers may respond to this advice by keeping a buffer between a patient's SpO_2 and the lower limit (for example, by keeping the SpO_2 close to 100%). Some guidelines advocate targeting a SpO_2 range. Proposed limits range from 98% for most patients, to an upper limit of 92% for patients with risk of hypercapnic respiratory failure, such as patients with chronic obstructive pulmonary disease.[15]

The evidence

A recent systematic review and meta-analysis of randomised controlled trials of acutely ill adults quantified whether inpatients were at greater risk of death with liberal or conservative oxygen therapy.[1] Patients randomised to liberal oxygen therapy were more likely to die (risk ratio 1.21 (95% confidence interval 1.03 to 1.43)). The increase in mortality was highest in the trials with the greatest increase in SpO_2; this suggests a dose-response relation and strengthens the inference that excessive oxygen is a cause of death. The review included 25 randomised controlled trials. Figure 2 outlines key study and participant characteristics. This shows that the results apply to a wide variety of patient groups.

Upper limit of oxygen therapy

The panel had moderate certainty that oxygen increases mortality when the SpO_2 is above 96%. Providing supplemental oxygen above a SpO_2 of 96% probably increases mortality by around 1%. There is probably no difference in length of hospitalisation or risk of hospital acquired infections. Average (median) SpO_2 was 96% in participants randomised to none or limited oxygen therapy. The evidence was rated down from high to moderate certainty for indirectness (uncertain applicability) because the trials used varying SpO_2 thresholds, leaving some uncertainty regarding the value above which mortality increases.

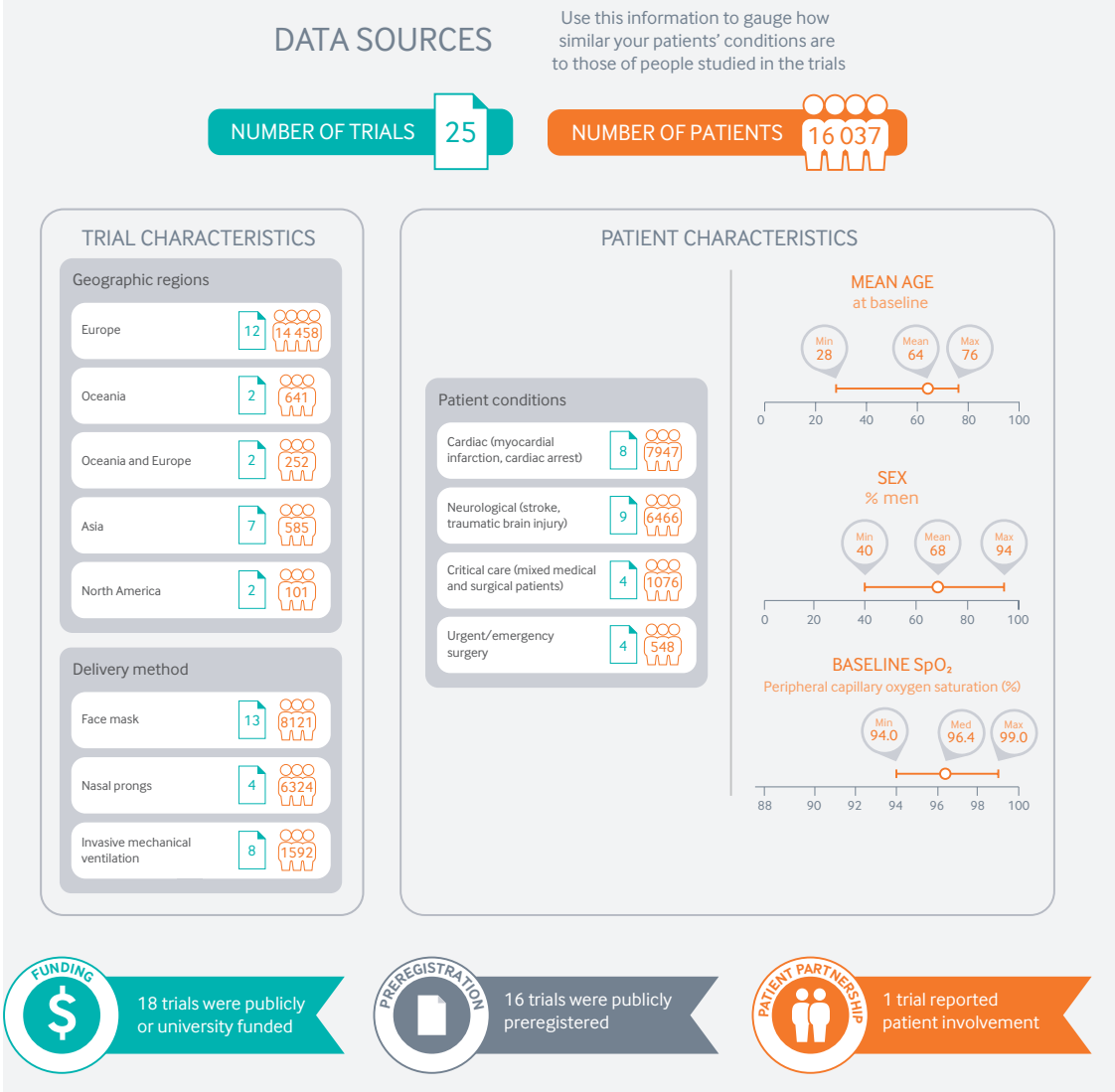

Fig 2| Characteristics of patients and trials included in systematic review of the use of oxygen therapy in acutely ill adults

Lower limit of oxygen therapy

The evidence regarding the lower limit comes from the patients who were included in the clinical trials with baseline SpO_2 over 90%. The evidence in patients with initially higher SpO_2 (>92%) is more certain because most patients in the trials had a baseline SpO_2 above 92%. For example, in the largest of eight trials of patients with stroke only 240 patients (3.1% of 7677 participants) had an initial SpO_2 of 90-93.9%.[16] For myocardial infarction, six trials enrolled 7898 patients: in the largest trial, 1062 patients (16.0%) had an initial SpO_2 ≤94%.[17] For all outcomes, the panel rated down the quality of the evidence for indirectness (uncertain applicability) in patients with a SpO_2 of 90-92%. Because trials informing the lower limit of when to start oxygen were restricted to patients with stroke and myocardial infarction, whether the evidence applies to patients without these conditions is uncertain.

The confidence intervals around the absolute effects in both stroke and myocardial infarction demonstrate that administering supplemental oxygen in patients with these conditions is unlikely to result in an important reduction in mortality. For stroke, supplemental oxygen probably does not reduce disability. In patients with acute myocardial infarction, supplemental oxygen probably does not reduce chest pain, recurrent myocardial infarction, or the need for a coronary revascularisation intervention.

Understanding the recommendations

The infographic summarises the benefits and harms of oxygen therapy.

Scope of recommendations

Our recommendations apply to critically ill or surgical patients with sepsis. They also apply to patients who are en route to hospital in an ambulance and to those who are hospitalised.

We did not consider patients with uncomplicated surgery. There is a separate body of evidence, mostly in the elective surgical setting.[18] There is an unresolved debate about whether supplemental oxygen reduces the risk of

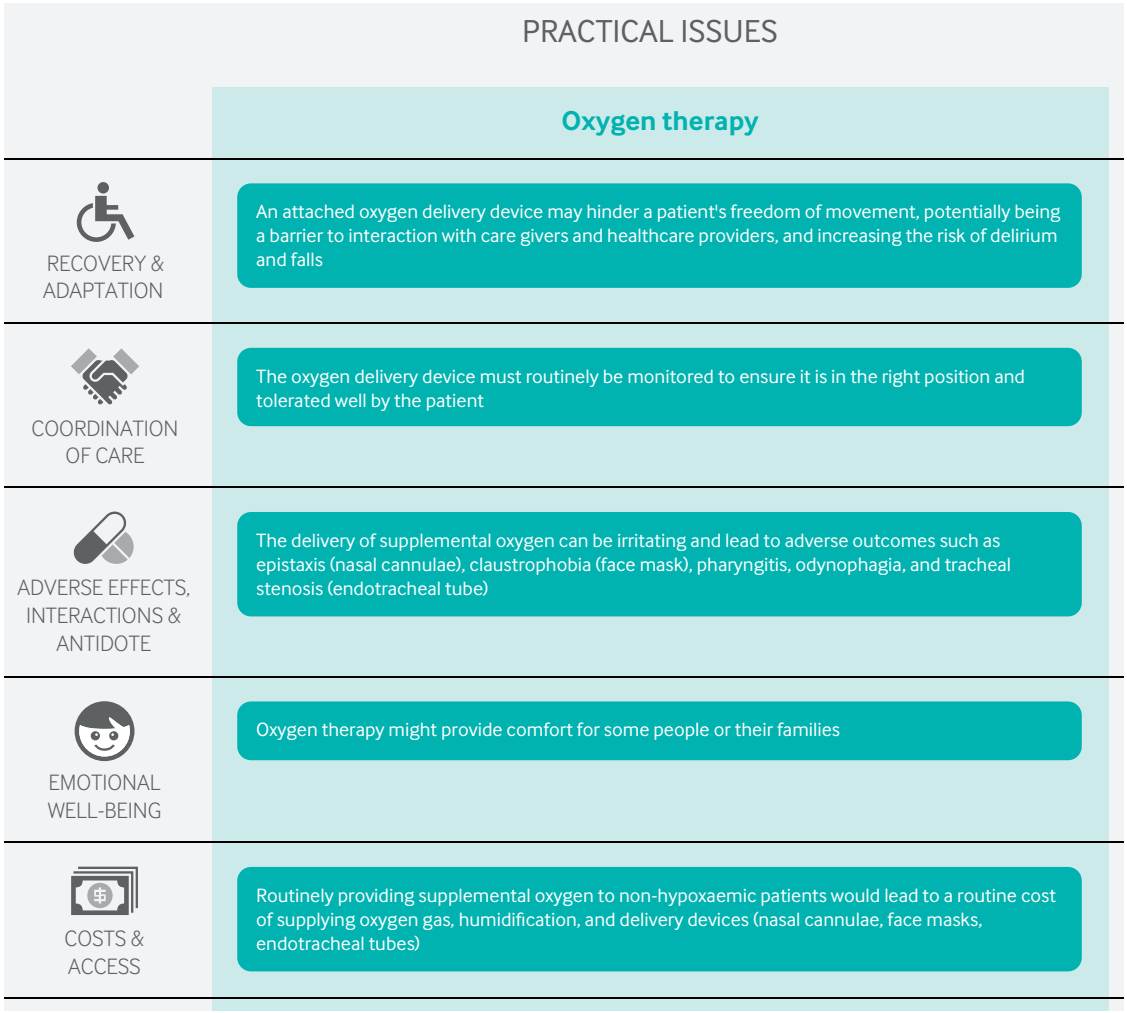

Fig 3| Practical issues about use of oxygen therapy for patients

surgical site infections. Our recommendations may not apply to young children (particularly neonates). There is a separate body of evidence and considerations such as necrotising enterocolitis and retinopathy of prematurity.[19]

Upper limit of oxygen therapy

- The panel makes a strong recommendation that, if supplemental oxygen is administered, clinicians ensure a maximum SpO_2 of 96%
  - This is because saturation above this level likely causes a small but important increased risk of death without plausible benefit. It is probable that the optimal upper SpO_2 limit is lower than 96%, but exactly how much lower is unknown. Patients randomised to more liberal oxygen therapy typically achieved a SpO_2 >96%. The data from the trials provide only limited support for any particular upper threshold, including the 96% chosen by the panel.

Lower limit of oxygen therapy

- For patients with myocardial infarction or stroke, the panel makes a strong recommendation against initiating supplemental oxygen when the initial SpO_2 is >92%
  - In patients with myocardial infarction or stroke, there are probably no benefits to initiating oxygen therapy when SpO_2 is >92%, and it may cause harm.
- The panel makes a weak recommendation against initiating oxygen in these patients with a SpO_2 of 90-92%
  - There may not be any benefits for patients with this lower SpO_2 (90-92%). Fewer patients with this SpO_2 range at baseline were included in the trials, so the panel had less certainty in the results. There is no evidence of benefit from supplemental oxygen initiated in patients with myocardial infarction and stroke whose SpO_2 is ≥90%, but there exists at least a modest risk of harm.

The panel did not issue recommendations for all patients or for other conditions because there were too few participants in the clinical trials who had a baseline SpO_2 <95%.

Values and preferences

The panel believes that almost all patients would value avoiding even a small increased risk of death with supplemental oxygen. Although the panel viewed nasal and throat irritation and a decrease in mobility from oxygen

Box 2 | Examples of conditions that might benefit from higher or lower oxygen saturation thresholds

Lower target (such as SpO_2 88-92%)

- Patients at risk of hypercapnic respiratory failure, for example:
  - Chronic obstructive pulmonary disease
  - Obesity hypoventilation
  - Neuromuscular respiratory diseases
  - Obstructive sleep apnoea
  - Decreased central respiratory drive (such as sedative overdose, stroke, encephalitis)

Higher target (such as SpO_2 approaching 100%)

- Carbon monoxide poisoning
- Cluster headaches
- Sickle cell crisis
- Pneumothorax

Table 2 | New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article.				

therapy as unimportant, they felt that most patients would not choose to endure even a minor inconvenience if there is probably no benefit.

Practical considerations

Figure 3 outlines the key practical issues about the use of oxygen therapy for patients.

A target SpO_2 range of 90-94% seems wide enough to allow for normal fluctuation, and is likely low enough to avoid harm.

Upper thresholds for SpO_2 in patients at risk of hypercapnic respiratory failure should be lower than for other patients (see box 2 for some common examples). Excessive oxygen could increase the risk of needing mechanical ventilation in these patients. Other existing evidence supports a target SpO_2 of about 88-92% in such patients.[20] Box 2 also shows a small number of acute illnesses with specific evidence to support more oxygen.

Shared decision making

The patient panellists said that oxygen therapy is often given to patients with insufficient discussion and explanation. Clearer information may reduce anxiety and improve patient satisfaction in patients where oxygen is needed.

Costs and resources

Patients are unlikely to view the modest cost of oxygen as excessive, particularly in settings where they do not directly pay for their care.

A target SpO_2 range (rather than a lower limit without an upper limit) will need closer monitoring by the healthcare team. Our recommendations do not consider healthcare payer considerations. We suggest a target SpO_2 range that is sufficiently wide that it does not require excessive attention (such as 90-94%). Some patients will have wider SpO_2 fluctuations and may therefore require a wider target range; these patients may also benefit from closer monitoring.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Three people with lived experience of acute medical conditions requiring hospitalisation were members of the panel. They identified and rated outcomes, and helped lead the discussion on values and preferences in a videoconference and email discussions before the full panel meetings. They noted that patients are often underinformed about the reason for and implications of supplemental oxygen therapy.

EDUCATION IN PRACTICE

- How do you use supplemental oxygen in medical patients?
- Based on this article, how do you think your practice might change? Is there anything that you would say to your patient or do differently?
- How might you share this information with your organisation or review local policies on oxygen targets?

Future research

There were no robust data comparing supplemental oxygen to no oxygen in patients with a SpO_2 <90%, so the impact of oxygen therapy in such patients is uncertain.

Addressing the following gaps in our knowledge may inform decision makers and future guideline recommendations:

- Does supplemental oxygen provide benefit to patients experiencing a stroke or myocardial infarction with a SpO_2 <92% (such as 85-92%)?
- Is supplemental oxygen harmful in patients with medical conditions other than stroke or myocardial infarction with a SpO_2 85-94%?

Possible mechanisms

The reasons why excessive supplemental oxygen increases mortality are uncertain. Excessive oxygen can lead to reduced cardiac output, vasoconstriction, inflammation, and oxidative stress.[21] In addition, excessive oxygen might lead to falsely reassuring SpO_2 values and make it difficult to recognise when a patient's condition worsens.

Updates to this article

Table 2 shows evidence that has emerged since the publication of this article. As new evidence is published, a group will assess the new evidence and make a judgment on to what extent it is expected to alter the recommendation.

Contributors: All panel members participated in the teleconferences or email discussions and met all authorship criteria.

Competing interests: All authors have completed the *BMJ* Rapid Recommendations interests disclosure form, and a detailed description of all disclosures is reported in appendix 2 on bmj.com. As with all *BMJ* Rapid Recommendations, the executive team and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions. DK Chu, LH-Y Kim, and W Alhazzani co-authored the systematic review that formed the evidence base for this guideline. RAC Siemieniuk, T Agoritsas, PO Vandvik, L Lytvyn, and GH Guyatt are members of the GRADE Working Group: *BMJ* Rapid Recommendations adheres to GRADE methods.

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Transparency: RAC Siemieniuk affirms that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

Provenance and peer review: Commissioned; externally peer reviewed

1 Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018;391:1693-705. 10.1016/S0140-6736(18)30479-3 pmid:29726345.
2 Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:i5191. 10.1136/bmj.i5191 pmid:27680768.
3 Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. 10.1136/bmj.39489.470347.AD pmid:18436948.
4 Hale KE, Gavin C, O'Driscoll BR. Audit of oxygen use in emergency ambulances and in a hospital emergency department. *Emerg Med J* 2008;25:773-6. 10.1136/emj.2008.059287 pmid:18955625.
5 Burls A, Emparanza JI, Quinn T, Cabello JB. Oxygen use in acute myocardial infarction: an online survey of health professionals' practice and beliefs. *Emerg Med J* 2010;27:283-6. 10.1136/emj.2009.077370 pmid:20385680.
6 Blodgett AN. The continuous inhalation of oxygen in cases of pneumonia otherwise fatal, and in other diseases. *Boston Med Surg J* 1890;123:481-410.1056/NEJM189011201232101.
7 Report of Societies. Oxygen therapy. *BMJ* 1920;i:150-2.
8 Kallstrom TJ. American Association for Respiratory Care (AARC). AARC clinical practice guideline: oxygen therapy for adults in the acute care facility—2002 revision & update. *Respir Care* 2002;47:717-20.pmid:12078655.
9 Powers WJ, Rabinstein AA, Ackerson T, et al. American Heart Association Stroke Council. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2018;49:e46-110. 10.1161/STR.0000000000000158 pmid:29367334.
10 Kobayashi A, Czlonkowska A, Ford GA, et al. European Academy of Neurology and European Stroke Organization consensus statement and practical guidance for pre-hospital management of stroke. *Eur J Neurol* 2018;25:425-33. 10.1111/ene.13539 pmid:29218822.
11 O'Gara PT, Kushner FG, Ascheim DD, et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127:e362-425.pmid:23247304.
12 Ibanez B, James S, Agewall S, et al. ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39:119-77. 10.1093/eurheartj/ehx393 pmid:28886621.
13 Roffi M, Patrono C, Collet JP, et al. ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:267-315. 10.1093/eurheartj/ehv320 pmid:26320110.
14 O'Driscoll BR, Howard LS, Earis J, Mak V. British Thoracic Society Emergency Oxygen Guideline Group BTS Emergency Oxygen Guideline Development Group. BTS guideline for oxygen use in adults in healthcare and emergency settings. *Thorax* 2017;72(Suppl 1):ii1-90. 10.1136/thoraxjnl-2016-209729 pmid:28507176.
15 Beasley R, Chien J, Douglas J, et al. Thoracic Society of Australia and New Zealand oxygen guidelines for acute oxygen use in adults: 'Swimming between the flags'. *Respirology* 2015;20:1182-91. 10.1111/resp.12620 pmid:26486092.
16 Roffe C, Nevatte T, Sim J, et al. Stroke Oxygen Study Investigators and the Stroke OxygenStudy Collaborative Group. Effect of routine low-dose oxygen supplementation on death and disability in adults with acute stroke: the Stroke Oxygen Study Randomized Clinical Trial. *JAMA* 2017;318:1125-35. 10.1001/jama.2017.11463 pmid:28973619.
17 Hofmann R, James SK, Jernberg T, et al. DETO2X–SWEDEHEART Investigators. Oxygen therapy in suspected acute myocardial infarction. *N Engl J Med* 2017;377:1240-9. 10.1056/NEJMoa1706222 pmid:28844200.
18 Wetterslev J, Meyhoff CS, Jørgensen LN, Gluud C, Lindschou J, Rasmussen LS. The effects of high perioperative inspiratory oxygen fraction for adult surgical patients. *Cochrane Database Syst Rev* 2015;(6):CD008884.pm id:26110757.
19 Askie LM, Darlow BA, Finer N, et al. Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration. Association between oxygen saturation targeting and death or disability in extremely preterm infants in the Neonatal Oxygenation Prospective Meta-analysis Collaboration. *JAMA* 2018;319:2190-201. 10.1001/jama.2018.5725 pmid:29872859.
20 Austin MA, Wills KE, Blizzard L, Walters EH, Wood-Baker R. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. *BMJ* 2010;341:c5462. 10.1136/bmj.c5462 pmid:20959284.
21 Hafner S, Beloncle F, Koch A, Radermacher P, Asfar P. Hyperoxia in intensive care, emergency, and peri-operative medicine: Dr. Jekyll or Mr. Hyde? A 2015 update. *Ann Intensive Care* 2015;5:42. 10.1186/s13613-015-0084-6 pmid:26585328.
22 Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;66:726-35. 10.1016/j.jclinepi.2013.02.003 pmid:23570745.
23 Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. Going from evidence to recommendations. *BMJ* 2008;336:1049-51. 10.1136/bmj.39493.646875.AE pmid:18467413.

[1]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton L8S 4K1, Canada
[2]Department of Medicine, McMaster University, Hamilton L8S 4K1, Canada
[3]Departament de Pneumologia, Hospital de la Santa Creu I Sant Pau. Barcelona, Catalonia 08041, Spain
[4]Division of Pulmonary Medicine, Geneva University Hospitals, 1211 Geneva, Switzerland
[5]Faculty of Medicine, Geneva University, 1206 Geneva, Switzerland
[6]Department of Surgery, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario M4N 3M5, Canada
[7]Division General Internal Medicine, University Hospitals of Geneva, 1205 Geneva, Switzerland
[8]Alberta Health Services, Calgary, Alberta T1Y 6J4, Canada
[9]Divisions of Pulmonology and Medical Intensive Care, Stellenbosch University, Cape Town 7505, South Africa
[10]Departments of Internal Medicine and Biochemistry & Molecular Genetics, American University of Beirut Faculty of Medicine and Medical Center, Beirut 1107 2020, Lebanon
[11]Salt Lake City, Utah 84106, USA
[12]Ottawa, Ontario K2P 1C8, Canada
[13]Hatley, Quebec J0B 4B0, Canada
[14]Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway
[15]Division Clinical Epidemiology, University Hospitals of Geneva, 1205 Geneva, 1205, Switzerland

Appendix 1. Rapid Recommendation panel members
Oxygen therapy for acutely ill medical patients: a Rapid Recommendation

Chair:
Gordon H. Guyatt, MD, MSc, FRCPC
General internal medicine
Guideline expert, methodologist
Department of Medicine and Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

Methods co-chair:
Reed A.C. Siemieniuk, MD, FRCPC
General internal medicine
PhD student
Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

Clinical experts:

Derek K Chu, MD, PhD, FRCPC
General internal medicine
Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Elvis M. Irusen, MB, ChB, FCP(SA), PhD, FCCP
Pulomonologist
Critical care clinician
Stellenboch University, Cape Town, South Africa

Jillian LK Siemieniuk, BScN, RN
Registered nurse
Alberta Health Services, Calgary, Alberta, Canada

Imran Satia, MA, MB, BChir, PhD, MRCP
Physician (Respiratory and General Internal Medicine)
McMaster University, Department of Medicine, Division of Respirology, Canada
Royal Blackburn Hospital, East Lancashire Hospitals NHS Trust, UK

Lisa Ha-Yeon Kim, MD, FRCPC
Clinical fellow
Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Maria-Rosa Güell-Rous, MD, PhD
Pulmonologist
Hospital de la Santa Creu I Sant Pau. Barcelona, (Catalonia), Spain

Marwan M. Refaat, MD, FACC, FAHA, FHRS, FESC
Cardiologist
American University of Beirut Faculty of Medicine and Medical Center, Beirut, Lebanon

Paola M. Soccal, MD
Division of Pulmonary Medicine, Geneva University Hospitals, Geneva, Switzerland
Faculty of Medicine, Geneva University, Geneva, Switzerland

Paul J. Karanicolas MD, PhD, FRCSC
General surgeon
Department of Surgery, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
University of Toronto, Toronto, Ontario, Canada

Pauline Darbellay Farhoumand, MD
General internal medicine
Division General Internal Medicine, University Hospitals of Geneva, 1205 Geneva, Switzerland

Waleed Alhazzani MD, MSc, FRCPC
Critical care clinician
Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Patient/carer partners:

Dian Cohen
Former patient
Centre de santé de la vallée Massawippi, Ayer's Cliff, Canada

J. Stephen Mikita
Former patient
Salt Lake City, Utah, 84106, USA

Maureen Smith
Former patient
Ottawa, Ontario, K2P 1C8, Canada

Methodology experts:
Lyubov Lytvyn, MSc
Patient partnership expert, methodologist
PhD student
Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada

Per Olav Vandvik, MD, PhD
General internal medicine
Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway
Department of Medicine, Innlandet Hospital Trust-division, Gjøvik, Norway
Norwegian Institute of Public Health, Oslo, Norway

Thomas Agoritsas, MD, PhD
General internal medicine
Expert in shared decision making research
Division General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland

Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada

Appendix 2: Full list of authors' declarations of interests

Pre-screening

All panel members were pre-screened for conflicts of interest prior to the guideline process that resulted in the *BMJ* Rapid Recommendations. The pre-screening was performed by the RapidRecs Executive team from the non-profit organisation MAGIC (www.magicproject.org) with support and approval from at least two unconflicted *BMJ* editors. No financial conflicts of interest were allowed (specifically, no financial ties to pharmaceutical companies with any stake in corticosteroids) and intellectual and professional conflicts of interest were managed appropriately (see appendix 3: Methods for *BMJ* Rapid Recommendations). Panel members could not have a conflict for the past three years and do not anticipate a conflict arising in the foreseeable future, which we defined as at least one year.

Disclosures

Financial disclosures: No panel members had any financial conflicts of interest to disclose related to this clinical question.

Professional disclosures: Almost all of the physician panel members routinely see patients to whom this guideline applies, but their practice and remuneration will be unaffected by these recommendations.

Intellectual disclosures: Derek Chu, Lisa Kim, and Waleed Alhazzani participated in writing the systematic review that formed the evidence base for this guideline (doi: 10.1016/S0140-6736(18)30479-3). Reed Siemieniuk, Thomas Agoritsas, Per Vandvik, Lyubov Lytvyn, and Gordon Guyatt are members of the GRADE Working Group: BMJ Rapid Recommendations adheres to GRADE methods. No panel member had any other intellectual conflict to disclose.

CHAPTER 12: Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline

The decision to use GI bleeding prophylaxis or not depends on the baseline risk of bleeding, and on the relative efficacy and harms of the available options. We guided the panel through the complex decision making process, and came to recommendations that can be tailored based on a GI bleeding risk score that we developed. There was a lot of forethought put into the interactive graphical presentation of the complex decision-making process, to make the guideline as useable as possible for frontline clinicians.

Citation:
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RAPID RECOMMENDATIONS

Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline

Zhikang Ye,[1 2] Annika Reintam Blaser,[3 4] Lyubov Lytvyn,[2] Ying Wang,[1] Gordon H Guyatt,[2 5] J Stephen Mikita,[6] Jamie Roberts,[7] Thomas Agoritsas,[2 8] Sonja Bertschy,[9] Filippo Boroli,[10] Julie Camsooksai,[11] Bin Du,[12] Anja Fog Heen,[13] Jianyou Lu,[14] José M Mella,[15] Per Olav Vandvik,[16] Robert Wise,[17 18] Yue Zheng,[19] Lihong Liu,[1] Reed A C Siemieniuk[2]

Full author details can be found at the end of the article

Correspondence to: L Liu
liulihong@bjcyh.com

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This *BMJ* Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (http://magicproject.org/) and *The BMJ*. A summary is offered here and the full version including decision aids is on the MAGICapp (https://app.magicapp.org), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualisation of our recommendations to local or other contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact *The BMJ* for permission to reuse content in this article.

ABSTRACT

Clinical question What is the role of gastrointestinal bleeding prophylaxis (stress ulcer prophylaxis) in critically ill patients? This guideline was prompted by the publication of a new large randomised controlled trial.

Current practice Gastric acid suppression with proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) is commonly done to prevent gastrointestinal bleeding in critically ill patients. Existing guidelines vary in their recommendations of which population to treat and which agent to use.

Recommendations This guideline panel makes a weak recommendation for using gastrointestinal bleeding prophylaxis in critically ill patients at high risk (>4%) of clinically important gastrointestinal bleeding, and a weak recommendation for not using prophylaxis in patients at lower risk of clinically important bleeding (≤4%). The panel identified risk categories based on evidence, with variable certainty regarding risk factors. The panel suggests using a PPI rather than a H2RA (weak recommendation) and recommends against using sucralfate (strong recommendation).

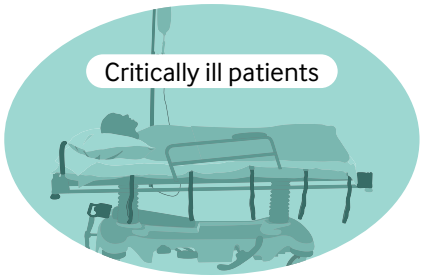
How this guideline was created A guideline panel including patients, clinicians, and methodologists produced these recommendations using standards for trustworthy guidelines and the GRADE approach. The recommendations are based on a linked systematic review and network meta-analysis. A weak recommendation means that both options are reasonable.

The evidence The linked systematic review and network meta-analysis estimated the benefit and harm of these medications in 12 660 critically ill patients in 72 trials. Both PPIs and H2RAs reduce the risk of clinically important bleeding. The effect is larger in patients at higher bleeding risk (those with a coagulopathy, chronic liver disease, or receiving mechanical ventilation but not enteral nutrition or two or more of mechanical ventilation with enteral nutrition, acute kidney injury, sepsis, and shock) (moderate certainty). PPIs and H2RAs might increase the risk of pneumonia (low certainty). They probably do not have an effect on mortality (moderate certainty), length of hospital stay, or any other important outcomes. PPIs probably reduce the risk of bleeding more than H2RAs (moderate certainty).

Understanding the recommendation In most critically ill patients, the reduction in clinically important gastrointestinal bleeding from gastric acid suppressants is closely balanced with the possibility of pneumonia. Clinicians should consider individual patient values, risk of bleeding, and other factors such as medication availability when deciding whether to use gastrointestinal bleeding prophylaxis. Visual overviews provide the relative and absolute benefits and harms of the options in multilayered evidence summaries and decision aids available on MAGICapp.

Visual summary of recommendation

Population



Including:

- ✔ Patients admitted to intensive care units

Does not apply to:

- ✖ Patients receiving gastric acid suppression for another therapeutic indication

On average, 4% of critically ill patients develop gastrointestinal bleeding. One cause is physiologic stress leading to stress ulcers in the oesophagus, stomach, or duodenum, but critical illness is also associated with other forms of upper gastrointestinal bleeding.

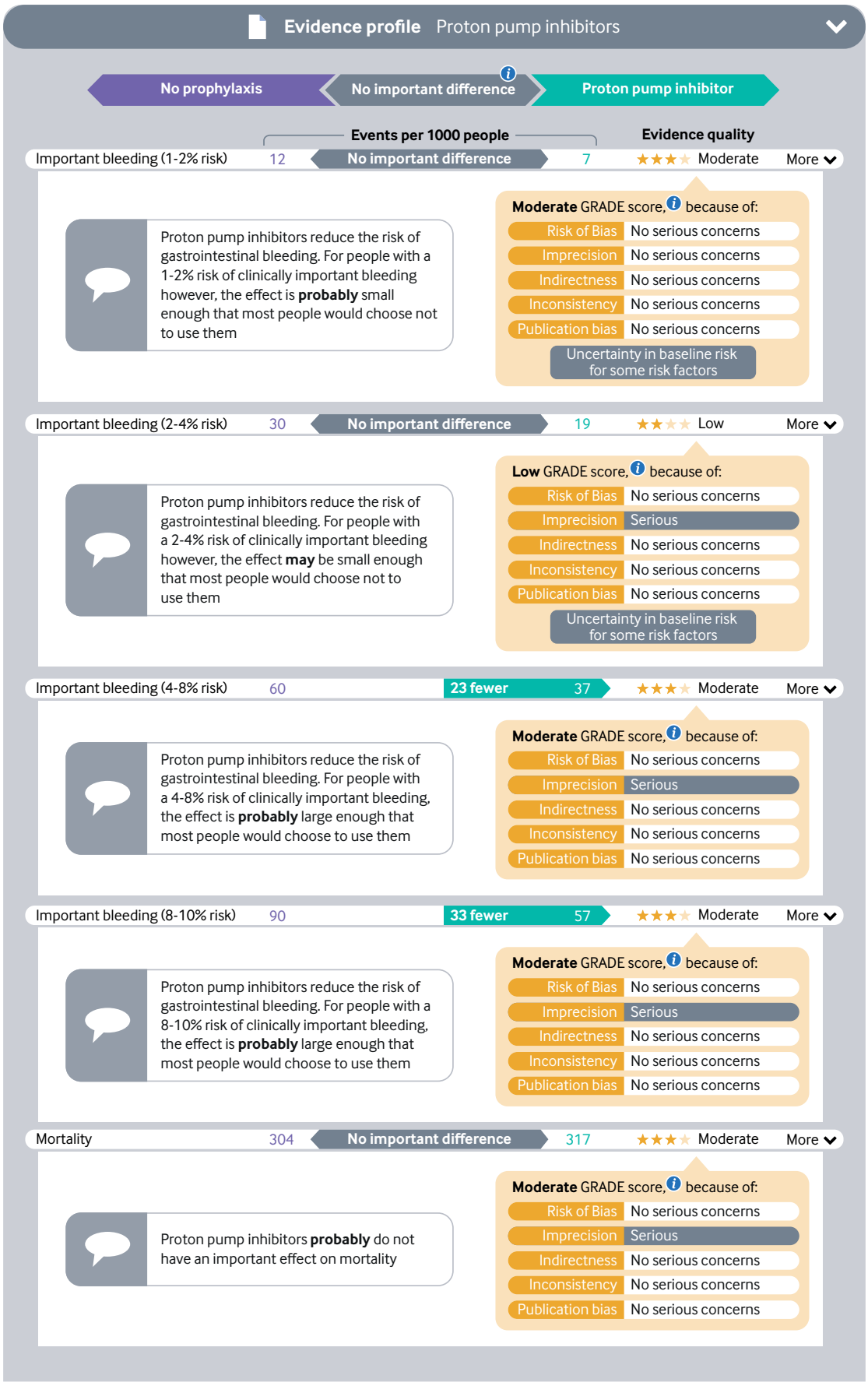
Recommendation 1

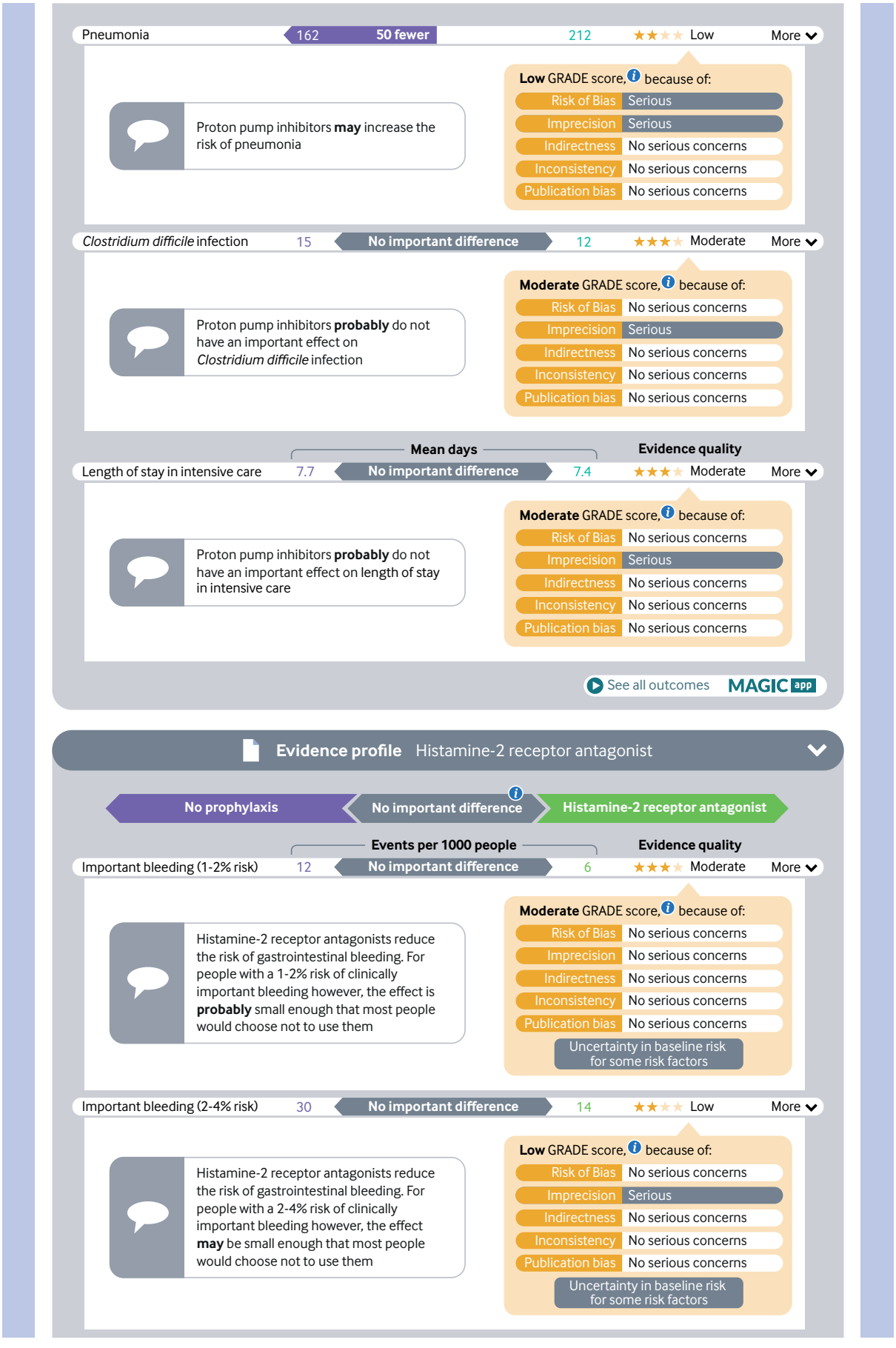
✖ No prophylaxis	or	Prophylaxis ✔
Strong ⓘ Weak ⓘ		**Weak** ⓘ Strong ⓘ

"We suggest using acid suppression prophylaxis for people with higher risk of gastrointestinal bleeding (4% or higher)"

Calculating bleed risk

Highest risk	8-10%	Mechanical ventilation without enteral nutrition Chronic liver disease ⓘ
High risk	4-8%	Concerning coagulopathy ⓘ 2 or more factors from 2-4% category
SUGGESTED CUT POINT FOR OFFERING PROPHYLAXIS		
		For patients near this threshold, individual values and preferences become more important
Moderate risk	2-4%	Mechanical ventilation with enteral nutrition Acute kidney injury Sepsis Shock ⓘ
Low risk	1-2%	Critically ill patients without any risk factor Acute hepatic failure Use of steroids or immunosuppression Use of anticoagulants ⓘ Cancer Male gender





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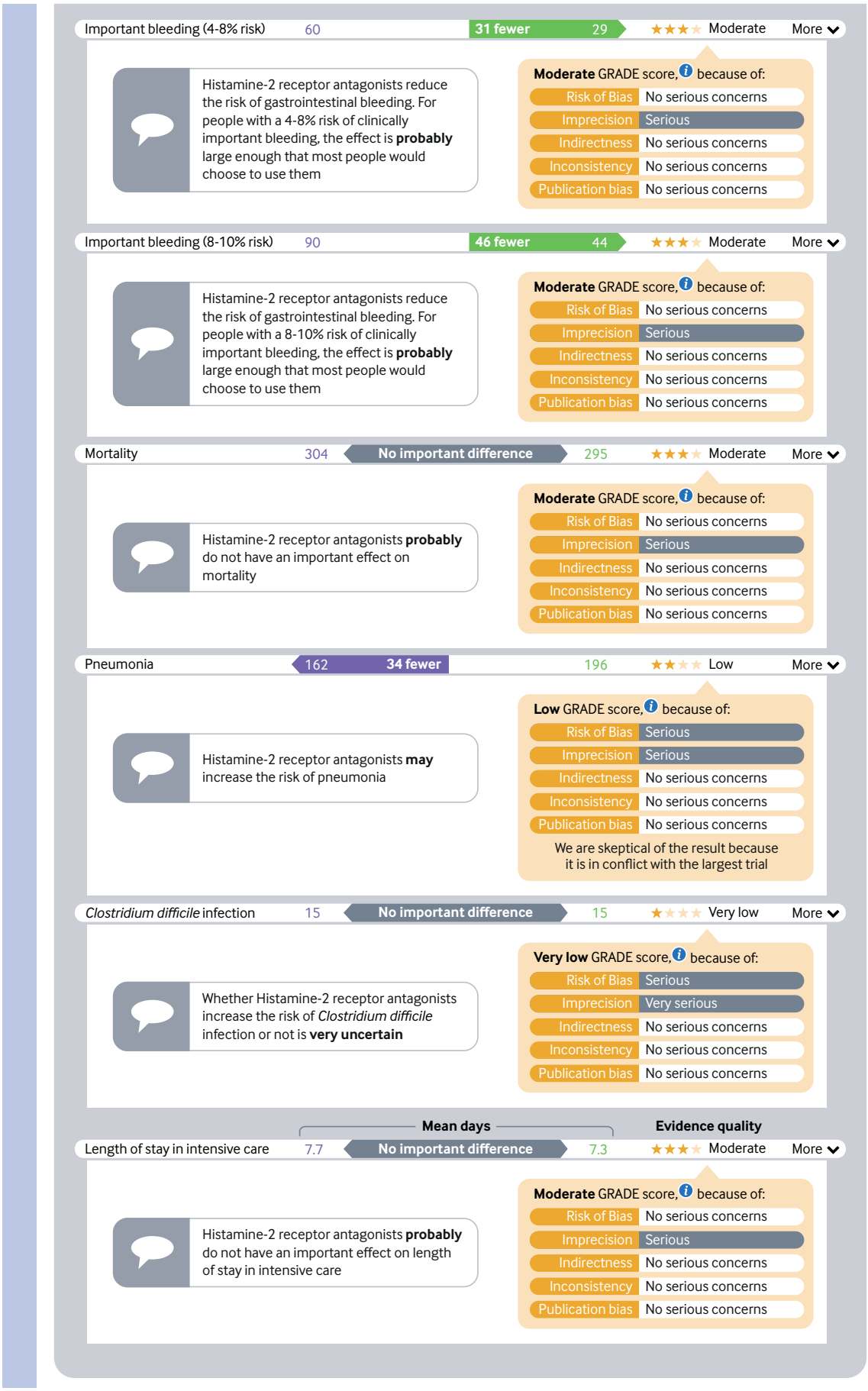


Individual considerations

Key practical issues

No prophylaxis	Proton pump inhibitors	Histamine-2 receptor antagonists
None	Can be administered intravenously or enterally	
	Typically administered once per day	Typically administered two or three times per day

Duration of treatment

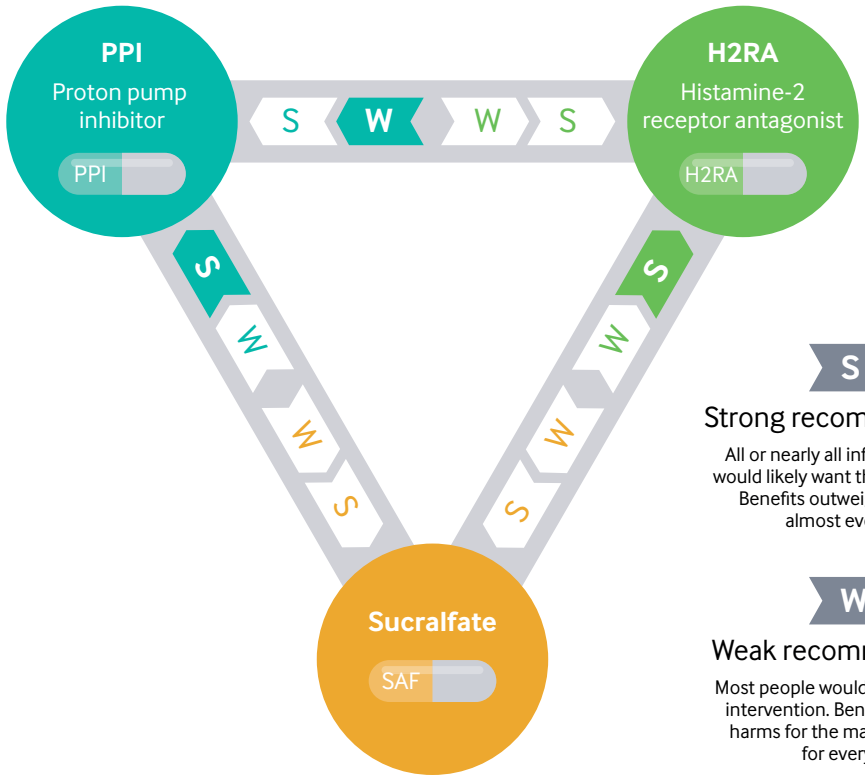
A system should be in place to prevent inadvertent continuation of gastric acid suppression

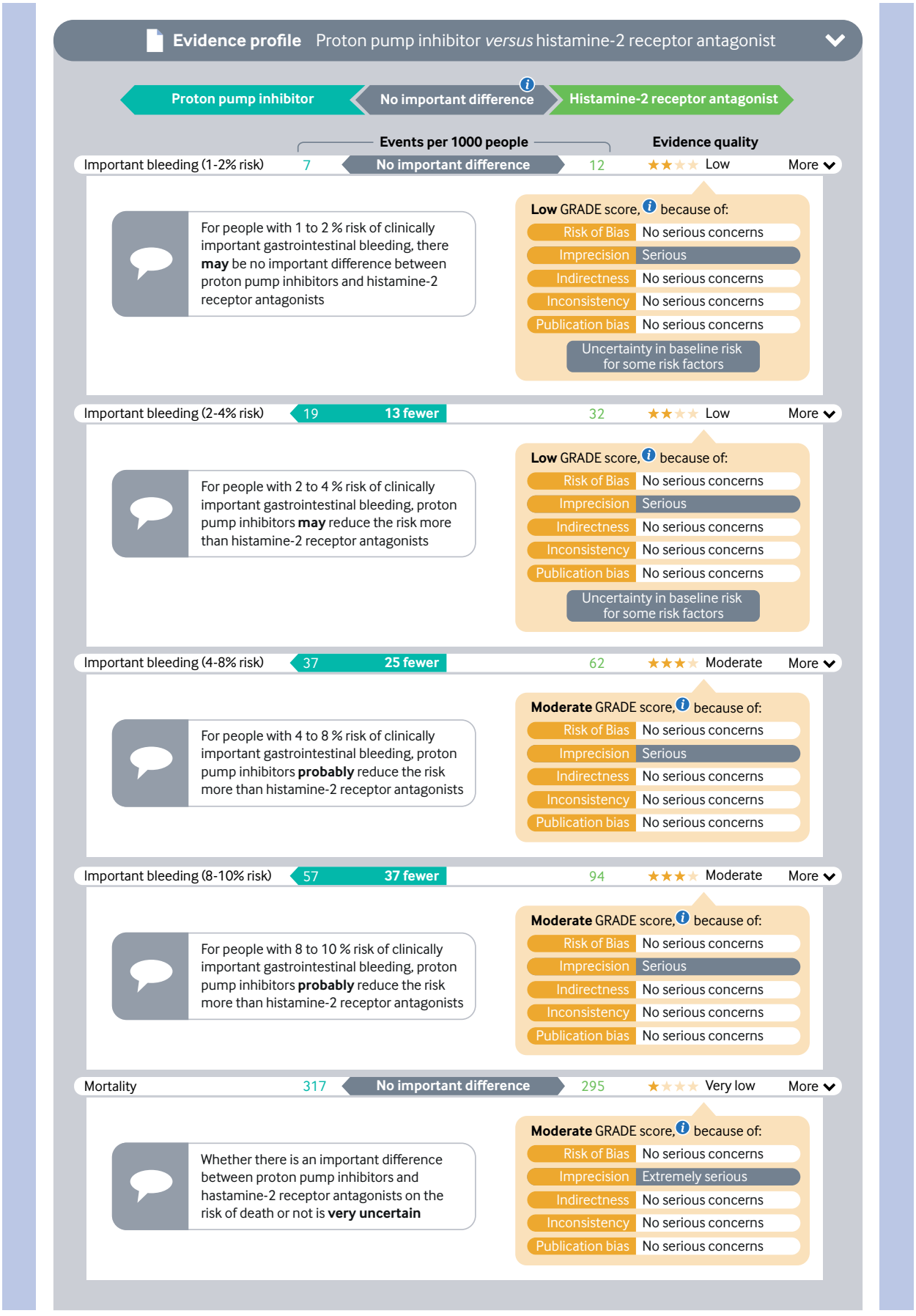
Values and preferences

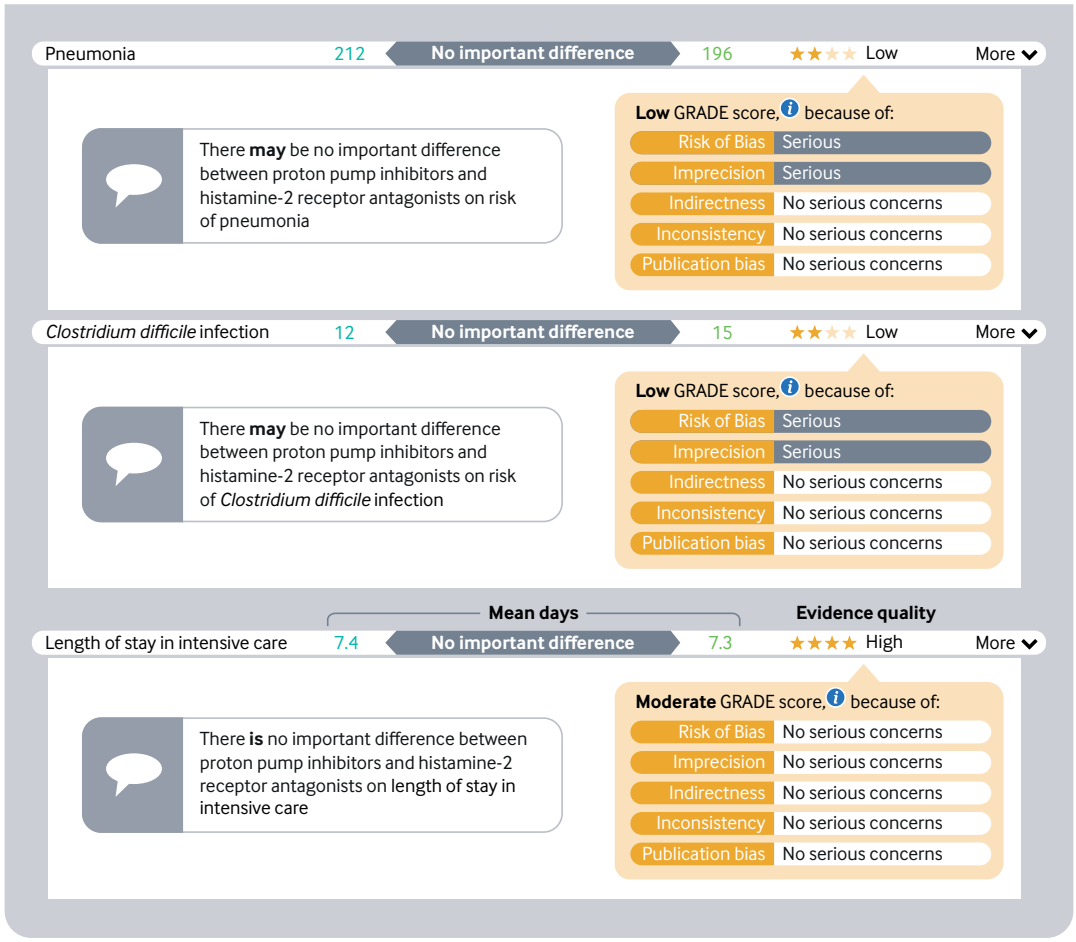
It may be challenging to implement shared decision making because there are often many other more important decisions. However, shared decision making should be pursued whenever possible.

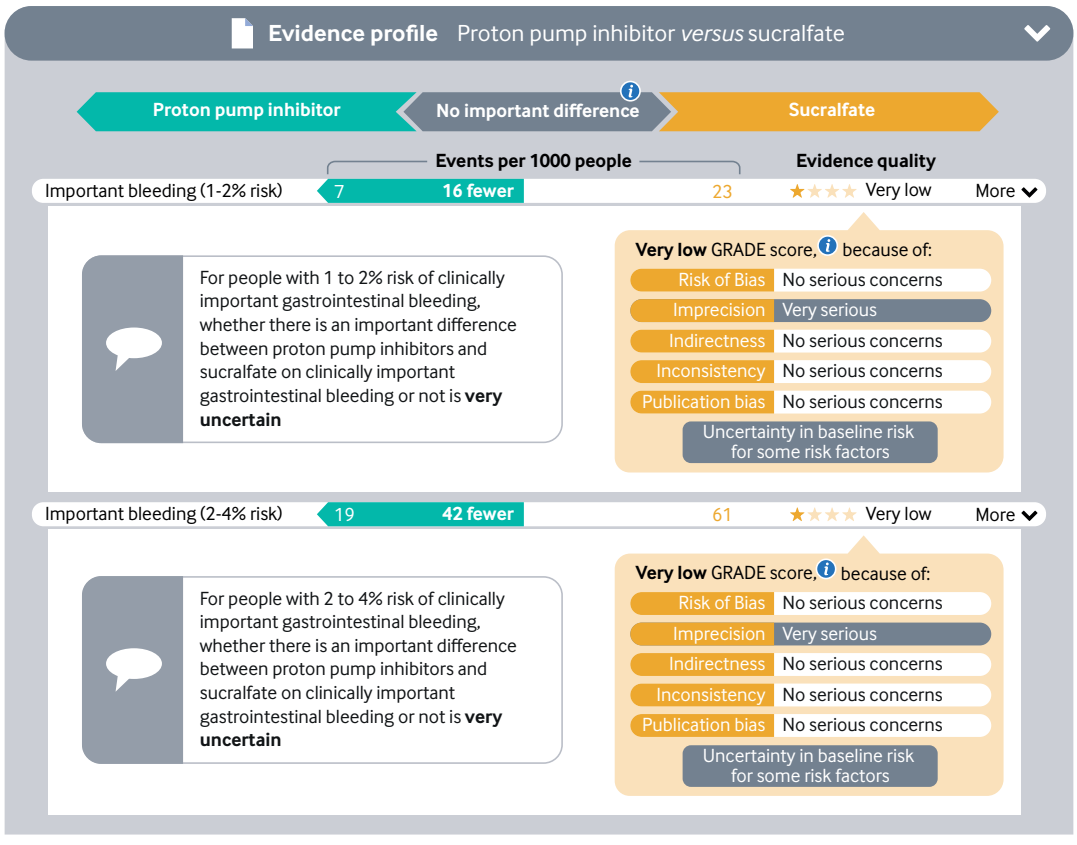
Recommendation 2

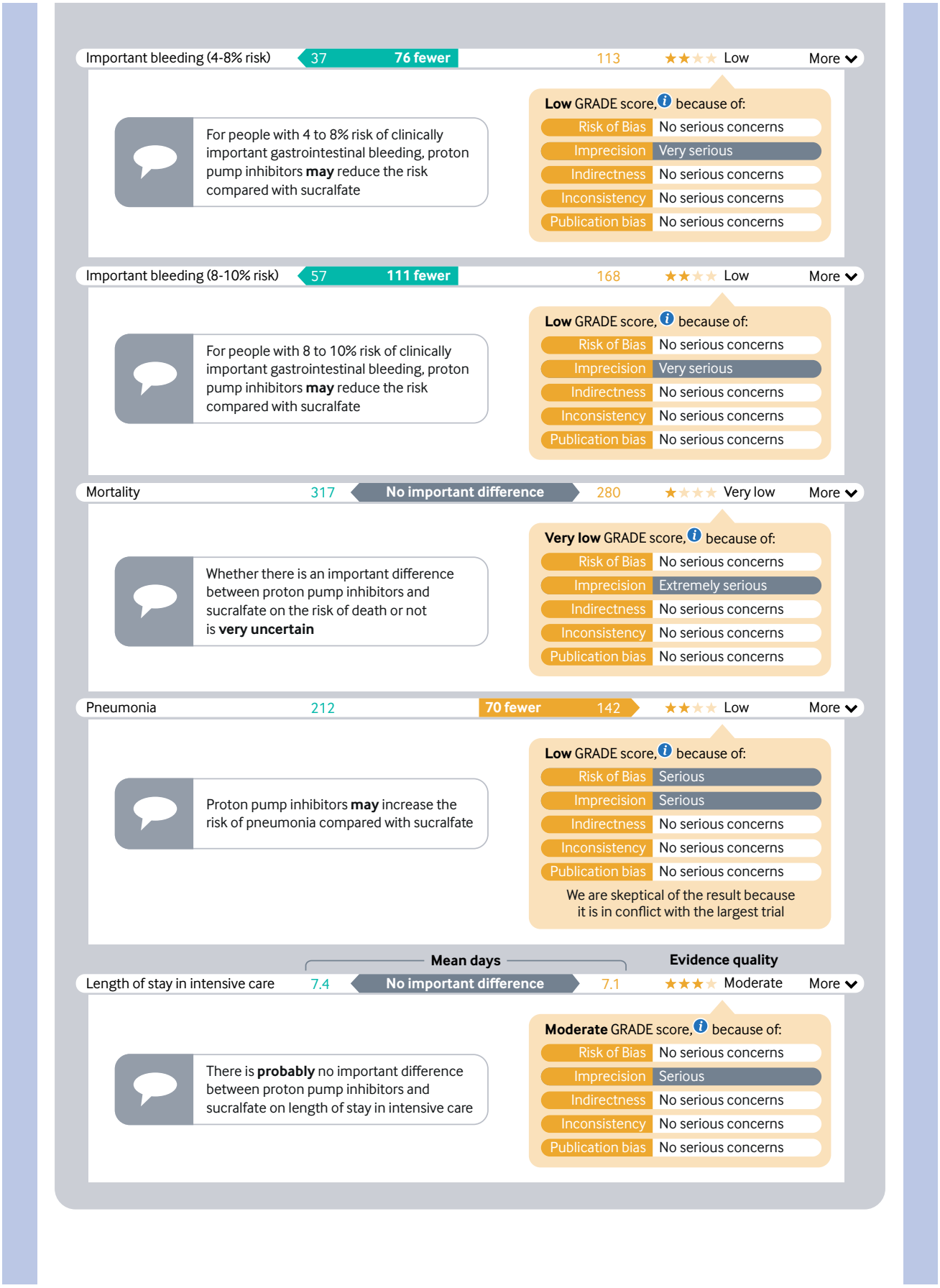
> In critically ill patients who are going to receive prophylaxis against gastrointestinal bleeding, we suggest a proton pump inhibitor. A histamine-2 receptor antagonist is also a reasonable choice. We recommend not using sucralfate

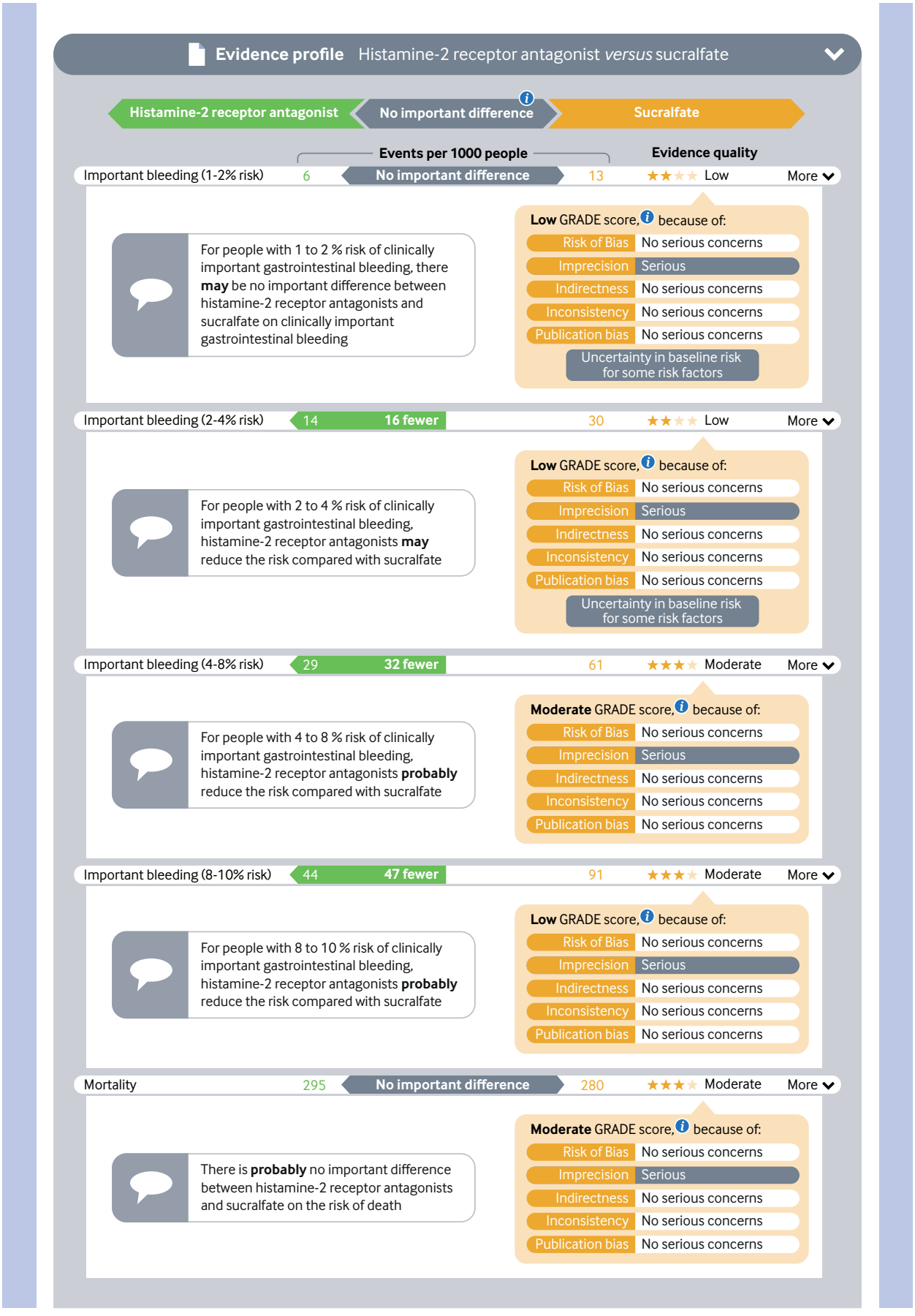




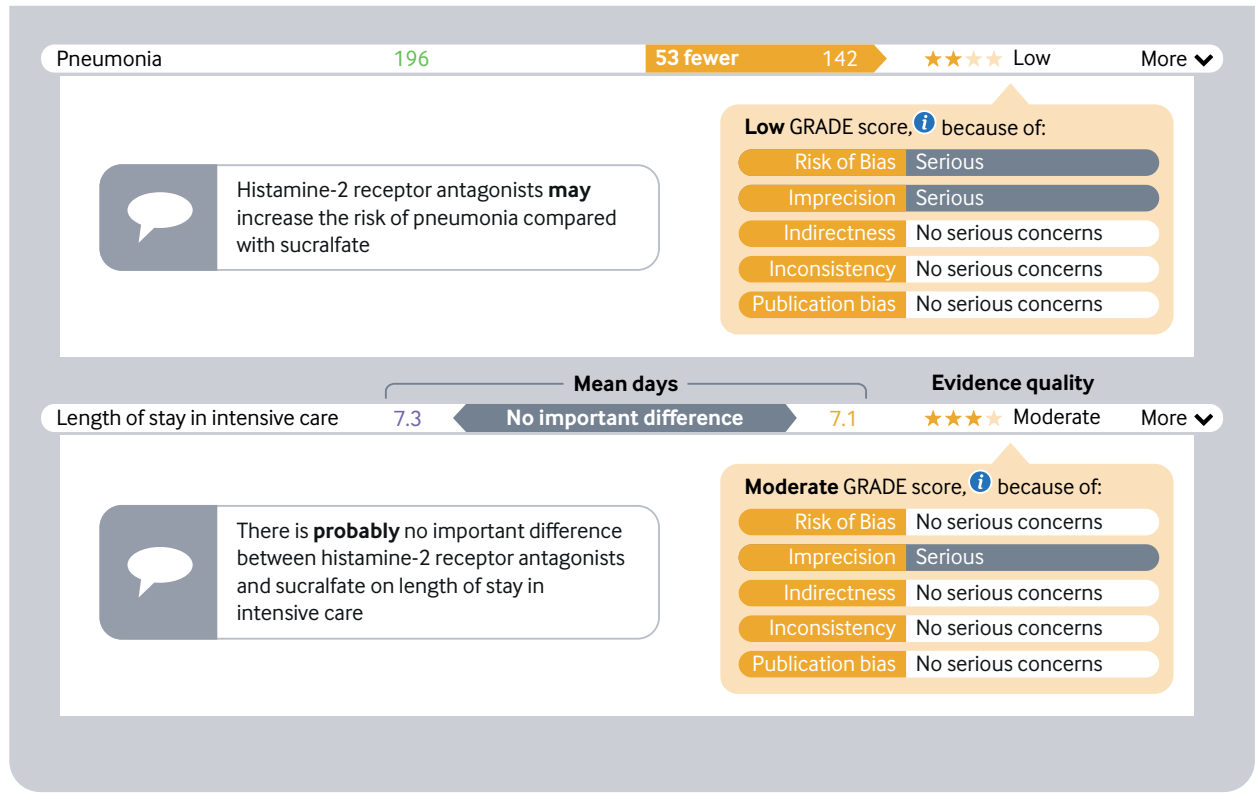








RAPID RECOMMENDATIONS



Individual considerations

Key practical issues

Proton pump inhibitors	Histamine-2 receptor antagonists	Sucralfate
Can be administered intravenously or enterally		Must be given enterally
Typically administered once per day	Typically administered two or three times per day	Typically administered four times per day

Values and preferences

We think that all or almost all patients would prefer to use a gastric acid suppressant with proven effectiveness

Costs

Intravenous formulations are usually more expensive than enteral formulations. Costs vary between specific agents

Critically ill patients are at risk of gastrointestinal bleeding. The mechanisms vary and include physiologic stress that can lead to stress ulcers in the oesophagus, stomach, or duodenum. Clinicians can prescribe gastric acid suppressants for prophylaxis against clinically important gastrointestinal bleeding in critically ill patients. Clinically important bleeding is overt and has important consequences: about half of affected patients receive endoscopy or surgery, and approximately half of patients receive a transfusion of at least two units of packed red blood cells.[1]

This *BMJ* Rapid Recommendation was triggered by SUP-ICU, a randomised controlled trial published in October 2018.[1] It found no significant net benefit, and raised questions about the widespread use of gastrointestinal bleeding prophylaxis.

We aimed to translate this new evidence for clinicians and patients using the GRADE approach and standards for trustworthy guidelines.[2 3] The guideline committee asked two key questions:

1 In which patients, if any, should gastrointestinal bleeding prophylaxis be used?
2 If gastrointestinal bleeding prophylaxis is used, what agent is best?

The box shows all publications linked in this rapid recommendation package. The main infographic provides an overview of the absolute benefits and harms for four interventions: proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), sucralfate, and no prophylaxis.

Current practice

Existing recommendations vary in the indications for gastrointestinal bleeding prophylaxis (see table 1). There are no recommendations for critically ill patients as a broad target group, and guidelines that apply to specific subgroups of patients (such as those with trauma or sepsis) do not consider differences in importance of individual risk factors. They also do not present the benefits and harms in a way that is usable for individualised decision making. Inappropriate overuse of gastrointestinal bleeding prophylaxis is not only a serious problem in critical care but also general inpatient and outpatient settings.[4 5]

Table 1 | Current recommendations for stress ulcer prophylaxis

Guideline	Agents to be used	Indications for prophylaxis
SCCM and ESICM "Surviving sepsis," 2016[15]	PPIs or H2RAs (weak recommendation)	Patients with sepsis or septic shock with risk factors for gastrointestinal bleeding, which include mechanical ventilation for >48 hours, coagulopathy, pre-existing liver disease, need for RRT, and higher organ failure scores
DASAIM and DSIT, 2014[16]	PPIs rather than H2RAs (weak recommendation)	Insufficient evidence to make any recommendation
Eastern Association for the Surgery of Trauma, 2008[17]	PPIs or H2RAs or cytoprotective agents	Mechanical ventilation; coagulopathy; traumatic brain injury; major burn; ICU patients with multi-trauma, sepsis, or acute renal failure; ICU patients with ISS>15 or receiving high dose corticosteroids

SCCM=Society of Critical Care Medicine; ESICM=European Society of Intensive Care Medicine; DASAIM=Danish Society of Anesthesiology and Intensive Care Medicine; DSIT=Danish Society of Intensive Care Medicine; PPIs=proton pump inhibitors; H2RAs=histamine-2 receptor antagonists; RRT=renal replacement therapy ICU=intensive care unit; ISS=Injury Severity Score.

Linked resources in this *BMJ* Rapid Recommendations cluster

- Ye Z, Reintam Blaser A, Lytvyn L, et al. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. *BMJ* 2019;367:l6722
  - Summary of the results from the Rapid Recommendation process
- Wang Y, Ye Z, Ge L, et al. Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: systematic review and network meta-analysis. *BMJ* 2019;367:l6744
  - Review and network meta-analysis of all available randomized trials that assessed prevention of gastrointestinal bleeding in critically ill patients
- MAGICapp (https://app.magicapp.org/public/guideline/j96g2L)
  - Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

PPIs are the most commonly used agents, followed by H2RAs; sucralfate and antacids are seldom used.[6 7] Most guidelines recommend using either a PPI or H2RA, but there is some variation in the preferred agent.[8]

The evidence

The SUP-ICU trial was incorporated into a linked systematic review and network meta-analysis comparing PPIs, H2RAs, and sucralfate versus one another or placebo (no prophylaxis). The review included 72 randomised controlled trials and 12 660 patients admitted to intensive care units comparing PPIs, H2RAs, sucralfate versus one another or no prophylaxis. Figure 2 provides an overview of the trials and participants.

How we stratified the risk of bleeding

Prophylaxis cannot reduce the risk of bleeding to zero, but the higher the risk of bleeding, the larger is the expected benefit of prophylaxis. Therefore, we first searched for evidence on risk factors for bleeding; we used evidence from a systematic review of risk factors.[9] Based on studies that we considered low risk of bias, we grouped patients into four categories: low risk, moderate risk, high risk, and highest risk (see table 2 and appendix 1 on bmj.com for details). We had varying degrees of certainty in different risk factors. In particular, the available evidence may underestimate the risk of bleeding for several possible risk factors in the low and moderate risk categories (that is, acute hepatic failure and use of anticoagulation might increase the risk of bleeding more than we estimated).

Gastrointestinal bleeding

Clinically important gastrointestinal bleeding is typically defined as evidence of upper gastrointestinal bleeding with any of the following: significant haemodynamic changes not explained by other causes, need for transfusion of more than two units of blood, significant decrease in haemoglobin level, evidence of bleeding on upper gastrointestinal endoscopy, or need for surgery to control bleeding. Both PPIs and H2RAs reduce the risk of clinically important bleeding compared with no

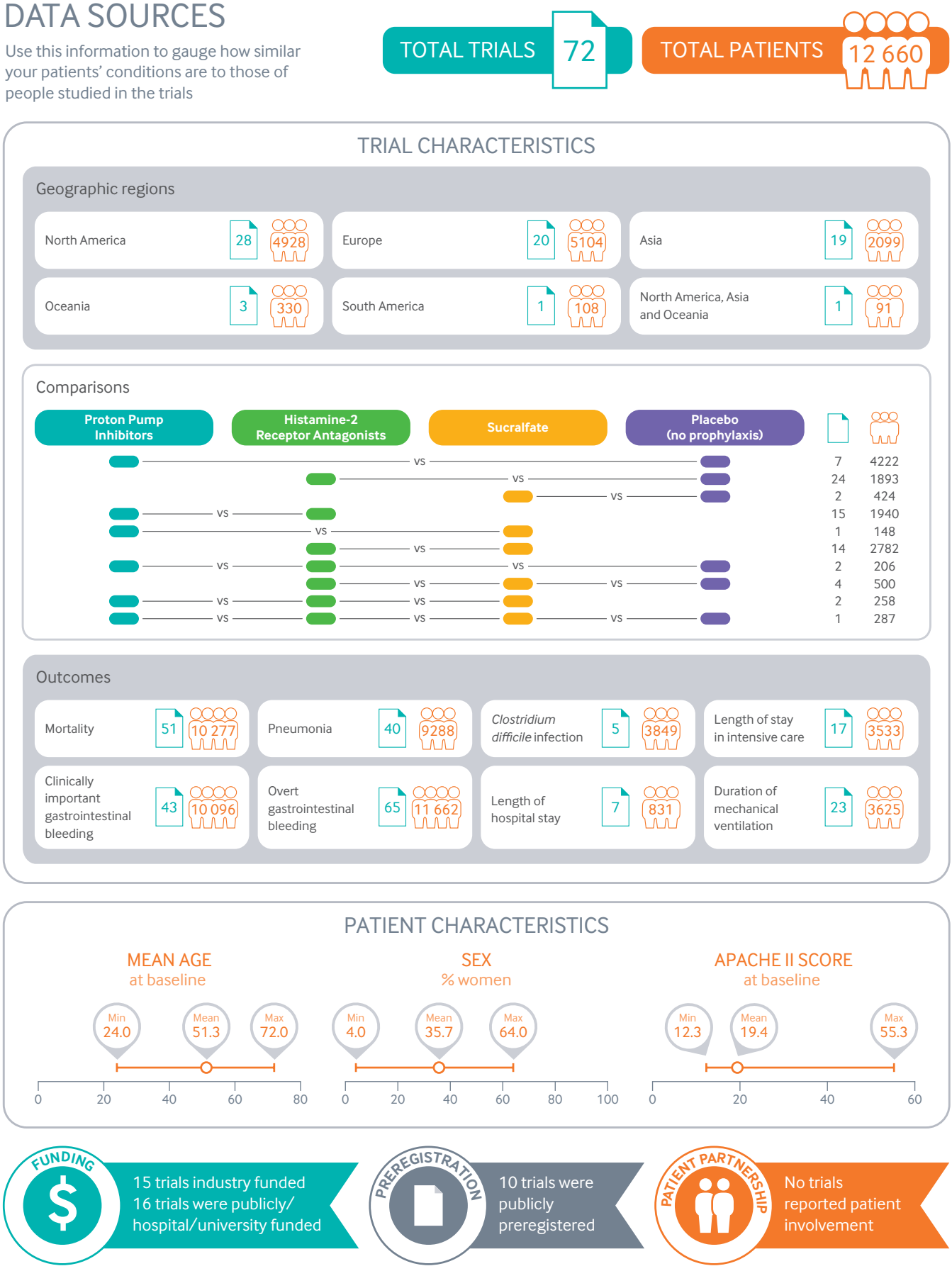


Fig 2| Characteristics of patients and trials included in systematic review of gastrointestinal bleeding prophylaxis in critically ill adults

Table 2 | Baseline risk of clinically important gastrointestinal bleeding for each risk factors

	Risk of clinically important gastrointestinal bleeding (per 1000)		Risk of overt gastrointestinal bleeding (per 1000)	
Risk factors	Baseline risk	Representative risk chosen for evidence profile	Baseline risk	Representative risk chosen for evidence profile
Low risk group*				
Critically ill without any risk factor Acute hepatic failure Use of corticosteroids or immunosuppression Use of anticoagulants† Cancer Male gender	10-20	12	20-60	26
Moderate risk group				
Mechanical ventilation with enteral nutrition Shock‡ Sepsis Acute kidney injury	21-40	30	61-90	75
High risk group				
Coagulopathy§ Two or more of factors in moderate risk group	41-80	60	91-160	125
Highest risk group				
Mechanical ventilation without enteral nutrition Chronic liver disease¶	81-100	90	161-220	190

*Including proposed risk factors without evidence that they substantially increase risk of gastrointestinal bleeding.
†Vitamin K antagonists, direct acting oral anticoagulants, therapeutic doses of unfractionated or low molecular weight heparin, intravenous direct thrombin (II) inhibitors, adenosine diphosphate receptor inhibitor and similar drugs.
‡Continuous infusion with vasopressors or inotropes, systolic blood pressure <90 mm Hg, mean arterial blood pressure <70 mm Hg, plasma lactate level ≥4 mmol/l.
§Platelets $<50\times10^9$/L, international normalised ratio >1.5, or prothrombin time >20 seconds.
¶Portal hypertension, cirrhosis proved by biopsy, computed tomography, ultrasound scan, or medical history of variceal bleeding or hepatic encephalopathy.

prophylaxis, but the magnitude of benefit depends on the baseline risk of bleeding without prophylaxis. In patients at highest risk (>8%), PPIs and H2RAs reduce clinically important bleeding by 3-5%. In critically ill patients at low risk (<2%), PPIs and H2RAs reduce clinically important bleeding by less than 1%.

Overt bleeding (that is visible as haematemesis, haematochezia, or melaena) does not always have important consequences: overt bleeding, which includes important and unimportant bleeding, is more common than clinically important bleeding. The absolute reduction of overt bleeding achieved with prophylaxis is approximately twice that of clinically important bleeding (see full evidence profile in MAGICapp).

In the linked meta-analysis, results from head-to-head clinical trials suggest that PPIs possibly reduce the risk of clinically important bleeding more than H2RAs, but the confidence interval includes no difference (odds ratio 0.58 (95% confidence interval 0.29 to 1.17)). PPIs do reduce the risk of overt bleeding more than H2RAs.

Sucralfate does not seem to reduce the risk of clinically important bleeding compared with placebo (odds ratio 0.76 (0.36 to 1.62)).

Pneumonia

Both PPIs and H2RAs might increase the absolute risk of pneumonia compared with no prophylaxis by approximately 4%, but certainty is low. The credible intervals include no difference, and the most recent and the largest blinded randomised controlled trial suggested that there may not be a difference in risk of pneumonia between the PPI and placebo groups.[1]

Other outcomes

Gastric acid suppression did not seem to affect any other important outcomes, including mortality, length of hospital stay, length of intensive care stay, duration of mechanical ventilation, or *C difficile* infection. Quality of evidence varied across these outcomes; for *C difficile* infection, quality was low.

Understanding the recommendations

Strong recommendations suggest that all or nearly all patients would choose the recommended option. Weak recommendations reflect the uncertainty in the typical patients' preferences, as well as the likely wide variability in preferences between patients.

Who does it apply to?

This guideline applies to critically ill patients. Patients who have a substantial short term risk of dying due to an acute illness are considered critically ill and are commonly treated in an intensive care unit. Accordingly, studies performed in patients admitted to intensive care were considered in the linked systematic review. However, admission practices of intensive care units are variable, and defining critical illness is difficult, so clinical judgment regarding whether this guideline applies to a specific patient may be warranted.

Our recommendations do not apply to patients who have other indications for gastric acid suppression (such as peptic ulcer disease, gastroesophageal reflux disease, Zollinger-Ellison syndrome, or eradication of *Helicobacter pylori*). Patients already taking gastric acid suppressants should probably continue to receive them during an acute illness because abrupt withdrawal may cause rebound acid hypersecretion.[10] However, prolonged use of acid suppressants without clear indication is not advocated.

Values and preferences

We did not find any published evidence addressing patient values and preferences (appendix 2 on bmj.com). Overall,

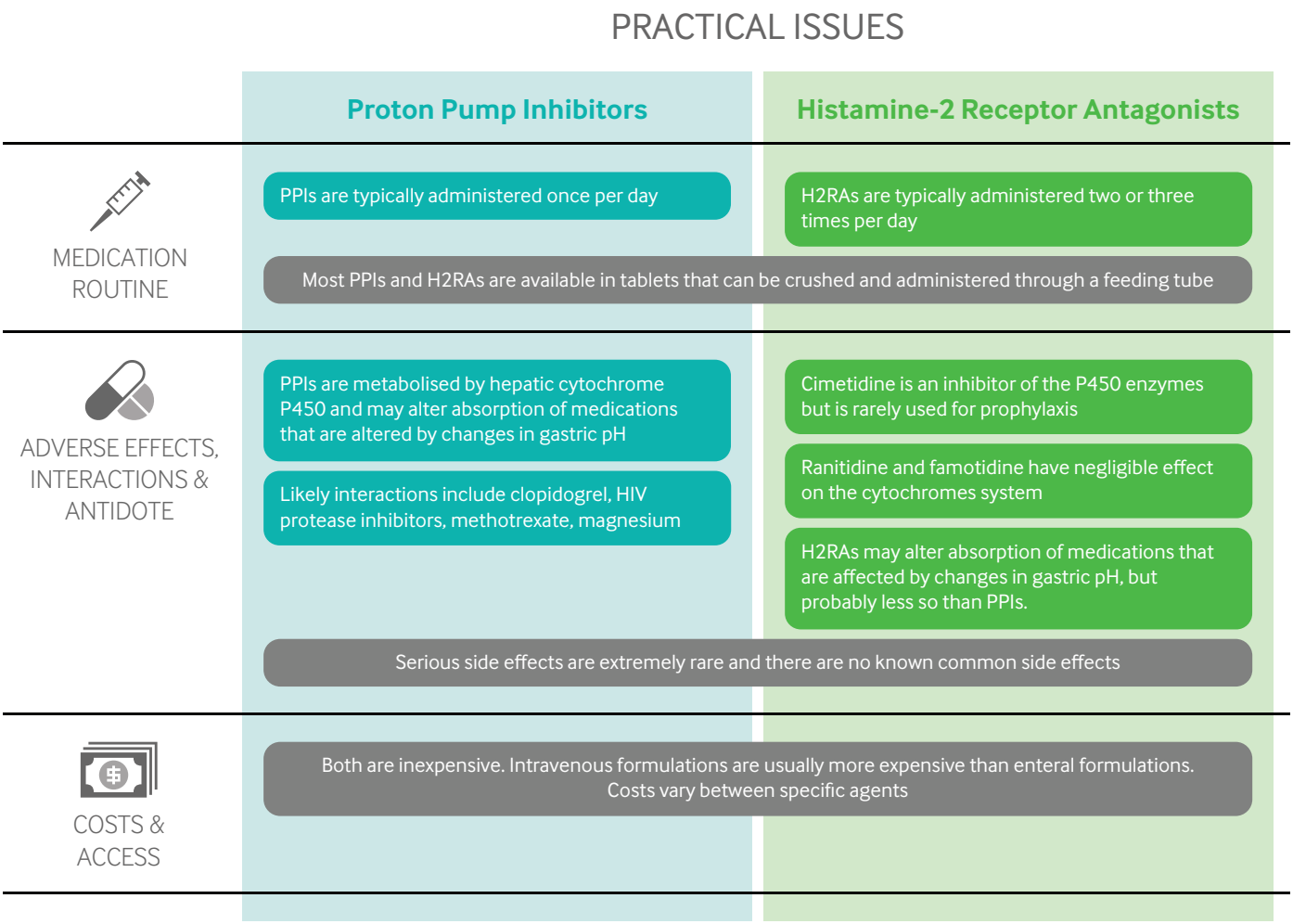


Fig 3| Practical issues about gastrointestinal bleeding prophylaxis for critically ill patients

most of our panellists thought that most patients would consider the benefits, harms, and burdens to be minimal. The panel agreed that there is probably great variability among patients in how much they value bleeding and a possible increased risk of pneumonia. Given the burdens and harms, including a possible increased risk of pneumonia, the panel believed that most patients would require a reduction in clinically important bleeding by at least about 20 per 1000 patients in order to choose acid suppression; the panel was, however, very uncertain about this threshold. The importance of overt bleeding not advancing to clinically important bleeding is questionable and may be altogether unimportant.

Shared decision making

Shared decision making should be pursued whenever possible. This will be challenging with critically ill patients because they are typically not able to have complex discussions about their care. Moreover, the effects of gastric acid suppression are modest, and there are many other more important decisions that often need to be made when caring for critically ill patients (such as probability of survival and/or regaining reasonable quality of life with or without different possible interventions).

Practical considerations

Figure 3 outlines the key practical issues regarding the use of acid suppressants for preventing gastrointestinal bleeding in critically ill patients. For both PPIs and H2RAs, the best specific agent is uncertain and was not addressed by our guideline panel. Pantoprazole, omeprazole, lansoprazole, esomeprazole, and rabeprazole were the most commonly used PPIs in the RCTs and are reasonable choices. Ranitidine and famotidine were the commonly used H2RAs in the RCTs and are reasonable choices.

Dosing and duration

Dose and duration varied between the included studies and were not specifically addressed in this guideline. Typically, PPIs were prescribed once per day and H2RAs two or three times per day. Both can be administered intravenously or enterally, and there is no evidence to suggest that the route of administration alters effectiveness. Unless there is another indication for gastric acid suppression, clinicians should take care to ensure that acid suppression medications are stopped when the patient is no longer critically ill or the risk factor triggering prophylaxis is no longer present. Long term use of gastric acid suppressants confers additional risks, costs, and burdens.[11 12]

Table 3 | New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article.				

Cost and resources

We did not explicitly consider cost effectiveness of gastric acid suppression. PPIs and H2RAs are generally inexpensive compared with the overall expense of intensive care and are widely available.

Future research

Future research should prioritise several areas:

- Randomised controlled trials to clarify
  - Whether gastric acid suppressants increase the risk of pneumonia
  - Whether gastric acid suppression is less effective in patients receiving enteral nutrition (subgroup analyses)
  - Possible impact on outcomes such as *C difficile* infection
  - Head to head comparison of PPIs and H2RAs.
- Observational studies of risk factors for gastrointestinal bleeding; development of a risk prediction model or score.
- Evidence about patient values and preferences on the importance of bleeding versus possible adverse effects.

HOW THIS RECOMMENDATION WAS CREATED

Our international panel included methodologists, intensivists, pharmacists, a gastroenterologist, a nurse, patient partners who have been hospitalised in intensive care, and a caregiver for a patient who had been hospitalised in intensive care and mechanically ventilated (see appendix 3 on bmj.com for details of panel members). The panel decided the scope of the recommendation and rated the outcome importance to patients.

The panel judged the following as patient-important outcomes for decision making: clinically important bleeding, pneumonia, *Clostridium difficile* infection, mortality, length of hospital stay, length of stay in intensive care, and duration of mechanical ventilation.

The panel met online to discuss the evidence and to formulate recommendations. No panel member had relevant financial conflicts of interest; intellectual and professional conflicts were minimised and transparently described (see appendix 4 on bmj.com).

The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation,[2] including using the GRADE approach to critically appraise the evidence and create recommendations (appendix 5 on bmj.com).[3] The panel considered the benefits, harms and burdens of gastrointestinal bleeding prophylaxis, the certainty (quality) of the evidence for each outcome, variations in patient values and preferences, acceptability, and feasibility.[13] Following the GRADE approach, recommendations can be either strong or weak for or against a specific course of action.[14] The recommendations take a patient-centred perspective. Healthcare systems can adapt these recommendations by including costs and other key issues of relevance, contextualised to national and local circumstances.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The Rapid Recommendation panel included three patients who have experienced intensive care and a family caregiver of a patient.

Updates to this article

Table 3 shows evidence that has emerged since the publication of this article. As new evidence is published, the BMJ Rapid Recommendations collaboration will assess the new evidence and if the new evidence might change the recommendation, we will update the meta-analysis and recommendations (see appendix 5 on bmj.com).

Contributors: All panel members participated in the teleconferences or email discussions and met all authorship criteria. We thank Dr Tessa Richards for providing input as a patient into discussions on selecting and rating patient-important outcomes and subgroups, and values and preferences related to outcomes, during one of the guideline panel meetings.

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Competing interests: All authors have completed the BMJ Rapid Recommendations interests disclosure form, and a detailed description of all disclosures is reported in appendix 4 on bmj.com. As with all *BMJ* Rapid Recommendations, the executive team and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions.

Transparency: ZY affirms that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

Provenance and peer review: Commissioned; externally peer reviewed

1 Krag M, Marker S, Perner A, et al. SUP-ICU trial group. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med* 2018;379:2199-208. 10.1056/NEJMoa1714919. pmid:30354950.
2 Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:i5191. 10.1136/bmj.i5191. pmid:27680768.
3 Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. 10.1136/bmj.39489.470347.AD. pmid:18436948.
4 Farrell CP, Mercogliano G, Kuntz CL. Overuse of stress ulcer prophylaxis in the critical care setting and beyond. *J Crit Care* 2010;25:214-20. 10.1016/j.jcrc.2009.05.014. pmid:19683892.
5 Bez C, Perrottet N, Zingg T, Leung Ki EL, Demartines N, Pannatier A. Stress ulcer prophylaxis in non-critically ill patients: a prospective evaluation of current practice in a general surgery department. *J Eval Clin Pract* 2013;19:374-8. 10.1111/j.1365-2753.2012.01838.x. pmid:22420909.
6 Barletta JF, Kanji S, MacLaren R, Lat I, Erstad BL. American-Canadian consortium for Intensive care Drug utilization (ACID) Investigators. Pharmacoepidemiology of stress ulcer prophylaxis in the United States and Canada. *J Crit Care* 2014;29:955-60. 10.1016/j.jcrc.2014.06.025. pmid:25081626.
7 Krag M, Perner A, Wetterslev J, et al. SUP-ICU Collaborators. Stress ulcer prophylaxis in the intensive care unit: an international survey of 97 units in 11 countries. *Acta Anaesthesiol Scand* 2015;59:576-85. 10.1111/aas.12508. pmid:25880349.
8 Ye ZK, Liu Y, Cui XL, Liu LH. Critical appraisal of the quality of clinical practice guidelines for stress ulcer prophylaxis. *PLoS One* 2016;11:e0155020. 10.1371/journal.pone.0155020. pmid:27152836.
9 Granholm A, Zeng L, Dionne JC, et al. GUIDE Group. Predictors of gastrointestinal bleeding in adult ICU patients: a systematic review and meta-analysis. *Intensive Care Med* 2019;45:1347-59. 10.1007/s00134-019-05751-6. pmid:31489445.
10 Reimer C, Søndergaard B, Hilsted L, Bytzer P. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. *Gastroenterology* 2009;137:80-7, 87.e1. 10.1053/j.gastro.2009.03.058. pmid:19362552.
11 Tariq R, Singh S, Gupta A, Pardi DS, Khanna S. Association of gastric acid suppression with recurrent Clostridium difficile infection: a systematic review and meta-analysis. *JAMA Intern Med* 2017;177:784-91. 10.1001/jamainternmed.2017.0212. pmid:28346595.

12 Shin S. Evaluation of costs accrued through inadvertent continuation of hospital-initiated proton pump inhibitor therapy for stress ulcer prophylaxis beyond hospital discharge: a retrospective chart review. *Ther Clin Risk Manag* 2015;11:649-57. 10.2147/TCRM.S81759. pmid:26005351.
13 Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;66:726-35. 10.1016/j.jclinepi.2013.02.003. pmid:23570745.
14 Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. Going from evidence to recommendations. *BMJ* 2008;336:1049-51. 10.1136/bmj.39493.646875.AE. pmid:18467413.
15 Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017;43:304-77. 10.1007/s00134-017-4683-6. pmid:28101605.
16 Madsen KR, Lorentzen K, Clausen N, et al. Danish Society of Intensive Care Medicine Danish Society of Anesthesiology and Intensive Care Medicine. Guideline for stress ulcer prophylaxis in the intensive care unit. *Dan Med J* 2014;61:C4811.pmid:24814922.
17 Guillamondegui OD, Gunter OL Jr, Bonadies JA, et al. Practice management guidelines for sress ulcer prophylaxis. https://www.east.org/education/practice-management-guidelines/stress-ulcer-prophylaxis 2008.

[1]Department of Pharmacy, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China
[2]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
[3]Department of Intensive Care Medicine, Lucerne Cantonal Hospital, Lucerne, Switzerland
[4]Department of Anaesthesiology and Intensive Care, University of Tartu, Tartu, Estonia
[5]Department of Medicine, McMaster University, Hamilton, Canada
[6]Spinal Muscular Atrophy Foundation, United States
[7]Duke University, United States
[8]Division of General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland
[9]Hospital of Lucerne, Switzerland
[10]Adult intensive care unit, Department of Acute Medicine, University Hospitals of Geneva, Geneva, Switzerland
[11]Critical Care, Poole Hospital NHS FT, United Kingdom
[12]Medical intensive care unit, Peking Union Medical College Hospital, Beijing, China
[13]Department of Medicine, Innlandet Hospital Trust, Gjøvik, Norway
[14]Peking KF Tech.co, Beijing, China
[15]Gastroenterology and Endoscopy Unit, Hospital Alemán, Buenos Aires, Argentina
[16]Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway
[17]Discipline of Anaesthesia and Critical Care, School of Clinical Medicine, University of KwaZulu-Natal, Durban, South Africa
[18]Adult Intensive Care, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, United Kingdom
[19]Surgical Intensive Care Unit, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Appendices

Appendix 1: Estimation of baseline risk of clinically important gastrointestinal bleeding for patients with different risk factors

Appendix 2: A systematic review of literature of critically ill patients' values and preferences on gastrointestinal bleeding

Appendix 3: Details of members of the Rapid Recommendation panel

Appendix 4: Details of panel members' declarations of interests

Appendix 5: Methodology for development of BMJ Rapid Recommendations

Appendix 1

How we estimated baseline risk of clinically important gastrointestinal bleeding for patients with different risk factors

1. We started with the event rate in the placebo group of the SUP-ICU trial[1], because it is the largest and most recent RCT, and we were not able to identify any observational studies of risk of bleeding exclusively in patients who did not receive gastric acid suppression. SUP-ICU included only patients with at least one hypothesised risk factor for bleeding and therefore the patients in this trial had a higher risk of bleeding than patients without risk factors.

   Baseline risk of clinically important bleeding (CIB) with any risk factor = 4.2%

2. The most common risk factors for gastrointestinal bleeding in the SUP-ICU trial were invasive mechanical ventilation (78.7%), vasopressors or inotropes (66.7%), use of anticoagulants (30.3%), and coagulopathy (19.8%). Based on observational studies, the risk ratios (RRs) of these most common risk factors were approximately 2.5 (septic shock and anticoagulation) to approximately 4.5 (mechanical ventilation and coagulopathy). We therefore used the median RR of 3.5 (2.5 to 4.5) of the most common risk factors to estimate the risk of bleeding in patients without these risk factors.

   Baseline risk of CIB without any risk factor =

   risk of CIB with any risk factor * 1 / relative risk increase with risk factor identified from individual observational studies = 4.2% * 1 / (3.5) = 4.2% * 1 / approximately 3.5 = approximately 1.2% (0.9% to 1.7%)

3. We then estimated the risk of bleeding with specific risk factors by applying specific relative risks from observational studies. We only included studies we judged to be low risk of bias, including reporting a multivariable regression analysis. The estimates were obtained from a concurrently performed systematic review and meta-analysis.[2]

Table S1. Estimated risk of clinically important and overt gastrointestinal bleeding in various groups of patients

Risk factor	Clinically important bleeding			Overt bleeding	
	Risk ratio	Risk (per 1000)	GRADE certainty*	Risk ratio	Risk (per 1000)
Low risk (estimated risk of clinically important bleeding is 10-20 per 1000)					
No risk factor	1.0 (reference)	12	Moderate	1.0 (reference)	26
Acute hepatic failure	1.6	19	Very low	3.1	81
Anticoagulants	1.4	17	Low	1.8	47
Cancer	1.4	16	Very low	0.8	22
Use of corticosteroids or immune suppressed	1.4	17	Low	1.5	40
Male	0.9	10	Moderate	0.8	21
Moderate risk (estimated risk of clinically important bleeding is 21-40 per 1000)					
Acute kidney injury	3.3	39	Low	3.5	90
Mechanical ventilation with enteral nutrition	2.4	29	Low	2.5	65
Sepsis	2.0	24	Low	2.0	52
Shock	2.6	31	Moderate	2.6	67
High risk (estimated risk of clinically important bleeding is 41-80 per 1000)					
Coagulopathy	4.8	57	Moderate	4.1	108
Highest risk (estimated risk of clinically important bleeding is 81-100 per 1000)					
Chronic liver disease	7.6	92	Moderate	4.5	117
Mechanical ventilation without enteral nutrition	8.1	97	Low	8.3	216

*GRADE ratings provided for clinically important bleeding only

Enteral nutrition appears to have a large protective effect on GI bleeding in patients who are receiving mechanical ventilation, RR 0.30 (0.13 - 0.67). We therefore estimated the risk of bleeding separately for mechanically ventilated patients who are and are not receiving enteral nutrition. We assumed that approximately 70% of patients received enteral nutrition. The risk of bleeding in patients with mechanical ventilation = approximately 4.9% = (baseline risk with mechanical ventilation with enteral nutrition * 0.7) + (baseline risk with mechanical ventilation without enteral nutrition * 0.3).

We simplified the baseline risk of clinically important bleeding into four natural groupings: low risk (0-20 bleeds per 1000 patients), moderate risk (21-40 bleeds per 1000 patients), high risk (41-80 bleeds per 1000 patients), and highest risk (81-100 bleeds per 1000 patients). Because

there was a lot of uncertainty in many of the estimates and to improve usability of the guideline, we used a single estimate for each of the risk groups: 12 per 1000 for low risk, 30 per 1000 for moderate risk, 60 per 1000 for high risk, and 90 per 1000 for highest risk.

How we estimated the risk for overt gastrointestinal bleeding for patients with different risk factors

We performed the same calculations for overt bleeding that we did for CIB. Patients randomised to the placebo arm of the SUP-ICU trial[1] had a 9.0% risk of overt bleeding. The relative and absolute risks of overt bleeding are reported in table S1, from the same studies.

References

1. Krag M, Marker S, Perner A, et al. Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU. *New England Journal of Medicine* 2018;379(23):2199-208.
2. Granholm A, Zeng L, Dionne JC, et al. Predictors of gastrointestinal bleeding in adult ICU patients: a systematic review and meta-analysis. *Intensive Care Med* 2019;45(10):1347-59. doi:10.1007/s00134-019-05751-6

Appendix 2

A systematic review of literature of critically ill patients' values and preferences on gastrointestinal bleeding

Summary

We set out to identify literature on how much critically ill patients value avoid gastrointestinal bleeding, and to identify any other relevant qualitative data that might inform the decision to use or not use gastric acid suppressants to prevent gastrointestinal bleeding. Our inclusion criteria included any quantitative or qualitative study on the values and/or preferences of critically ill patients on gastric acid suppression or gastrointestinal bleeding.

Search terms and strategies

We searched MEDLINE, EMBASE, and PsycINFO, using a combination of keywords and MeSH terms for "critically ill" and "gastrointestinal bleeding", and using a search filters for patient values and preferences, which includes terms related to health behaviours, patient values, and patient preferences. We reviewed the references of the included studies for other potentially eligible studies. We searched for grey literature through Google in first five pages.

The following databases were searched on March 1, 2019:
MEDLINE (1946 to February 28, 2019)
EMBASE (1974 to February 28, 2019)
PUBMED (epublications ahead of print only)
PsycInfo (1806 to February Week 1, 2019)
In total 2,196 citations were retrieved.

MEDLINE, EMBASE and PUBMED epublications

Embase <1974 to 2019 February 28>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1 exp Peptic Ulcer/ or Ulcer*.mp. or lesion*.mp.
2 (bleed* or re-bleed* or rebleed* or h?emorrhag*).mp.

3 1 and 2

4 (stress adj3 ulcer*).mp.

5 3 or 4

6 exp Gastrointestinal Hemorrhage/

7 ((gastrointestinal or gastro-intestinal) adj5 (bleed* or re-bleed* or rebleed* or h?emorrhag*)).mp.

8 (h?ematochezia* or h?ematemese* or mel?ena*).mp.

9 exp injury/ and exp gastric mucosa/

10 (mucos* adj5 injur*).tw.

11 (stomach or antrum or antral or pyloric or pylorus or gastri* or gastropathy or epigastr* or duodenal or duodenum or gastro-duodenal or gastroduodenal or oeso*ag* or esp*ag* or "upper GI" or UGI or "upper gastrointestinal" or "upper gastrointestinal").mp.

12 2 and 11

13 exp Gastritis/

14 2 and 13

15 or/5-10,12,14

16 exp Critical Care/

17 exp intensive care/

18 exp Critical Illness/

19 exp Intensive Care Units/

20 ICU*.tw.

21 ((critical or intensive) adj3 (care or illness)).tw.

22 exp Intubation, Gastrointestinal/

23 exp Monitoring, Physiologic/

24 exp Multiple Organ Failure/

25 exp Acid-Base Equilibrium/

26 exp Multiple Trauma/

27 (serious* adj injur*).tw.

28 (severe adj (traum* or shock)).tw.

29 exp Perioperative Care/

30 ((preoperative or intraoperative or perioperative) adj (care or procedure* or period)).tw.
31 exp Resuscitation/
32 exp Shock/
33 exp sepsis/
34 exp Ventilator Weaning/
35 exp Ventilators, Mechanical/
36 exp Ventilators, Negative-Pressure/
37 (protocol* adj weaning).mp.
38 (ventilat* adj weaning).mp.
39 ((artificial or mechanical) adj ventilat*).mp.
40 ventilat*.tw.
41 or/16-40
42 15 and 41
43 Attitude to Health/
44 Patient Participation/
45 Patient Preference/
46 preference*.ti,ab.
47 choice.ti.
48 choices.ti.
49 value*.ti.
50 health state values.ti,ab.
51 valuation*.ti.
52 expectation*.ti,ab.
53 attitude*.ti,ab.
54 acceptab*.ti,ab.
55 knowledge.ti,ab.
56 point of view.ti,ab.
57 user participation.ti,ab.
58 users participation.ti,ab.
59 users' participation.ti,ab.

60 user's participation.ti,ab.
61 patient participation.ti,ab.
62 patients participation.ti,ab.
63 patients' participation.ti,ab.
64 patient's participation.ti,ab.
65 patient perspective*.ti,ab.
66 patients perspective*.ti,ab.
67 patients' perspective.ti,ab.
68 patient's perspective*.ti,ab.
69 user perspective*.ti,ab.
70 users perspective*.ti,ab.
71 users' perspective*.ti,ab.
72 user's perspective*.ti,ab.
73 patient perce*.ti,ab.
74 patients perce*.ti,ab.
75 patients' perce*.ti,ab.
76 patient's perce*.ti,ab.
77 health perception*.ti,ab.
78 user perce*.ti,ab.
79 users perce*.ti,ab.
80 users' perce*.ti,ab.
81 user's perce*.ti,ab.
82 user view*.ti,ab.
83 users view*.ti,ab.
84 users' view*.ti,ab.
85 user's view*.ti,ab.
86 patient view*.ti,ab.
87 patients view*.ti,ab.
88 patients' view*.ti,ab.
89 patient's view*.ti,ab.

90 ((decision* and mak*).ti. or decision mak*.ti,ab. or decisions mak*.ti,ab.) and (patient* or user* or men or women).ti,ab.
91 discrete choic*.ti,ab.
92 decision board*.ti,ab.
93 decision analy*.ti,ab.
94 decision-support.ti,ab.
95 decision tool*.ti,ab.
96 decision aid*.ti,ab.
97 discrete-choice*.ti,ab.
98 Decision Making/ and (patient* or user* or men or women).ti.
99 Decision Support Techniques/
100 (health and utilit*).ti.
101 gamble*.ti,ab.
102 prospect theory.ti,ab.
103 preference score.ti,ab.
104 preference elicitation.ti,ab.
105 health utilit*.ti,ab.
106 utility value*.ti,ab.
107 utility score*.ti,ab.
108 Utility estimate*.ti,ab.
109 health state.ti,ab.
110 feeling thermometer*.ti,ab.
111 best-worst scaling.ti,ab.
112 standard gamble.ti,ab.
113 time trade-off.ti,ab.
114 TTO.ti,ab.
115 probability trade-off.ti,ab.
116 utility score.ti,ab.
117 preference based.ti,ab.
118 preference score*.ti,ab.

119 multiattribute.ti,ab.

120 multi attribute.ti,ab.

121 EuroQol 5D.ti,ab.

122 EuroQol5D.ti,ab.

123 EQ5D.ti,ab.

124 EQ 5D.ti,ab.

125 SF6D.ti,ab.

126 SF 6D.ti,ab.

127 HUI.ti,ab.

128 15D.ti,ab.

129 or/43-128

130 42 and 129

131 remove duplicates from 130

PsycInfo (1806 to February Week 1 2019)

1 exp Gastrointestinal Ulcer/ or Ulcer*.mp. or lesion*.mp.

2 (bleed* or re-bleed* or rebleed* or h?emorrhag*).mp.

3 1 and 2

4 (stress adj3 ulcer*).mp.

5 3 or 4

6 ((gastrointestinal or gastro-intestinal) adj5 (bleed* or re-bleed* or rebleed* or h?emorrhag*)).mp.

7 (h?ematochezia* or h?ematemese* or mel?ena*).mp.

8 (mucos* adj5 injur*).tw.

9 (stomach or antrum or antral or pyloric or pylorus or gastri* or gastropathy or epigastr* or duodenal or duodenum or gastro-duodenal or gastroduodenal or oeso*ag* or esp*ag* or "upper GI" or UGI or "upper gastrointestinal" or "upper gastrointestinal").mp.

10 2 and 9

11 gastritis.tw.

12 2 and 11
13 or/5-8,10,12
14 exp intensive care/
15 ICU*.tw.
16 ((critical or intensive) adj3 (care or illness)).tw.
17 gastrointestinal intubation.tw.
18 (physiologic* adj2 monitoring).tw.
19 organ failure.tw.
20 Acid-Base Equilibrium.tw.
21 exp Trauma/
22 (serious* adj injur*).tw.
23 (severe adj (traum* or shock)).tw.
24 ((preoperative or intraoperative or perioperative) adj (care or procedure* or period)).tw.
25 resuscitation.tw.
26 exp Shock/
27 sepsis.tw.
28 (protocol* adj weaning).mp.
29 (ventilat* adj weaning).mp.
30 ((artificial or mechanical) adj ventilat*).mp.
31 ventilat*.tw.
32 or/14-31
33 13 and 32
34 Health Attitudes/
35 Client Participation/
36 Preferences/
37 preference*.ti,ab.
38 choice.ti.
39 choices.ti.
40 value*.ti.
41 health state values.ti,ab.

42 valuation*.ti.
43 expectation*.ti,ab.
44 attitude*.ti,ab.
45 acceptab*.ti,ab.
46 knowledge.ti,ab.
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48 user participation.ti,ab.
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50 users' participation.ti,ab.
51 user's participation.ti,ab.
52 patient participation.ti,ab.
53 patients participation.ti,ab.
54 patients' participation.ti,ab.
55 patient's participation.ti,ab.
56 patient perspective*.ti,ab.
57 patients perspective*.ti,ab.
58 patients' perspective.ti,ab.
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60 user perspective*.ti,ab.
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63 user's perspective*.ti,ab.
64 patient perce*.ti,ab.
65 patients perce*.ti,ab.
66 patients' perce*.ti,ab.
67 patient's perce*.ti,ab.
68 health perception*.ti,ab.
69 user perce*.ti,ab.
70 users perce*.ti,ab.
71 users' perce*.ti,ab.

72 user's perce*.ti,ab.

73 user view*.ti,ab.

74 users view*.ti,ab.

75 users' view*.ti,ab.

76 user's view*.ti,ab.

77 patient view*.ti,ab.

78 patients view*.ti,ab.

79 patients' view*.ti,ab.

80 patient's view*.ti,ab.

81 ((decision* and mak*).ti. or decision mak*.ti,ab. or decisions mak*.ti,ab.) and (patient* or user* or men or women).ti,ab.

82 discrete choic*.ti,ab.

83 decision board*.ti,ab.

84 decision analy*.ti,ab.

85 decision-support.ti,ab.

86 decision tool*.ti,ab.

87 decision aid*.ti,ab.

88 discrete-choice*.ti,ab.

89 Decision Making/ and (patient* or user* or men or women).ti.

90 Decision Support Systems/ or Decision Theory/

91 (health and utilit*).ti.

92 gamble*.ti,ab.

93 prospect theory.ti,ab.

94 preference score.ti,ab.

95 preference elicitation.ti,ab.

96 health utilit*.ti,ab.

97 utility value*.ti,ab.

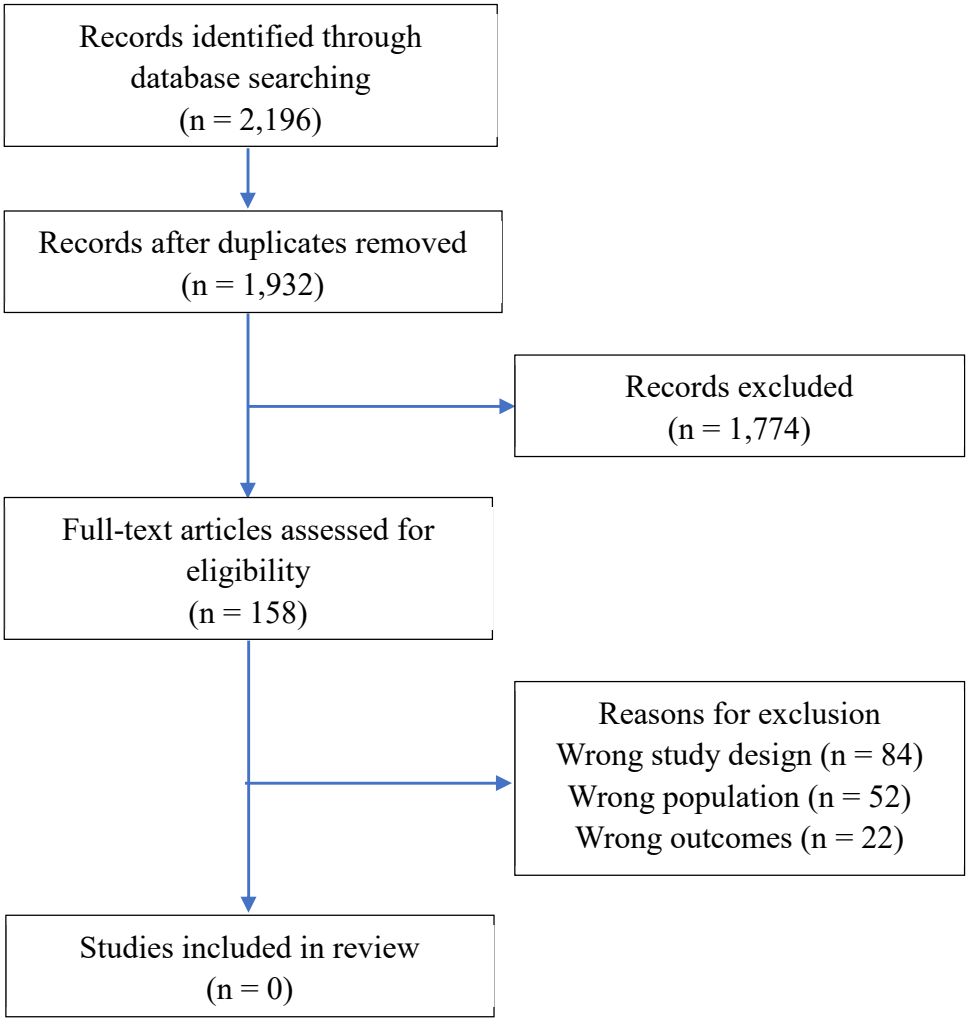
98 utility score*.ti,ab.

99 Utility estimate*.ti,ab.

100 health state.ti,ab.

101 feeling thermometer*.ti,ab.
102 best-worst scaling.ti,ab.
103 standard gamble.ti,ab.
104 time trade-off.ti,ab.
105 TTO.ti,ab.
106 probability trade-off.ti,ab.
107 utility score.ti,ab.
108 preference based.ti,ab.
109 preference score*.ti,ab.
110 multiattribute.ti,ab.
111 multi attribute.ti,ab.
112 EuroQol 5D.ti,ab.
113 EuroQol5D.ti,ab.
114 EQ5D.ti,ab.
115 EQ 5D.ti,ab.
116 SF6D.ti,ab.
117 SF 6D.ti,ab.
118 HUI.ti,ab.
119 15D.ti,ab.
120 or/34-119
121 33 and 120

Searching results



Appendix 3: Rapid Recommendation panel members
Gastrointestinal bleeding prophylaxis for critically ill patients: a Rapid Recommendation

Clinical co-chair:
Annika Reintam Blaser, MD, PhD
Intensivist
Department of Intensive Care Medicine, Lucerne Cantonal Hospital, Lucerne, Switzerland
Department of Anaesthesiology and Intensive Care, University of Tartu, Tartu, Estonia

Methods co-chair:
Reed A.C. Siemieniuk, MD, FRCPC
General internal medicine
PhD candidate
Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

Guideline coordinator:
Zhikang Ye, Master of Pharmacy
PhD student
Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
Department of Pharmacy, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Clinical experts:
Anja Fog Heen, MD
Internal Medicine
Department of Medicine, Innlandet Hospital Trust, Gjøvik, Norway

Bin Du, MD
Intensivist
Medical Intensive Care Unit, Peking Union Medical College Hospital, Beijing, China

Filippo Boroli, MD
Intensivist
Adult Intensive Care Unit, Department of Acute Medicine, University Hospitals of Geneva, Geneva, Switzerland

José M. Mella, MD
Gastroenterologist
Gastroenterology and Endoscopy Unit, Hospital Alemán, Buenos Aires, Argentina

Julie Camsooksai
Senior research nurse
Critical Care, Poole Hospital NHS FT, United Kingdom

Lihong Liu, PhD
Pharmacist
Department of Pharmacy, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Robert Wise, MD
Intensivist
Discipline of Anaesthesia and Critical Care, School of Clinical Medicine, University of KwaZulu-Natal, Durban, South Africa
Adult Intensive Care, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, United Kingdom

Sonja Bertschy, MD
Senior consultant, Infectious diseases
Hospital of Lucerne, Switzerland

Ying Wang, MSc
Systematic reviewer
Department of Pharmacy, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Yue Zheng, MD
Intensivist
Surgical Intensive Care Unit, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Patient/Caregiver partners:
Tessa Richards, MD
Former patient
BMJ, BMA House, Tavistock Square, London, UK

J. Stephen Mikita, JD
Former patient
Spinal Muscular Atrophy Foundation, United States

Jamie Roberts
Former patient
Duke University, United States

Jianyou Lu
Caregiver
Peking KF Tech.co.,Ltd, Beijing, China

Methodology experts:
Gordon H. Guyatt, MD, MSc, FRCPC
General internal medicine
Guideline expert, methodologist
Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
Department of Medicine, McMaster University, Hamilton, Canada

Lyubov Lytvyn, MSc
Methodologist
PhD candidate
Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada

Per Olav Vandvik, MD, PhD
General internal medicine
Guideline expert, methodologist
Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway

Thomas Agoritsas, MD, PhD
General internal medicine
Expert in guidelines, methodology and shared decision making
Division General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland
Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada

Appendix 4: Full list of authors' declarations of interests

Pre-screening

All panel members were pre-screened for conflicts of interest prior to the guideline process that resulted in the BMJ Rapid Recommendations. The pre-screening was performed by the RapidRecs steering committee, affiliated with the non-profit organisation MAGIC (www.magicproject.org) and with support and approval from at least two unconflicted BMJ editors. No financial conflicts of interest were allowed (specifically, no financial ties to pharmaceutical companies with any stake in gastric acid suppressants) and intellectual and professional conflicts of interest were managed appropriately (see appendix 5: Methods for BMJ Rapid Recommendations). Panel members could not have a conflict for the past three years and do not anticipate a conflict arising in the foreseeable future, which we defined as at least one year.

Disclosures

Financial disclosures: No panel members had any financial conflicts of interest to disclose related to this clinical question.

Professional disclosures: Almost all of the physician panel members routinely see patients to whom this guideline applies, but their practice, rank, and remuneration will be unaffected by these recommendations.

Intellectual disclosures: Zhikang Ye, Reed A.C. Siemieniuk, and Gordon H. Guyatt participated in writing the systematic review that formed the evidence base for this guideline (doi:). Reed A.C. Siemieniuk, Thomas Agoritsas, Per Vandvik, Lyubov Lytvyn, and Gordon H. Guyatt are members of the GRADE Working Group: BMJ Rapid Recommendations adheres to GRADE methods.
Gordon H. Guyatt may be predisposed to weak rather than strong recommendations to justify the necessity of the REVISE trial that compare the benefits and harms of pantoprazole versus placebo (doi: 10.5144/0256-4947.2016.427; NCT02290327). Bin Du is the corresponding author of meta-analysis on stress ulcer prophylaxis in patients receiving enteral feeding, which concluded that gastric acid suppression may be harmful in patients receiving enteral nutrition (doi: 10.1186/s13054-017-1937-1). Julie Camsooksai is a site research nurse coordinator for the ongoing PEPTIC trial that is comparing a proton-pump inhibitor versus a histamine-2 receptor antagonist and may be predisposed to a weak rather than strong recommendation for that recommendation (PMID: 30153780; ANZCTRN 12616000481471).

CHAPTER 13: The next frontier in critical care guidelines: rapid and trustworthy recommendations

This editorial paper introduces a spin-off of the *Rapid Recommendations:* Rapid Recommendations in Intensive Care. This network produced *Rapid Recommendations* on two important topics in Critical Care. This is one example of how the processes we developed can be adapted by other guideline developers.

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EDITORIALS

The next frontier in critical care guidelines: rapid and trustworthy recommendations

Reed A. C. Siemieniuk, MD · Gordon H. Guyatt, MD, MSc

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Optimal clinical care requires application of the best available evidence to patient care decisions.[1] Trustworthy clinical practice guidelines synthesize the available evidence and provide suggestions for front-line clinicians.

Historically, guideline panels take months to, most commonly, years to process the evidence and produce their recommendations. Many conventional guidelines are outdated by the time of publication, and almost all are outdated before the panel produces an update. In the hiatus between the publication of new evidence and its inclusion in a guideline, clinicians and patients are left wondering whether the new evidence should change practice—assuming they are even aware of the new evidence. As a result, many patients are at risk of receiving inadequate or inappropriate care.

The Canadian Critical Care Society (CCCS) and the Scandinavian Society of Anaesthesiology and Intensive Care (SSAI) have taken a leap forward in guideline creation. The accompanying guidelines are the first in a series of rapid recommendations.[2,3] The project is part of a collaborative initiative with the MAGIC Project (www.magicproject.org) called WikiRecs—"Wiki" means "rapid" in Hawaiian—modelled after the new *BMJ* series, "Rapid Recommendations".[4,5]

A recently published randomized trial addressed an important topic, i.e., optimal blood pressure targets in critically ill patients.[6] In response, the leaders of the Critical Care-WikiRecs group developed a rapid clinical practice guideline by following the WikiRecs process.[4]

The process starts when the WikiRecs team identifies a new study that might initiate a change in practice. A guideline panel then convenes to determine which populations, outcomes, and subgroups to consider. A semi-independent systematic review team then quickly synthesizes all the evidence for all patient-important outcomes and subgroups identified by the panel. The panel considers the evidence in the context of patient values and preferences and makes a recommendation—either strong or weak—in favour of the intervention or the comparator.

Notwithstanding the rapidity of the process, the recommendations adhere to the stringent Institute of Medicine standards[7]—standards that most conventional guidelines fail to achieve.[8] A standard that WikiRecs meets but is often neglected by conventional guideline panels includes participation by a complete spectrum of stakeholders, including critical care specialists, a surgeon, a nurse, methodologists, and a former patient. The patient panel member was key in identifying all of the most patient-important outcomes, including long-term quality of life, an outcome not captured in any relevant randomized trials (and thus representing a gap in current knowledge).

The recommendations, based on systematic reviews using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach,[9] include a formal assessment of the certainty and magnitude of the effects on each outcome.[10,11] The

R. A. C. Siemieniuk, MD (✉) · G. H. Guyatt, MD, MSc
Department of Health Research Methods, Evidence, and Impact, McMaster University, 1280 Main St W, Hamilton, ON L8S 4L8, Canada
e-mail: reed.siemieniuk@medportal.ca

R. A. C. Siemieniuk, MD
Department of Medicine, University of Toronto, Toronto, ON, Canada

G. H. Guyatt, MD, MSc
Department of Medicine, McMaster University, Hamilton, ON, Canada

authors use the GRADE evidence profiles which utilize formats tested in randomized trials[12,13] in a multilayered format available on all devices electronically through MagicApp (www.magicapp.org). Moreover, the guideline panel considered and presented all practical issues, together with the key implementation issues, including nursing resources—a subject that guideline panels do not always consider.

Although the issue of conflict of interest on guideline panels has received considerable attention[14] and authors have suggested solutions,[15] it is not uncommon for guideline panels to continue including panellists with serious conflicts of interest.[8] In this case, any persons with any potential financial conflicts were excluded.

Managing intellectual conflicts is more difficult to navigate because the leading content experts have often participated in research or have made public statements that are likely to leave them attached to certain viewpoints. In this case, a panel member (F.L.) was the first author of a randomized trial on blood pressure targets in shock.[6] The panel appears otherwise free of conflicts.

The panel made a weak recommendation for a lower (mean arterial pressure = 60-70 mmHg) rather than a higher blood pressure target.[3] The rationale is clearly articulated, i.e., the panel judged that most patients would prefer to avoid a possible increased risk of myocardial infarction (very low certainty) and arrhythmias (moderate certainty) in the absence of evidence that a higher target reduces mortality (low certainty) or has any other benefits. Further, the panel recognized the substantial resources required to implement a higher blood pressure target—mostly due to increased nursing demands. The recommendation was weak rather than strong because of the low-quality evidence available regarding outcomes most important to patients, i.e., mortality and quality of life.

For vasopressors in early traumatic shock, the panel considered the trade-offs between risks and benefits too close and the uncertainty too great to make a recommendation.[2] One could question the panel's decision not to make a recommendation: it is unlikely that anyone will have perused the evidence as thoroughly as the panel, and clinicians need guidance from those who have. The authors do, however, provide a GRADE-style evidence summary in the publication and in an interactive multilayered format on MagicApp—a summary that clinicians can use to arrive at their own conclusions.

The goal of the WikiRecs project is simple, i.e., to move evidence more quickly into practice using a process that clinicians can trust. These first CCCS and SSAI co-led rapid recommendations demonstrate that this is possible. The success of the project requires buy-in from front-line clinicians and a willingness to adapt to criticism. Most importantly, the success of rapid recommendations depends on a commitment to adhere stringently to standards for trustworthiness. It is possible that these CCCS/SSAI recommendations, rapid and trustworthy, represent an early sign of broader change within the guideline industry towards more collaborative, trustworthy, timely, and user-friendly recommendations.

Prochaine étape pour les directives en soins intensifs : des recommandations rapides et dignes de confiance

Pour offrir des soins cliniques optimaux, il faut appliquer les meilleures données probantes disponibles lorsqu'on prend des décisions en matière de soins aux patients.[1] Pour être dignes de confiance, les directives de pratique clinique doivent résumer les données probantes disponibles et proposer des solutions aux cliniciens de première ligne.

Historiquement, les panels en charge de rédiger les directives prennent des mois, même des années, à examiner les données probantes et émettre leurs recommandations. De nombreux guides d'exercice conventionnels ne sont déjà plus en ligne avec les dernières données probantes au moment de leur publication, et la vaste majorité de ces guides sont surannés lorsque le panel en charge en propose enfin une mise à jour. Entre le moment de publication de nouvelles données probantes et leur inclusion dans une directive, cliniciens et patients se demandent bien souvent si ces nouvelles données devraient avoir un impact sur la pratique - en prenant pour acquis que ces individus aient connaissance de ces nouvelles données. Par conséquent, de nombreux patients courent le risque de recevoir des soins inadéquats ou inadaptés.

La *Société canadienne de soins intensifs* (CCCS) et la *Société scandinave d'anesthésiologie et de soins intensifs* (*Scandinavian Society of Anaesthesiology and Intensive Care* - SSAI) ont fait un véritable bond en avant dans la création de directives. Les directives qui découlent de cette initiative sont les premières d'une série de recommandations rapides.[2,3] Le projet s'inscrit dans le cadre d'un projet réalisé en collaboration avec l'organisme MAGIC (www.magicproject.org), intitulé *WikiRecs* - « *wiki* » signifie « rapide » en hawaïen -, qui s'est inspiré du modèle lancé par la nouvelle série de BMJ, les « *BMJ Rapid Recommendations* » ou « Recommandations rapides du BMJ ».[4,5]

Une étude randomisée récemment publiée a abordé un sujet important : les cibles de tension artérielle optimales chez les patients en état critique.[6] Suite à cette étude, les chefs de file du groupe des Soins intensifs de *WikiRecs* ont mis ont point une directive de pratique clinique rapide selon le processus des *WikiRecs*.[4]

Le processus débute lorsque l'équipe des *WikiRecs* identifie une nouvelle étude qui pourrait modifier la pratique. Un panel de rédaction de directive se réunit alors et détermine de quelles populations, de quels critères d'évaluation et de quels sous-groupes tenir compte. Un compte rendu méthodique semi-indépendant résume ensuite rapidement toutes les données probantes concernant tous les critères d'évaluation importants pour les patients et tous les sous-groupes préalablement identifiés par le panel. Le panel étudie les données probantes selon les valeurs et les préférences des patients et émet une recommandation, forte ou faible, en faveur de l'intervention ou du comparateur.

Hormis la rapidité du processus, ces recommandations respectent les normes rigoureuses de *l'Institute of Medicine* américain[7] - des normes que la plupart des guides d'exercice conventionnels ont de la peine à respecter.[8] Une des normes respectées par *WikiRecs*, souvent négligée par d'autres, est la participation d'un éventail complet d'intervenants, y compris des spécialistes des soins intensifs, un chirurgien, une infirmière, des méthodologues et un ancien patient. Le patient membre du panel a joué un rôle essentiel dans l'identification de tous les critères et pronostics importants aux yeux des patients, notamment la qualité de vie à long terme, un critère non évalué par les études randomisées pertinentes (mettant ainsi le doigt sur une lacune majeure des connaissances actuelles).

Les recommandations, fondées sur des comptes rendus méthodiques utilisant l'approche dite GRADE (pour *Grading of Recommendations, Assessment, Development and Evaluation* - soit Classification des recommandations, de l'analyse, de la mise au point et de l'évaluation),[9] comprennent une évaluation formelle du degré de certitude et de l'ampleur des effets sur chaque critère d'évaluation.[10,11] Les auteurs utilisent les profils de données probantes de GRADE, lesquels se fondent sur des formats testés dans des études randomisées[12,13] dans un format multicouche disponible électroniquement sur tous les dispositifs grâce à l'application MagicApp (www.magicapp.org). Le panel a également tenu compte de et présente toutes les questions pratiques, notamment les principaux défis d'implantation (y compris les ressources en personnel infirmier - une donnée souvent oubliée par les panels responsables d'émettre des recommandations).

Bien que la question des conflits d'intérêt au sein des panels d'élaboration de recommandations ait fait l'objet de beaucoup d'attention[14] et que plusieurs auteurs aient suggéré des solutions possibles,[15] il est malheureusement encore fréquent que certains panélistes entretiennent d'importants conflits d'intérêt.[8] Dans le cas du panel dont il est question ici, toute personne présentant un conflit d'intérêt potentiel d'ordre financier a été exclue.

La gestion des conflits intellectuels est plus difficile à naviguer parce que les experts d'une question donnée ont souvent pris part à des recherches, ou fait des déclarations publiques qui pourraient probablement les rattacher à certaines opinions. Dans le cas que nous présentons ici, un membre du panel (F.L.) est le premier auteur d'une étude randomisée sur les cibles de tension artérielle en cas de choc.[6] Le panel semble autrement n'entretenir aucun conflit d'intérêt.

Le panel a émis une recommandation faible pour une cible de tension artérielle plus basse (tension artérielle moyenne = 60-70 mmHg) plutôt qu'une cible plus élevée.[3] La raison est clairement expliquée : le panel a estimé que la plupart des patients préfèreraient éviter un risque potentiellement accru d'infarctus du myocarde (certitude très basse) et d'arythmie (certitude modérée) en l'absence de données probantes soutenant qu'une cible plus élevée réduirait la mortalité (certitude basse) ou aurait tout autre bienfait. En outre, le panel a reconnu l'ampleur des ressources nécessaires à la mise en œuvre d'une cible de tension artérielle plus élevée - principalement en raison des exigences plus grandes ainsi imposées au personnel infirmier. La recommandation était faible plutôt que forte en raison de la qualité médiocre des données probantes disponibles concernant les critères les plus importants pour les patients - soit la mortalité et la qualité de vie.

En ce qui touche à l'administration précoce de vasopresseurs après un choc traumatique, le panel a considéré que le compromis entre risques et bienfaits était trop fragile et que l'incertitude était trop grande pour émettre une recommandation, quelle qu'elle soit.[2] On peut certes remettre en question la décision du panel, mais il est peu probable que quiconque ait examiné les données probantes avec autant d'attention et de soin que le panel, et les cliniciens ont besoin de conseils de personnes qui ont fait ce travail. Les auteurs fournissent toutefois un résumé des données probantes de style GRADE dans leur publication et dans un format multicouche interactif sur MagicApp, et les cliniciens peuvent utiliser ce résumé pour parvenir à leurs propres conclusions.

L'objectif du projet *WikiRecs* est simple : faire que les données probantes soient appliquées plus rapidement à la pratique grâce à un processus auquel les cliniciens peuvent se fier. Les premières recommandations rapides codirigées par le CCCS et la SSAI démontrent qu'une telle démarche est possible. Le succès du projet dépend du soutien des médecins de première ligne et d'une ouverture d'esprit

pour pouvoir s'adapter aux critiques. Mais le succès des recommandations rapides dépend encore plus d'un engagement à respecter de façon rigoureuse des normes de fiabilité. Peut-être que ces recommandations des CCCS et SSAI, rapides et fiables, constitueront un signe avant-coureur d'un changement plus important encore au sein de l'industrie des directives, vers l'élaboration de recommandations plus collaboratives, dignes de confiance, publiées en temps opportun et faciles à utiliser pour le clinicien.

Disclosures Drs Reed A.C. Siemieniuk and Gordon H. Guyatt are members of the GRADE Working Group and MAGIC non-profit organization (Making GRADE the Irresistible Choice). The MAGIC organization and the authors are leaders of the WikiRecs and Rapid Recommendation projects. Drs Reed A.C. Siemieniuk and Gordon H. Guyatt are co-authors of the systematic reviews that informed the guidelines.

Conflicts of interest None declared.

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Déclarations Les Drs Reed A.C. Siemieniuk et Gordon H. Guyatt sont membres du groupe de travail GRADE et de l'organisme à but non lucratif MAGIC (*Making GRADE the Irresistible Choice* - Faire de GRADE le choix irrésistible). L'organisme MAGIC et les auteurs de cet éditorial sont à la tête des projets WikiRecs et Rapid Recommendation (*recommandations rapides*). Les Drs Reed A.C. Siemieniuk et Gordon H. Guyatt sont les co-auteurs des comptes rendus méthodiques qui ont permis d'élaborer ces directives.

Conflit d'intérêt Aucun.

Responsabilité éditoriale Cet article a été traité par Dr Hilary P. Grocott, rédacteur en chef, *Journal canadien d'anesthésie*.

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References

1. *Evidence-Based Medicine Working Group*. Evidence-based medicine. A new approach to teaching the practice of medicine. Jama 1992; 268: 2420-5.
2. *Rochwerg B, Hylands M, Moller M, et al.* CCCS-SSAI WikiRecs Clinical Practice Guideline: vasopressors in early traumatic shock. Can J Anesth 2017; 64: this issue. DOI: 10.1007/s12630-017-0877-1
3. *Rochwerg B, Hylands M, Moller M, et al.* CCCS-SSAI WikiRecs Clinical Practice Guideline: vasopressor blood pressure targets in critically ill adults with hypotension. Can J Anesth 2017; 64: this issue. DOI: 10.1007/s12630-017-0878-0
4. *Siemieniuk RA*, *Agoritsas T*, *Macdonald H*, *Guyatt GH*, *Brandt L*, *Vandvik PO*. Introduction to BMJ rapid recommendations. BMJ 2016; 354: i5191.
5. *Vandvik PO*, *Otto CM*, *Siemieniuk RA*, *et al*. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. BMJ 2016; 354: i5085.
6. *Lamontagne F*, *Meade MO*, *Hebert PC*, *et al*. Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. Intensive Care Med 2016; 42: 542-50.
7. *Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. In:* Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E (Eds). Clinical Practice Guidelines We Can Trust. Washington (DC): The National Academies Press; 2011.
8. *Kung J*, *Miller RR*, *Mackowiak PA*. Failure of clinical practice guidelines to meet institute of medicine standards: two more decades of little, if any, progress. Arch Intern Med 2012; 172: 1628-33.
9. *Guyatt GH*, *Oxman AD*, *Vist GE*, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336: 924-6.
10. *Hylands M, Moller MH, Asfar P, et al.* A systematic review of vasopressor blood pressure targets in critically ill adults with hypotension. Can J Anesth 2017; 64: this issue. DOI: 10.1007/s12630-017-0879-z
11. *Hylands M, Kwong J, Toma A, at al.* Vasopressor use following traumatic injury: protocol for a systematic review. BMJ Open 2017; 7: e014166.
12. *Carrasco-Labra A*, *Brignardello-Petersen R*, *Santesso N*, *et al*. Improving GRADE evidence tables part 1: a randomized trial shows improved understanding of content in summary of findings tables with a new format. J Clin Epidemiol 2016; 74: 7-18.
13. *Carrasco-Labra A*, *Brignardello-Petersen R*, *Santesso N*, *et al*. Comparison between the standard and a new alternative format of the summary-of-findings tables in Cochrane review users: study protocol for a randomized controlled trial. Trials 2015; 16: 164.
14. *Norris SL*, *Holmer HK*, *Ogden LA*, *Burda BU*. Conflict of interest in clinical practice guideline development: a systematic review. PloS one 2011; 6: e25153.
15. *Guyatt G*, *Akl EA*, *Hirsh J*, *et al*. The vexing problem of guidelines and conflict of interest: a potential solution. Ann Intern Med 2010; 152: 738-41.

CHAPTER 14: CONCLUSION

This thesis suggests that creating rapid and trustworthy guidance is possible. This concluding chapter reviews the success of the project and explores challenges as well as opportunities for future research.

Key findings

In Chapter 2,[1] we outline the concept of a *Rapid Recommendation* and justify their urgent need. We make the case that the current clinical practice guideline paradigm has a lot of room to improve to meet the needs of practitioners and patients. Most guidelines are too slow: in the years between the publication of new practice-changing evidence and guideline publication, many patients receive outdated care. In the best case, this adds avoidable costs, in the worse cases, it leads to harm. We also make the case that most clinical practice guidelines are not trustworthy: many are based on unsystematic reviews, do not include patients in the process, do not systematically consider patient values and preferences, do not explicitly consider baseline risk, are developed by people with important conflicts of interest, and are not readily useable by busy clinicians.

In chapter 3, we expand on the methods for creating a *Rapid Recommendation*. This paper goes into detail about the steps necessary to produce rapid and trustworthy guidance. It can be used by guideline developers who want to follow our process.

Chapter 4 is a systematic review that informed the first *Rapid Recommendation* in the series.[2 3] We show that transfemoral transcatheter aortic valve implantation (TAVI) is an acceptable alternative to surgery for many patients with aortic stenosis. The use and grading of evidence from reconstructed time-based individual patient data from Kaplan-Meier curves allowed the guideline panel to make recommendations stratified by life expectancy: the benefits of TAVI were confirmed in the early stages, with less certainty about the relative impact beyond two years. The systematic review was completed within a month with close oversight by the guideline panel, which allowed us to justify the need for ongoing reviews. The review also separated transapical from transfemoral TAVI, and found that transapical TAVI increased risk of death compared to surgery: this led to the first of several guidelines recommending against transapical TAVI.

Chapter 5 is a *Rapid Recommendation* that made a strong recommended against arthroscopic surgery for degenerative knee disease.[4] At the time, the procedure was one of the most common surgical procedures performed globally, including in Canada.[5] Our guideline was the first in the area to systematically consider patient values and preferences by using evidence from a linked systematic review on minimally important differences. The guideline panel included representation from all key stakeholders.

Chapters 6 and 7 are linked: a *Rapid Recommendation* on antiretroviral therapies in pregnant women and a linked systematic review on the same.[6 7] The process highlighted the importance of placing individual patients at the centre of the guideline process: because the recommendation conflicts with guidelines that take a public health perspective, but puts the

unborn children of pregnant women at risk.[8] The systematic review of values and preferences provided us with strong standing to make a recommendation in line with the values of individual women.[9] The network meta-analysis of relative effects also incorporated evidence from similar but different populations: women with hepatitis B and non-pregnant adults.[6] The review also demonstrates the importance of carefully considering where the most reliable evidence comes from for each outcome critical for decision making. A typical systematic review might have only considered evidence in pregnant women living with HIV. In doing so, the panel would not have had the most reliable evidence, and may have made different recommendations.

In chapter 8, we performed a rapid systematic review of one or two doses of a corticosteroid for patients with sore throat.[10] The systematic review was completed in one month and submitted within two months, allowing for the guideline panel to make a recommendation rapidly.

In chapters 9 through 12, we demonstrate the ongoing feasibility of creating *Rapid Recommendations*.[11-14] In all cases, the guideline panels included representation from all key stakeholders, including patients. In most cases, they also included representation from every continent and included representative gender diversity. None of the panelists had any financial conflict of interest, and people with intellectual or professional conflicts were included only if necessary and were never more than a small minority of panel members. All of the guidelines carefully considered published evidence on patient values and preferences, as well as prognosis. All of the guidelines were published well before any guideline on the same topic from professional societies; in many cases, professional societies are still updating their recommendations. The guidelines all include iterative interactive infographics to help users readily understand the recommendations and the evidence. The latest includes a new risk stratification score, as well as a new way of presenting evidence from multiple treatment comparisons.

Chapter 13 describes a related project focused on issues in intensive care. It shows that other groups can emulate the methods developed in *Rapid Recommendations* – a critical step if we are going to succeed in our goal of reinventing the way clinical practice guidelines are developed and presented.

Measuring success and ongoing challenges

Reach

At the start of this thesis, we were concerned that our guidelines would not be accessed and used when there were already guidelines from well-established and respected guideline organizations available. As of 11 April 2020, the publications associated with *BMJ Rapid Recommendations* have been accessed 2.3 million times. The guidelines have been accessed a median of 73,500 times (min 32,000; max 335,000). It is the most highly accessed publication type in the 180 year history of *The BMJ*. Clearly, clinicians are open to using guidance from new informal networks if they are timely and trustworthy.

Trustworthiness

Rapid Recommendations meet or exceed almost all of the Institute of Medicine's (IOM) criteria for trustworthy guidelines (Table 1).[15] A systematic survey of clinical practice guidelines revealed that no guideline met all of the IOM's trustworthiness criteria, and most met less than half.[16] The ECRI guidelines trust is an independent repository of clinical practice guidelines that evaluates guidelines based on the IOM's trustworthiness criteria.[17] *Rapid Recommendations* have consistently scored very well – much higher than other guideline organizations. The time constraints in *Rapid Recommendations* have thus far prevented us from meeting all of criteria 7.1 and 7.4 in full, but we are working on solutions. We have had some difficulty keeping our recommendations up to date with our constrained resources (criteria 8.3); we are making our best efforts to update our recommendations when necessary.

Table. How *Rapid Recommendations* meet each of the Institute of Medicine's criteria for guideline trustworthiness

IOM Trustworthiness criteria	*Rapid Recommendations* approach
1.1 The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible	The methods for Rapid Recommendations are detailed in an appendix accompanying each guideline. Funding, if any, is explicitly detailed in the footnotes.
2.1 Prior to selection of the Guideline Development Group (GDG), individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity, by written disclosure to those convening the GDG.	Each potential panelist completes a comprehensive COI form online, including disclosure of all potential financial, intellectual, and professional conflicts.
2.2 Disclosure of COIs within GDG: All COI of each GDG member should be reported and discussed by the prospective development group prior to the onset of their work. Each panel member should explain how their COI could influence the CPG development process or specific recommendations.	The *Rapid Recommendations* steering committee and the BMJ editorial board independently reviews each potential conflict and approves or excludes each potential panelist. A detailed description of any potential conflict is presented in an appendix to each guideline.
2.3 Divestment: Member of the GDG should divest themselves of financial investments they or their family members have in, and not participate in marketing activities or advisory boards of, entities whose interests could be affected by CPG recommendations.	No panelist can have any financial COI.
2.4 Exclusions: Members with COIs should represent not more than a minority of the GDG. The chair or co-chairs should not be a person(s) with COI. Funders should have no role in CPG development.	No panelist can have any financial COI. If it is necessary to include people with professional conflicts (e.g., cardiac surgeons in guidelines on cardiac surgery), they are the minority. No chair can have any professional, intellectual, or financial COI. Funders, where they exist, cannot have any role in the CPG development.
3.1 The GDG should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG.	All *Rapid Recommendations* include all stakeholders, including allied health care workers, practicing doctors with representation from all relevant specialties, patients, and methodologists.
3.2 Patient and public involvement should be facilitated by including (at least at the time of clinical question formulation and draft CPG review) a current or former patient and a patient advocate or patient/consumer organization representative in the GDG.	Two or more patients with lived experience of the disease at hand are included in each *Rapid Recommendation.* They are included throughout the process.
3.3 Strategies to increase effective participation of patient and consumer representatives, including training in appraisal of evidence, should be adopted by GDGs.	A patient-partner liaison is involved for each *Rapid Recommendation*. The liaison meets with the patient partners prior to the full guideline panel meetings to train them on the details of evidence appraisal specific to the question at hand.
4.1 CPG developers should use systematic reviews that meet standards set by the Institute of Medicine's Committee on Standards for Systematic Reviews of Comparative Effectiveness Research.	Each *Rapid Recommendation* is informed by a systematic review on comparative effectiveness, which meets or exceeds all of the standards.
4.2 When systematic reviews are conducted specifically to inform particular guidelines, the GDG and systematic review team should interact regarding the scope, approach, and output of both processes.	The lead of each systematic review is a full panelist. The methods co-chair functions as an intermediary and ensures that the review provides all the highest quality evidence available for each outcome. The panel chooses the scope of the review(s) and all of the outcomes that the review team considers.
5.1 For each recommendation, the following should be provided:	All of the criteria are included in the text of each *Rapid Recommendation.* The first five points are also included in the

IOM Trustworthiness criteria	*Rapid Recommendations* approach
An explanation of the reasoning underlying the recommendation, including: • A clear description of potential benefits and harms. • A summary of relevant available evidence (and evidentiary gaps), description of the quality (including applicability), quantity (including completeness), and consistency of the aggregate available evidence. • An explanation of the part played by values, opinion, theory, and clinical experience in deriving the recommendation. • A rating of the level of confidence in (certainty regarding) the evidence underpinning the recommendation. • A rating of the strength of the recommendation in light of the preceding bullets. • A description and explanation of any differences of opinion regarding the recommendation.	interactive infographic. Dissenting panellists have the option of including an anonymous detailed description of any differences of opinion in an appendix. While we always endeavour to reach consensus, we have not always included details of dissenting opinions because we leave it to the discretion of the dissenters.
6.1 Recommendations should be articulated in a standardized form detailing precisely what the recommended action is and under what circumstances it should be performed.	All recommendations are actionable, and clear and follow the GRADE Working Group's recommendations for writing recommendations.
6.2 Strong recommendations should be worded so that compliance with the recommendation(s) can be evaluated.	Strong recommendations are accompanied by text detailing whether or not they can be used as an indicator of quality care.
*7.1 External reviewers should comprise a full spectrum of relevant stakeholders, including scientific and clinical experts, organizations (e.g., health care, specialty societies), agencies (e.g., federal government), patients, and representatives of the public.	External reviewers include a statistician/methodologist, clinical experts, and at least one patient. They do not routinely include organizations or agencies because they are unlikely to be able to meet our ambitious timelines.
7.2 The authorship of external reviews submitted by individuals and/or organizations should be kept confidential unless that protection has been waived by the reviewer(s).	Peer reviewer comments are made publicly available. The external reviewers are asked to waive anonymity, but do have the option to ask for it if they think it is necessary.
7.3 The GDG should consider all external reviewer comments and keep a written record of the rationale for modifying or not modifying a CPG in response to reviewers' comments.	The panel's responses to external reviewer comments is provided in detail, and is available to the public.
*7.4 A draft of the CPG at the external review stage or immediately following it (i.e., prior to the final draft) should be made available to the general public for comment. Reasonable notice of impending publication should be provided to interested public stakeholders.	Our timelines do not allow for public posting prior to publication but do include a submission form for public comment after publication. All comments are publicly available and the co-chairs commit to responding to each comment in a timely manner for the first six months. We are currently exploring the possibility of using a preprint server to make the guidelines publicly available prior to publication.
8.1 The CPG publication date, date of pertinent systematic evidence review, and proposed date for future CPG review should be documented in the CPG.	The publication data and date of the date(s) of the systematic search(es) are published. Our guidelines are updated on a continuous basis using the same study screening tool that we use for current evidence.
8.2 Literature should be monitored regularly following CPG publication to identify the emergence of new, potentially relevant evidence and to evaluate the continued validity of the CPG.	The evidence is monitored centrally by the *Rapid Recommendations* steering committee using the screening tool developed.
*8.3 CPGs should be updated when new evidence suggests the need for modification of clinically important recommendations. For example, a CPG should be updated if new evidence shows that a recommended intervention causes previously unknown substantial harm, that a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective, or that a recommendation can be applied to new populations.	All *Rapid Recommendations* include a table that can be updated with new evidence. If a new study might change practice, the systematic review is updated and the panel considers whether or not the new evidence will change the recommendation. The GRADE Evidence Profile available in MAGICapp is updated in real time to include the new evidence. Keeping our recommendations up to date is an ongoing challenge with our currently constrained resources.

IOM, Institute of Medicine; CPG, clinical practice guideline; GDG, guideline development group; COI, conflict of interest
*Criteria that we have had some difficulty meeting in full

Speed

We have only managed to meet our ambitious three month timeline from new evidence to publication twice;[18 19] however, all of our guidelines have been published months or years before those of traditional guideline organizations on the same topics. One of the challenges is the rapid recruitment of interested experts that meet our stringent conflict of interest policies while

maintaining geographic and gender representation. We have had increasing success rapidly recruiting panelists as *BMJ Rapid Recommendations* has gained global recognition. Involving experts from previous panels who are familiar with the process has also improved the process.

In no circumstance have we sacrificed the quality of any of our systematic reviews that inform the guidelines. However, some of them include upwards of 100 individual papers, and they often require examining multiple populations or interventions at once (thus becoming two or three concurrent reviews). In several circumstances, we have needed to learn or develop novel methods in order to provide the panel with the most trustworthy evidence. For example, we have synthesized evidence on minimally important differences, prognosis, forced-choice studies, qualitative research on patient values and preferences, and in one case created a microsimulation model.[9 14 20-24]

As we gain experience with each of these methods, speed will increase. Involving experts in each of these research types has also improved efficiency. We also face challenges finding efficiencies in the time from paper submission to publication. Involving journal editors early in the process, identifying peer reviewers in advance, involving journal editors from alternative journals throughout the process, and creating a stable publication format has improved speed to publication. *Rapid Recommendations* is an iterative project: with each new one, we use lessons learned from those that came before.

Resources

Each *Rapid Recommendation* takes a massive amount of human resources. We have been lucky have access to a motivated base of volunteers that participate for academic reasons. Most guideline organizations are not so lucky to have such an engaged network of academics. Our sixteen published *Rapid Recommendations* include 535 publication authorships by 280 people (mean per guideline = 33 authorships). There are additional demands for each on MAGICapp web developers, graphics designers, journal editors, and peer reviewers. In each instance, the contributors dedicated substantial time on short notice to create the final product. One option for guideline organizations is to create guidelines with fewer questions. Many guideline organizations are already moving towards more focused guidelines. While these guidelines will undoubtedly be more trustworthy for the recommendations they do have, they will not be able to answer all of the important questions clinicians face.

Publication format

The traditional publication format is a major barrier to implementation of guidelines that are responsive to new evidence. Currently, each document receives a unique digital object identifier (DOI) and unique code in each of the indexing databases (e.g., MEDLINE). Every update of the document requires a new DOI and submission to the indexes. A frequently updated guideline would add to the denominator of the impact factor with every update: a major deterrent for journals interested in protecting their impact factor.

A web-based publishing model can solve many of these issues. The MAGICapp is one of several available web-based publishing models: individual recommendations can be updated without

developing the entire publication.[25] However, the traditional academic incentive and publishing model conflicts with its widespread implementation. Recommendations published individually, disaggregates full guidelines. Clinicians often use full guidelines because they can view multiple sources of information in one place. Electronic publishing formats can overcome this problem.

Publication bias

Responsive guidelines probably compound the pervasive problem of publication bias. Studies with promising results are more likely to be published and are published sooner than studies with negative results. This may be a small risk when evidence from large trials of a net benefit is definitive; but when risks are closely balanced, or the *Rapid Recommendation* process is initiated based on smaller less definitive studies, they may erroneously make recommendations that must be changed when negative studies are published later. There was evidence that this might have happened in our Rapid Recommendation for TAVI. A trial[26] that did not show a short-term mortality benefit was completed before but published after our systematic review.[3] Thankfully in this case, the interpretation of the pooled effect estimate did not substantially change and additional trials confirmed an early mortality benefit with TAVI.[27] Authors of responsive recommendations need to pay particular attention to unpublished trials(G. H. Guyatt, A. D. Oxman, V. Montori, et al., 2011).[28]

Opportunities for future research

While the *Rapid Recommendations* project has thus far successfully met almost all of the feasibility criteria within its limited scope, it is yet to be determined whether the same approach can work on the large scale. The most important research questions are primarily those of implementation. How can large guideline organizations adapt their organizational structure to develop responsive guidelines rather than using fixed updates? How can publishers overcome the necessity to pursue ever higher impact factors, and publish living guidelines? Can online publication formats meet the needs of frontline clinicians?

We have heard informally that our interactive infographics have been extremely useful for users. Their development has been iterative with informal feedback from the public through social media, external reviewers, and from successive guideline panels. However, they have not undergone formal user testing, which would help validate or refute our assumption that they are useful. Focused user testing would help us further improve the useability of our infographics. In addition, some clinicians use the infographics while engaging in shared decision making conversations with patients. It is not yet clear that their use in this situation enhances informed decision making.

User testing of our full *Rapid Recommendations* might help improve the publication format by identifying areas that should be expanded, reorganized, or removed because they are less helpful. We hope that our format includes all of the necessary information to make informed decisions, because we include all of the components suggested by the Institute of Medicine and the GRADE Working Group.

Summary

Rapid Recommendations are a new responsive approach to the development of clinical practice guidelines. We show that, at least within a limited scope, it is feasible to produce trustworthy guidance in a very short time period. They have engaged a broad and increasing readership. Questions remain about the feasibility of implementing the approach on a larger scale, but for important questions the approach can and has been adopted by traditional guideline creating organizations.

References

1. Siemieniuk RA, Agoritsas T, Macdonald H, et al. Introduction to BMJ Rapid Recommendations. *Bmj* 2016;354:i5191. doi: 10.1136/bmj.i5191 [published Online First: 2016/09/30]
2. Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *Bmj* 2016;354:i5085. doi: 10.1136/bmj.i5085 [published Online First: 2016/09/30]
3. Siemieniuk RA, Agoritsas T, Manja V, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis. *Bmj* 2016;354:i5130. doi: 10.1136/bmj.i5130 [published Online First: 2016/09/30]
4. Siemieniuk RAC, Harris IA, Agoritsas T, et al. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *Bmj* 2017;357:j1982. doi: 10.1136/bmj.j1982 [published Online First: 2017/05/12]
5. Frketich J. Millions of health dollars wasted on useless surgery: researcher. *The Hamilton Spectator* 2017 12 May 2017.
6. Siemieniuk RA, Foroutan F, Mirza R, et al. Antiretroviral therapy for pregnant women living with HIV or hepatitis B: a systematic review and meta-analysis. *BMJ Open* 2017;7(9):e019022. doi: 10.1136/bmjopen-2017-019022 [published Online First: 2017/09/13]
7. Siemieniuk RAC, Lytvyn L, Mah Ming J, et al. Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline. *Bmj* 2017;358:j3961. doi: 10.1136/bmj.j3961 [published Online First: 2017/09/13]
8. Welbourn A. WHO and the rights of women living with HIV. theBMJopinion: BMJ, 2017.
9. Lytvyn L, Siemieniuk RA, Dilmitis S, et al. Values and preferences of women living with HIV who are pregnant, postpartum or considering pregnancy on choice of antiretroviral therapy during pregnancy. *BMJ Open* 2017;7(9):e019023. doi: 10.1136/bmjopen-2017-019023 [published Online First: 2017/09/13]
10. Sadeghirad B, Siemieniuk RAC, Brignardello-Petersen R, et al. Corticosteroids for treatment of sore throat: systematic review and meta-analysis of randomised trials. *Bmj* 2017;358:j3887. doi: 10.1136/bmj.j3887 [published Online First: 2017/09/22]
11. Lamontagne F, Rochwerg B, Lytvyn L, et al. Corticosteroid therapy for sepsis: a clinical practice guideline. *Bmj* 2018;362:k3284. doi: 10.1136/bmj.k3284 [published Online First: 2018/08/12]

12. Siemieniuk RAC, Chu DK, Kim LH, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. *Bmj* 2018;363:k4169. doi: 10.1136/bmj.k4169 [published Online First: 2018/10/26]
13. Vermandere M, Aertgeerts B, Agoritsas T, et al. Antibiotics after incision and drainage for uncomplicated skin abscesses: a clinical practice guideline. *Bmj* 2018;360:k243. doi: 10.1136/bmj.k243 [published Online First: 2018/02/14]
14. Ye Z, Reintam Blaser A, Lytvyn L, et al. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. *Bmj* 2020;368:l6722. doi: 10.1136/bmj.l6722 [published Online First: 2020/01/08]
15. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice G. In: Graham R, Mancher M, Miller Wolman D, et al., eds. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US)

16. Kung J, Miller RR, Mackowiak PA. Failure of clinical practice guidelines to meet institute of medicine standards: Two more decades of little, if any, progress. *Arch Intern Med* 2012;172(21):1628-33. doi: 10.1001/2013.jamainternmed.56 [published Online First: 2012/10/24]
17. Jue JJ, Cunningham S, Lohr K, et al. Developing and Testing the Agency for Healthcare Research and Quality's National Guideline Clearinghouse Extent of Adherence to Trustworthy Standards (NEATS) Instrument. *Ann Intern Med* 2019;170(7):480-87. doi: 10.7326/m18-2950 [published Online First: 2019/03/19]
18. Poolman RW, Agoritsas T, Siemieniuk RA, et al. Low intensity pulsed ultrasound (LIPUS) for bone healing: a clinical practice guideline. *Bmj* 2017;356:j576. doi: 10.1136/bmj.j576 [published Online First: 2017/02/24]
19. Rochwerg B, Almenawer SA, Siemieniuk RAC, et al. Atraumatic (pencil-point) versus conventional needles for lumbar puncture: a clinical practice guideline. *Bmj* 2018;361:k1920. doi: 10.1136/bmj.k1920 [published Online First: 2018/05/24]
20. Devji T, Guyatt GH, Lytvyn L, et al. Application of minimal important differences in degenerative knee disease outcomes: a systematic review and case study to inform BMJ Rapid Recommendations. *BMJ Open* 2017;7(5):e015587. doi: 10.1136/bmjopen-2016-015587 [published Online First: 2017/05/13]
21. Kuijpers T, Spencer FA, Siemieniuk RAC, et al. Patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy alone for management of cryptogenic stroke? A clinical practice guideline. *Bmj* 2018;362:k2515. doi: 10.1136/bmj.k2515 [published Online First: 2018/07/27]
22. Hao Q, Devji T, Zeraatkar D, et al. Minimal important differences for improvement in shoulder condition patient-reported outcomes: a systematic review to inform a BMJ Rapid Recommendation. *BMJ Open* 2019;9(2):e028777. doi: 10.1136/bmjopen-2018-028777 [published Online First: 2019/02/23]
23. Buskermolen M, Cenin DR, Helsingen LM, et al. Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a microsimulation modelling study. *Bmj* 2019;367:l5383. doi: 10.1136/bmj.l5383 [published Online First: 2019/10/04]
24. Foroutan F, Guyatt GH, O'Brien K, et al. Prognosis after surgical replacement with a bioprosthetic aortic valve in patients with severe symptomatic aortic stenosis:

systematic review of observational studies. *Bmj* 2016;354:i5065. doi: 10.1136/bmj.i5065 [published Online First: 2016/09/30]
25. Vandvik PO, Brandt L, Alonso-Coello P, et al. Creating clinical practice guidelines we can trust, use, and share: a new era is imminent. *Chest* 2013;144(2):381-89. doi: 10.1378/chest.13-0746 [published Online First: 2013/08/07]
26. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med* 2017;376(14):1321-31. doi: 10.1056/NEJMoa1700456 [published Online First: 2017/03/18]
27. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med* 2019;380(18):1695-705. doi: 10.1056/NEJMoa1814052 [published Online First: 2019/03/19]
28. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *J Clin Epidemiol* 2011;64(12):1277-82. doi: 10.1016/j.jclinepi.2011.01.011 [published Online First: 2011/08/02]