VENOUS THROMBOEMBOLISM AND BLEEDING IN MEDICAL INPATIENTS

RISK ASSESSMENT OF VENOUS THROMBOEMBOLISM AND BLEEDING IN HOSPITALIZED MEDICAL PATIENTS

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LAY ABSTRACT

Measuring the probability of an individual experiencing a specific health outcome in a certain period of time based on that individual's risk factors is important to improve health. Prediction tools are often used to calculate the probability of an outcome. Health care practitioners use prediction tools to assess an individual's risk of a certain health outcome and in turn provide individualized management. Prediction tools include a number of agreed upon risk factors that should be assessed in order to best estimate the risk of an outcome. These risk factors are usually selected through exploring sets of data or by consulting a group of experts in the field. However, these methods have limitations. Therefore, we recognized that it is important, when developing prediction tools, to select risk factors that are evidence-based and clinically relevant by adopting a systematic, comprehensive, structured and transparent approach. These sets of risk factors can then aid health researchers when developing new prediction tools or updating existing ones and help clinicians predicting risk. In this thesis, I highlight the methods used to select factors for prediction tools that evaluate the risk of having a venous clot or a bleeding event in patients that are hospitalized for a medical condition. However, the same methods can be applied to any clinical condition and outcome of interest.

This work presents a new approach that we conceptualized and tested to select risk factors for venous clots and bleeding events in hospitalized medical patients that are

evidence-based, clinically meaningful and relevant. Our findings may inform the development of new prediction tools, the update of widely used tools, and the design of studies to validate these tools. Also, these findings may assist decision makers in evaluating the risk of an individual having an outcome to optimize patient care.

ABSTRACT

Determining the prognosis or risk of an individual experiencing a specific health outcome within a certain time period is essential to improve health. An important aspect of prognostic research is the development of risk assessment models (RAMs). In support of the movement towards personalized medicine, health care professionals have employed RAMs to stratify an individual patient's absolute risk of developing a health condition and select the optimal management strategy for that patient. The development of RAMs is generally conducted using data driven methods or through expert consensus. However, these methods present limitations. Accordingly, we recognized the need to select factors for RAM development or update that are evidence-based and clinically relevant using a structured and transparent approach. In this sandwich thesis, I highlight the methods used to select prognostic factors for VTE and bleeding RAMs for hospitalized medical patients. However, the same methods can be applied to any clinical outcome of interest.

This work presents a conceptualized and tested novel mixed methods approach to select prognostic factors for VTE and bleeding in hospitalized medical patients that are evidence-based, clinically meaningful and relevant. Our findings may inform the development of new RAMs, the update of widely used RAMs, and external validation and prospective impact assessment studies. Also, these findings may assist decision

makers in evaluating the risk of an individual having an outcome to optimize patient care.

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I believe that what you make of yourself is not a testament to yourself but rather a testament to the people around you.

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Andrea J. Darzi

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PREFACE

The work in this dissertation is presented as a "sandwich thesis" that includes three manuscripts which have been published, accepted for publication or prepared for submission. The manuscript in Chapter 2, Risk assessment models for venous thromboembolism and bleeding in hospitalized medical patients: An overview of systematic reviews, was accepted for publication on 27 August 2020 to *Blood Advances*. The manuscript in Chapter 3, Prognostic factors for VTE and bleeding in hospitalized medical patients: a systematic review and meta-analysis, was published on 14 May 2020 in *Blood*, Journal of the American Society of Hematology. The manuscript in Chapter 4, Risk models for VTE and bleeding in medical inpatients: Systematic identification and expert assessment, was published on 15 June 2020 in *Blood Advances*.

The overview of reviews presented in Chapter 2 was an effort conducted to inform the 2018 American Society of Hematology guidelines led by my supervisor, Dr. Holger Schünemann. I developed the protocol and search strategies with the help of Dr. Elie Akl and input from Dr. Holger Schünemann. I screened, abstracted data and drafted summaries of our findings to present to the guideline panel. I drafted the manuscript which was circulated to co-authors. I incorporated feedback from the co-authors, prepared the manuscript for submission and responded to reviewer comments. Chapter 3 was a systematic review effort that I coordinated under the supervision of Dr. Holger Schünemann. I developed the protocol and received feedback from the co-authors. I

screened and abstracted data from studies along with a research team. I analysed the data and wrote the systematic review manuscript. I incorporated comments from co-authors and submitted the manuscript for publication. Dr. Holger Schünemann and I responded to reviewer comments. I conceived of and conducted the work in Chapter 4 under the supervision of Dr. Holger Schünemann and with the clinical and methodological input of an expert panel. I drafted the manuscripts, incorporated feedback from the co-authors, submitted the manuscript for publication and prepared responses to reviewer comments.

The overview of reviews presented in Chapter 2 in this dissertation was funded by American Society of Hematology (ASH) to inform the VTE guidelines. The systematic review and novel approach described in Chapters 3 and 4 respectively were funded by a subcontract from the U.S Centers for Disease Control and Prevention (CDC) through Karna LLC.

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LIST OF ABBREVIATIONS AND SYMBOLS

ASH: American Society of Hematology

CDC: Centers for Disease Control and Prevention

U.S: United States

RAM: Risk assessment model

VTE: Venous thrombo-embolism

DVT: Deep vein thrombo-embolism

PE: Pulmonary embolism

GRADE: Grading of Recommendations Assessment, Development and Evaluations

ETD: Evidence to Decision

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

ROBIS: Risk of bias in Systematic Reviews

PROBAST: Prediction study Risk Of Bias Assessment tool

QUIPS: Quality in Prognosis Studies tool

RCT: Randomized controlled trial

ICD-9: International Clinical Diagnosis Code version 9

AUC: Area under the curve

MITH: Medical Inpatients and Thrombosis

NIHSS: National institute of Health Stroke Scale

n: Sample size

OR: Odds ratio

RR: Risk ratio

HR: Hazard ratio

CI: Confidence interval

SD: Standard deviation

SE: Standard error

CRP: C-reactive protein

BI: Barthel index

ICU: Intensive care unit

CCU: Coronary care unit

WBC: White blood count

CAD: Coronary artery disease

CVC: Central venous catheter

GFR: glomerular filtration rate

DECLARATION OF ACADEMIC ACHIEVEMENT

I declare that I, jointly with my supervisor, Professor Holger J. Schünemann, played the primary role in the conception, design, and execution of the studies here included. We obtained feedback and advice from Professors Akl, Iorio, and Spencer, as well as from clinical and methodological experts that co-authored the work, the American Society of Haematology (ASH), the United States (U.S.) Centers for Disease Control and Prevention (CDC) and Karna LLC.

This work is original research that I conducted. I am the principle contributor and first author of all the manuscripts contained in this dissertation. I am responsible for and made the following contributions to all the projects in this dissertation including design, conception, analysis, and writing of materials. I designed the search strategy, screening, and data extraction for the overview of systematic reviews of risk assessment models and for the systematic review of prognostic factors for venous thromboembolism and bleeding in hospitalized medical patients. I designed surveys and collated both quantitative and qualitative information. I reviewed comments and feedback that resulted from the face to face panel meeting with methodological and clinical experts in prognosis, risk assessment model development and venous thromboembolism and bleeding prevention and management.

I conducted all analyses, designed figures and tables, and organized meetings. I wrote the manuscripts with editorial advice and supervision of Professor Schünemann, and

with feedback from Professors Akl, Iorio, and Spencer. The authors on each paper contributed significantly with important comments and advice for the final manuscripts.

For all three manuscripts composing this "sandwich" thesis, earlier drafts of parts of this research have been presented in the U.S Centers for Disease Control and Prevention (CDC) Public Health Webinar Series on Blood Disorders that was hosted by the National Blood Clot Alliance in March 2020. The first manuscript (Chapter 2) was accepted in *Blood Advances in August 2020*. The second manuscript (Chapter 3) was published in *Blood*, Journal of the American Society of Hematology in May 2020. The third manuscript (Chapter 4) was published in *Blood Advances* in June 2020.

CHAPTER 1. INTRODUCTION

Introduction

Prognosis and risk assessment models

Determining the prognosis or risk of an individual experiencing a specific health outcome within a certain time period is essential to improve health (1). One important component of prognostic research is the development of risk assessment models (RAMs). RAMs include a formal combination of multiple variables that can be used to calculate an individual patients' absolute risk or probability of developing an outcome (1, 2). RAMs play a role in supporting the movement towards stratified medicine (3). This has led researchers to improve the methods with a goal to develop an ideal RAM (4).

An ideal risk assessment model

An ideal RAM is defined as a model that is appropriately based on all candidate prognostic factors, is externally validated and has undergone an impact assessment (4). Additionally, an ideal RAM should be clinically relevant, easy to use in clinical practice, and cost-effective (4). An ideal RAM for risk of development of venous thromboembolism (VTE) should be able to accurately identify patients at increased risk and reliably exclude those who are at low risk (4). This ensures optimal selection of patients who will most benefit from pharmacological thromboprophylaxis and the identification of patients who may not benefit due to a higher risk-to-benefit ratio in terms of bleeding as a potential adverse event.

Limitations in the development methods of risk assessment models

In 2018 the American Society of Hematology (ASH) together with the Michael G. DeGroote Cochrane Canada and MacGRADE Centres at McMaster University developed clinical practice guidelines for the prevention of VTE in hospitalized medical patients (5). To inform the ASH guidelines, we conducted an overview of systematic reviews to identify and summarize evidence related to VTE or bleeding RAMs in hospitalized medical patients (Chapter 2) (6). With the increasing number of RAMs published and systematic reviews available, this study design allowed us to compare and contrast the findings of separate systematic reviews we identified, thus providing the guideline panel with the evidence they need for decision making (7). However, we identified several concerns with previously developed RAMs. One concern relates to using the optimum method where all potential factors are included in a RAM because of statistical significance. This often leads to overfitting and non-generalizable results (3). Also, the use of prognostic factor selection approaches such as the backward elimination or stepwise selection methods or univariable screening, where decisions for prognostic factor inclusion in a RAM are based on statistical significance, pose a concern. These approaches may lead to eliminating relevant factors from RAMs due to lack of power in the datasets or due to relying on statistical significance only (3, 8, 9). The reliance on the P-value alone without accounting for the magnitude of effect and the confidence interval may lead to the inclusion of prognostic factors that are statistically significant

but have small associations with the outcome (3). These factors may not be clinically relevant and therefore not helpful in a RAM (3). Also, these methods of selection may lead to the inclusion of multiple prognostic factors in a single RAM that may be highly correlated, which impairs the performance of the model. By testing for correlation, researchers can make decisions to either collapse correlated prognostic factors into a single factor or remove prognostic factors that are highly correlated with other factors thus developing more usable and efficient RAMs (3). Another concern noted in the literature related to the patient data used to develop a RAM which often comes from a selected cohort, database or registry of patients. This concern is due to a subset of the selected patients being under a pharmacological intervention prior, during, or post the assessment of the prognostic factor (e.g. during follow-up that may bias the predictive power of the developed RAM (10-12). In order to develop a RAM that predicts an untreated individual's risk of developing a certain outcome, one should ideally include participants that have not been on any management option before or during follow-up (1, 12). In practice, this is not generally the case and therefore models that are based on treated patients may underestimate the risk of the outcome of interest in untreated individuals, and could thus lead to under-treatment when such a model is implemented for individualized care (10, 13).

Why is this research important?

As stated by Wyatt et al. (1995):

"We believe that the main reasons why doctors reject published prognostic models are lack of clinical credibility and lack of evidence that a prognostic model can support decisions about patient care (that is, evidence of accuracy, generality, and effectiveness)" (14).

Accordingly, we recognized the need to select factors for RAM development or update that are evidence-based and clinically relevant using a structured and transparent approach. Our aim was to overcome the limitations noted above regarding developed RAMs and prevent the inclusion of nonsensical, less relevant, more invasive or costly variables or variables that are more difficult to measure in a RAM.

To do so, it is important to find a balance between clinical and statistical significance when selecting prognostic factors for a RAM by building on what is known in clinical practice and on the research done in the field using a systematic and transparent approach (15). Without a systematic and transparent process, experts may exclude important prognostic factors, have different views on candidate factors that are not transparently displayed or presented explicitly, overlook or give unwarranted value to some criteria, or not base their decision making on the best available evidence (15).

Goals and scope

The goals of this dissertation were threefold:

1. Identify and describe RAMs and their clinical utility for VTE and bleeding in hospitalized medical patients to inform the ASH guidelines, health care practitioners and health systems;
2. Provide a comprehensive list of candidate prognostic factors for VTE and bleeding in hospitalized medical patients with their pooled effect estimates and certainty of the evidence;
3. Conceptualize and test a novel approach based on systematic reviews and GRADE criteria that can be used to systematically and transparently select prognostic factors for the development, update or validation of RAMs

To achieve the first goal, we conducted an overview of systematic reviews to identify and describe VTE and bleeding RAMs and their clinical utility in hospitalized medical patients. The aim of this overview was to identify an ideal RAM that could be used to individualize population-based recommendations by stratifying an individual patient's risk of developing a VTE or bleeding event. This could aid health care practitioners in their decision-making process regarding the choice of preventive measures for their patients (6).

For the second goal, we conducted a systematic review and meta-analysis to identify all candidate prognostic factors for VTE and bleeding in hospitalized medical patients (16). This was a crucial step as most evidence-based RAMs are limited by the variables measured in the dataset(s) used to derive and validate them. Also, many prognostic

studies are published each year and the variability in design, the factors measured and the inconsistency in the findings make a systematic review an appealing candidate method to better identify which factors have prognostic value (17). We also assessed the certainty of the evidence, identified in the systematic review, by considering the five Grading of Recommendations, Assessment, Development and Evaluations (GRADE) domains (18). Assessing the certainty of the evidence based on a structured framework allowed for an expression of the confidence in the prognostic ability of the identified factors (18).

The third and final goal was to apply a novel mixed-methods approach to select risk factors for VTE and bleeding RAMs in hospitalized medical patients (Chapter 4) (19). This was done with clinical and methodological experts. Initially, the expert provided input on the list of candidate prognostic factors identified in the systematic review (19). We then asked them to make judgements on whether to include, potentially include, or exclude each of the prognostic factors from the final RAMs using the GRADE Evidence to Decision (EtD) criteria and the Delphi process (19). The use of the GRADE criteria, including benefits and harms, resource requirements, equity, acceptability and feasibility, provided a structured and transparent approach to facilitate the panel's decision-making process (15). The aim was to include risk factors that were both evidence-based and clinically relevant irrespective of data driven results. As part of the third goal, we standardized the definitions of the included and potentially included

prognostic factors to decrease variability in methods of measurement across settings (19). This was done based on the definitions of each of the factors in the included studies and input from the expert panel (19). Our aim was to decrease variability in methods of measurement across settings and provide more clarity to health care professionals, including researchers, when evaluating and weighing patients' risks of VTE and bleeding and subsequent management options (19).

Thesis overview

This work comprises three main research chapters that address each of the processes described above with a final chapter bringing the work back together and raising the implications of our findings for future research and practice. These research questions are explored, evaluated and discussed in Chapters 2, 3, and 4 of this thesis, with an overarching discussion and conclusion in Chapter 5.

As stated above, Chapter 2 presents the overview of systematic reviews conducted to identify and describe RAMs and their clinical utility for VTE and bleeding in hospitalized medical patients to assist experts in selecting a RAM to integrate in their health care systems. Chapter 3 entails a systematic review we conducted to identify all reported candidate prognostic factors for VTE and bleeding in hospitalized medical patients from the literature. Chapter 4 includes the systematic identification and expert assessment of prognostic factors for VTE and bleeding in hospitalized medical patients for RAM development or update. Also, we presented standardized definitions of prognostic

factors of the included and potentially included prognostic factors. Finally, chapter 5 presents an overall summary of findings and a discussion including implications for future research and practice.

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CHAPTER 2. RISK ASSESSMENT MODELS FOR VTE AND BLEEDING IN HOSPITALIZED MEDICAL PATIENTS: AN OVERVIEW OF REVIEWS

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Risk Assessment Models for VTE and Bleeding in Hospitalized Medical Patients: An Overview of Systematic Reviews

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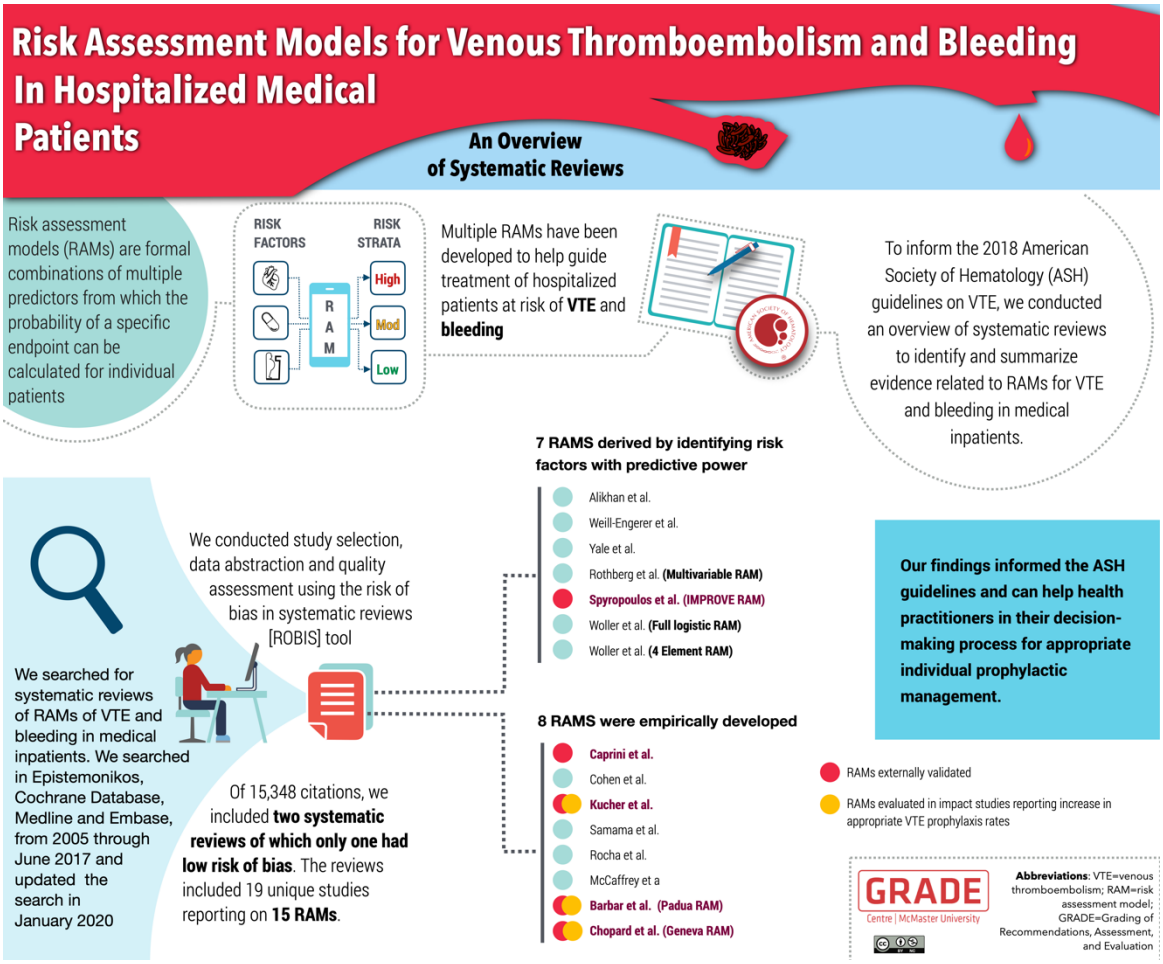
Key points

1. We identified 15 existing venous thromboembolism (VTE) risk assessment models (RAMs), however none were ideal.
2. Our findings may help experts select a RAM to integrate in their health care systems to standardize their approach to estimating patients' risks of VTE.

Visual abstract



Abstract

Multiple risk assessment models (RAM) for venous thromboembolism (VTE) in hospitalized medical patients have been developed. To inform the 2018 American Society of Hematology (ASH) guidelines on VTE, we conducted an overview of systematic reviews to identify and summarize evidence related to RAMs for VTE and bleeding in medical inpatients. We searched Epistemonikos, Cochrane Database, Medline and Embase from 2005 through June 2017 and then updated the search in January 2020 to identify systematic reviews that included RAMs for VTE and bleeding in medical inpatients. We conducted study selection, data abstraction and quality assessment (using the risk of bias in systematic reviews [ROBIS] tool) independently and in duplicate. We described the characteristics of the reviews and their included studies, and compared the identified RAMs using narrative synthesis. Of 15,348 citations, we included two systematic reviews of which only one had low risk of bias. The reviews included 19 unique studies reporting on 15 RAMs. Seven of the RAMs were derived using individual patient data where risk factors were included based on their predictive ability in a regression analysis. The other eight RAMs were empirically developed using consensus approaches, risk factors identified from a literature review, and clinical expertise. The RAMs that have been externally validated include the Caprini, Geneva, IMPROVE, Kucher and Padua RAMs. The Padua, Geneva and Kucher RAMs have been evaluated in impact studies that reported an increase in appropriate VTE prophylaxis

rates. Our findings informed the ASH guidelines. They also aim to guide health care practitioners in their decision-making process regarding appropriate individual prophylactic management.

Keywords: risk assessment model, prediction, prognosis, venous thromboembolism, hospitalized medical patients, GRADE, guidelines.

Introduction

The clinical and economic burden of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is immense (20). VTE is a complex multifactorial disease, influenced by acquired or inherited predispositions to thrombosis (e.g. thrombophilia), environmental exposures (e.g. clinical risk factors) and the interaction between them (21). The annual incidence of VTE in adult populations is approximately 1 in a 1000 (5, 22). Around 50% of all VTE events occur during or shortly after hospitalization for surgery (24%) or acute medical illness (22%) (5, 23, 24). Patients hospitalized for an acute medical illness have an eightfold increased risk of VTE compared to the general population (25, 26). Medical costs are estimated at approximately $17,000 more for patients who have a VTE event during or after a recent hospitalization compared to their hospitalized counterparts who do not experience a VTE event (20).

The use of pharmacological thromboprophylaxis reduces the incidence of VTE in a cost-effective manner in many patient populations but increases the risk of bleeding (24, 27). To inform optimal management, risk assessment models (RAM) can be used to aid in stratifying individual patients' risk of developing a VTE or bleeding event. A RAM is defined as a formal combination of multiple predictors from which risks of a specific endpoint can be calculated for individual patients. A RAM may also be called a prognostic model, risk (or clinical) prediction model, or predictive model (2). A RAM

undergoes three main phases: model development (including internal validation), external validation, and investigations of impact on decision making and patient outcomes (2).

In 2018 the American Society of Hematology (ASH) together with the Michael G. DeGroote and MacGRADE Centres at McMaster University developed clinical practice guidelines for the prevention of VTE in hospitalized medical patients (5). The methods used to develop these guidelines were based on the GIN-McMaster Guideline Development Checklist (28), the GRADE approach (29), and the Cochrane Handbook for systematic review methodology (30). We conducted an overview of systematic reviews to identify and describe RAMs and their clinical utility for VTE and bleeding in hospitalized medical patients to inform the ASH guidelines (5).

Methods

We conducted an overview of reviews to identify systematic reviews that report on RAM development, validation or impact studies for VTE and bleeding in hospitalized medical patients. We developed a protocol which was reviewed and revised by the co-authors, but we did not register it.

Data sources and searches

We initially searched Epistemonikos, Cochrane Database of Systematic Reviews, Medline and Embase from 2005 through June 2017 with the help of an information specialist and conducted an update of the search in January 2020. eTable 1 in the Supplement provides detailed descriptions of the search strategies. Our search included both MesH terms and text-word terms that combined VTE-related terms with prognosis terms. We added a systematic review filter when using Medline and Embase. We used no language restrictions.

Study selection

Prior to starting the screening process, four teams of two reviewers participated in training and calibration exercises. Teams of two reviewers screened independently and in duplicate the titles and abstracts of all the identified citations. They then retrieved full texts of all citations judged as potentially eligible by at least one of the reviewers on each team. The reviewers screened the full texts independently and in duplicate and compared results. A third, senior reviewer resolved disagreements when necessary. Reviewers used standardized screening forms throughout the process. The eligibility criteria for study selection included the following characteristics:

Types of studies: We included studies that explicitly stated the use of the 'systematic review' methodology, with or without conducting a meta-analysis, in the title or abstract. Also, the study must have reported conducting a search for individual studies in at least one database. We included systematic reviews that reported on development,

validation or impact studies of multivariable prediction/RAMs, tools, or scores, proposed for individual risk estimation of any future VTE or bleeding outcome in hospitalized medical patients.

Population: We included systematic reviews that addressed adult patients hospitalized for an acute, critical or chronic medical illness. An acute medical illness is defined as an illness that requires urgent, non-operative care such as heart failure, respiratory insufficiency, stroke, and infectious or inflammatory diseases (5). A critical illness is one that presents as an immediately life-threatening condition that requires care in an intensive or critical care unit (5). A chronic medical illness is defined as an acute exacerbation of a chronic medical condition that requires hospitalization (5).

Intervention: We investigated all RAMs that assessed risk of VTE or bleeding in adults hospitalized for medical illness and were reported in the eligible systematic reviews.

Comparison: Standard care without the use of RAMs or a different RAM than the one used in the intervention.

Outcomes: We evaluated the outcomes of VTE and bleeding. We defined VTE as any symptomatic or asymptomatic DVT or PE from hospital admission up to 90 days post discharge. We considered bleeding as any major or non-major but clinically significant bleeding up to 90 days post discharge (31).

Setting: We included systematic reviews that reported on studies in which the patients were admitted to an inpatient ward or intensive care unit for medical illness.

Data extraction

We conducted calibration exercises and piloting of the data extraction form prior to the start of the process. Using a standardized form, a team of two reviewers (AJD and RC) extracted data independently and in duplicate from all eligible studies and compared results. They consulted a third reviewer (HJS) in case of any disagreement.

For the identified RAM systematic reviews, the reviewers abstracted data on the following characteristics:

Characteristics of the systematic review:

- Main elements of the search strategy (including databases searched, date of search)
- Approach used to synthesize findings (narrative synthesis, meta-analysis)
- Risk of bias tool used to assess individual studies and results
- Authors' assessment and conclusions

Findings pertaining to the studies included in the systematic review:

- Type of prognostic model studies included (i.e. development, validation or impact)
- Population

- Outcomes
- Setting
- Timeframe of prognostic measurement
- Results (predictive performance)

Risk of bias assessment of systematic reviews

We assessed the risk of bias in systematic reviews using the ROBIS tool. The tool includes three phases: assessing relevance (optional), identifying concerns with the review process and judging risk of bias (32). We focused on phases two and three. Phase two considers the following four domains: study eligibility criteria, identification and selection of studies, data collection and study appraisal and synthesis and findings. The signalling questions in each of the domains are judged as yes, probably yes, probably no, no or no information. In phase three, we rated the overall risk of bias as low, high or unclear depending on the rating of the individual domains. For the individual studies included in the systematic reviews, we reported on the risk of bias tool used and the judgements made by the authors when available.

Synthesis and presentation of findings

We used a narrative synthesis of included systematic reviews to summarise our findings. We presented the findings of any qualitative or quantitative syntheses conducted by the authors of the reviews. We focused on identifying and describing the RAMs, their

performance, and gaps in their development, validation or assessment of impact. If a meta-analysis was presented in one of the included systematic reviews, we presented the results and the relevant methodological aspects (e.g. types of data, effects measured, heterogeneity, sensitivity analysis). If different information regarding the same RAM was provided in the reviews, we narratively described all findings to provide a comprehensive description of that model. We did not perform a quantitative synthesis of the RAMs, as the main aim of an overview of reviews is to provide a summary of existing research synthesis and not re-synthesizing evidence (7).

Results

Figure 1 illustrates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (24). In our original search, we identified 6,095 citations of which we included 144 studies for full text assessment. From those, we included two systematic reviews. Both reviews evaluated RAMs for VTE in hospitalized medical patients (4, 33). We did not identify any systematic review that evaluated RAMs for bleeding. When we conducted an update of our search in January 2020, we identified an additional 4,122 citations, none of which fulfilled our inclusion criteria after full evaluation.

Description of the included systematic reviews

The included systematic reviews aimed to identify RAMs developed to calculate the risk of VTE in hospitalized non-surgical patients and to evaluate their generalizability, validity and utility (4, 33). Stuck et al. focused only on acutely ill medical patients and searched for English, German, French or Italian studies in only one database (MEDLINE), from inception till May 30, 2016 (4). They then performed an additional search to identify impact analysis studies that may have been missed (4). The authors did not conduct a quality appraisal of the included studies (4). Huang et al. included a comprehensive search for English articles across four databases from inception till December 2011 (33). The authors of that review appraised the evidence by using a modified Downs and Black checklist for the RAMs developed using individual patient data, and the modified Appraisal of Guidelines for Research and Evaluation (AGREE) instrument for the RAMs generated based on consensus approaches, published data and clinical expertise (33). The reviews included 19 unique primary studies that reported on 15 RAMs. Of those, three studies and four RAMs were common in both systematic reviews (34-52). Stuck et al. identified four additional impact studies from their supplementary search (4). Neither systematic review conducted a meta-analysis of the results (4, 33). Huang et al. highlighted that pooling was not possible due to variability in the methods to develop the RAMs, in the outcome measurements and in the number, type and strength of association of the included VTE risk factors (33). Authors of both reviews concluded that there is a lack of generalizability and adequate validation of the published RAMs which hinders their use in clinical practice (4, 33). However, Stuck et al. encouraged the

implementation of any of the available RAMs to improve the consistency of use of thromboprophylaxis until further evidence is available (4). Characteristics of the systematic reviews are detailed in Table 1.

Risk of bias assessment of systematic reviews and included studies

We rated the overall risk of bias for the systematic review by Huang et al. as low (33), and the review by Stuck et al. as high (4). We judged both reviews as low risk in terms of study eligibility criteria (domain one). However, we originally rated both systematic reviews at high risk for their identification and selection of studies for inclusion (domain two), but each review came with different concerns. stuck et al. searched only one database (4), and did not conduct a sufficiently sensitive search to identify all potentially eligible studies (4). On the other hand Huang et al. made no mention of conducting an independent and duplicate screening process (33), or using standardized screening forms throughout the screening and abstraction processes (33). Also, both reviews placed restrictions on language which may have led to missing studies (4, 33). Despite originally rating Huang et al. as high risk of bias for the domain identification and selection of studies for inclusion, we considered it low risk of bias in our overall judgement (33). We made this decision because our results revealed that all relevant studies were captured within the search date, from inception through May 2011, despite the methodological limitations noted above (33). Regarding data collection and study appraisal (domain three), we rated the review by Huang et al. as low risk of bias

for appraising the included studies and the review by Stuck et al. as high risk of bias for not conducting a critical appraisal (4, 33). Neither of the reviews conducted a meta-analysis which made it challenging to assess their methods of synthesis and presentation of findings domain (domain four) using ROBIS. However, our rationale for rating Huang et al. as low risk was due to the authors stating that the results were too heterogeneous and could not be pooled (33). We rated the review by Stuck et al. as high risk because the authors did not provide a reasoning for not pooling the results (4). eTable 2 in the Supplement provides the risk of bias assessment of the systematic reviews by phase and domain.

Huang et al. described that the quality assessment, using the modified Downs and Black checklist, ranged between 55 and 88% for the RAMs derived using individual patient data (33). The quality appraisal score ranged between 48 and 77% for the RAMs developed by consensus based on the modified AGREE instrument (33). Tables 2 and 3 report the quality assessment score for each of the RAMs.

Risk assessment models for VTE in hospitalized medical patients

Development of Risk Assessment Models

Table 2 provides a detailed description of the included RAMs. From the 15 included RAMs, seven were derived by identifying risk factors with predictive power using individual patient data mainly from medical records. These include the RAMs by Alikhan

et al., Weill-Engerer et al., Yale et al., Spyropoulos et al. (IMPROVE RAM), Rothberg et al. (Multivariable RAM), and Woller et al. (4-Element and the full logistic RAMs) (35, 43, 45-48). The individual studies included cohort studies (n=3) (43, 45, 47), case control studies (n=2) (46, 48), and a study based on a randomised controlled trial (RCT) (35). The studies were all multicenter with two being multinational (35, 45), and sample sizes ranged between 380 (48) to around 243,000 patients (43). The eligibility criteria of individual studies differed mainly in the age cut-offs ranging from >18 to >65 years, the inclusion of history of surgery or trauma, length of hospital stay, known thrombophilia, and the exclusion of patients on pharmacologic thromboprophylaxis or anticoagulation. The proportion of cancer patients included in the derivation cohorts also varied widely ranging between 9% (46) and 44% (47). Two studies reported on DVT alone (n=2) (46, 48), while the rest of the studies used VTE (DVT, PE, and both) as their primary endpoint. All but one study considered symptomatic events only (35); however, the definitions and the methods of diagnosis of the outcomes varied. Two studies used International Clinical Diagnosis Code version 9 (ICD-9) to define VTE (43, 47). One of these two studies included codes for upper-extremity, superficial, and chronic DVT that were excluded from other studies and did not use diagnostic test results and evidence of VTE treatment to validate the outcome (47). The other study validated the outcomes identified using ICD-9 (43). Only four studies described their methods for diagnosis of DVT (ultrasonography or venography) or PE (lung scan, pulmonary angiography, or spiral computed tomography scanning) (35, 43, 45, 46). The follow-up time ranged from the

index hospitalization up to 90 days post discharge. The methods for selection of candidate risk factors also varied among the RAMs, with only one study using Kaplan–Meier and Cox multiple regression analyses to adjust for timing of events (45) and another considering hospital clustering as a factor (43). The number of risk factors ranged between 4 and 14 in all the RAMs except the full logistic model that included 86 risk factors (47). The measure of discrimination of the RAMs was reported in terms of the area under the curve (AUC) and ranged between 0.65 and 0.89 (4, 33). VTE prophylaxis administered in the hospital was considered as a potential confounder in only two of the included studies (43, 45). Both studies reported no statistically significant impact of VTE prophylaxis on the outcome, and only one study included it as a prognostic factor in the RAM (43). Table 3 details the individual study characteristics related to these RAMs.

The other eight RAMs included in the systematic review were empirically developed based on consensus approaches, risk factors identified from a literature review, and input from clinical experts (ranging between 3 to 24 members). These include the RAMs described by Caprini et al. (Caprini RAM), Cohen et al., Samama et al., Rocha et al., McCaffrey et al., Kucher et al., Barbar et al. (Padua RAM), and Nendaz et al. (Geneva RAM) (36-38, 40, 41, 44, 51, 53). Only one of the eight RAMs conducted a comprehensive systematic review of the literature to identify all potential risk factors prior to developing the model (51). One study focused on symptomatic DVT as the

primary endpoint (40). Another study considered VTE as an outcome, but it was unclear whether it was symptomatic VTE only or symptomatic and asymptomatic VTE (36). The rest of the studies only considered symptomatic VTE as their primary endpoint. The number of risk factors included ranged between 8 and 39 for all except four RAMs whose risk factors were not described in the systematic reviews (38, 40, 44, 51). Table 4 describes the individual study characteristics related to these RAMs.

Validation of Risk Assessment Models

The systematic reviews identified five RAMs that underwent internal validation without external validation. The RAMs by Woller et al. (4-Element RAM and full logistic RAM) and the RAM by Rothberg et al. (Multivariable RAM) were developed based on individual patient data where risk factors were included based on their predictive ability identified in a regression analysis and compared in one retrospective study to one another (43, 47). Comparing the two RAMs by Woller et al. showed that the full logistic RAM reported a slightly higher AUC (0.86) compared to the 4-Element RAM (0.84) (47). The study that assessed the Multivariable RAM described by Rothberg et al. (Multivariable RAM) in a validation cohort reported an AUC of 0.75 (47). The other two RAMs developed empirically by Samama et al. and McCaffrey et al. were internally validated using clinical cases (33, 40, 44). Samama et al. reported a 70% agreement between the levels of risk and judgments by clinicians in a validation effort (44). McCaffrey et al.

found that the mean total risk score in the VTE group was significantly higher than in the non-VTE group (40).

Only Stuck et al. reported on external validation efforts of the RAMs (4). The authors of the systematic review reported the results of the validation studies conducted for the RAMs by Caprini et al. (Caprini RAM), Nendaz et al. (Geneva RAM), Spyropoulos et al. (IMPROVE RAM), Kucher et al. and Barbar et al. (Padua RAM), all of which were multicenter except for the Caprini RAM (34, 39, 41, 42, 45, 47, 49, 50). The Caprini RAM was validated in three studies. The first describes the validation of the Caprini RAM in a population including cancer patients and reported that the incidence rate of VTE in low-risk patients was 0% compared to 4.2% in high-risk patients (34). The second study compared the Caprini RAM to the RAMs by Kucher et al. and Barbar et al. (Padua RAM) and found that the Caprini RAM assigned VTE patients into high or highest risk groups compared to the other two RAMs (50). The third study compared the cumulative risk of inpatients with VTE versus those without VTE using the Caprini and Padua RAMs. The authors reported that the high-highest risk group compared to the low-moderate risk group had similar ORs using both RAMs with an OR of 3.01 for the Caprini RAM and 2.9 for the Padua RAM. However, 82.3% of VTE patients were found to be in the high-highest risk group according to the Caprini RAM while 30.1% of VTE patients were found to be in the high-risk group using the Padua RAM. A prospective multicenter study compared the RAM described by Nendaz et al. (Geneva RAM) to the RAM by Barbar et

al. (Padua RAM) in around 1500 patients with VTE and reported a favorable prediction of VTE and VTE-related mortality using the Geneva RAM (41). The study also found that the Geneva RAM more accurately identified low-risk patients who do not require thromboprophylaxis with a negative likelihood ratio of 0.28 compared to 0.51 for the RAM by Barbar et al. (Padua RAM). The internal validation of the RAM by Spyropoulos et al. (IMPROVE RAM) reported that during hospitalization, the observed VTE rate for an IMPROVE-RAM score of 2 or 3 points (1.5 %) and 4 points (5.7 %) correlated with predicted VTE risk with an AUC of 0.69 (45). The IMPROVE RAM was then externally validated in two studies. The first study reported an AUC of 0.77 based on high, moderate and low risk groups (39). The second study found good discrimination of low- and at-risk medical patients with an AUC of 0.70 despite using different cut-offs for risk classification, with more than two thirds in the low-risk group not requiring prophylaxis (42). The RAM by Kucher et al. was compared to the RAMs by Woller et al. (4-Element and full logistic RAMs) in one study and was found to have the lowest AUC (0.76) among the three RAMs. In the internal validation cohort, the RAM by Barbar et al. (Padua RAM) identified a 32-fold increased risk of VTE in the group of patients not on prophylaxis with a high score compared to a low score. It was then externally validated in four studies, three of which were described previously, including the study that compared the RAM by Barbar et al. (Padua RAM) to the RAMs by Caprini et al. (Caprini RAM) and Kucher et al., the study that compared Padua to the Caprini RAM alone and the third that compared Padua to the Geneva RAM. A fourth study assessed the Padua RAM alone and

found a correlation between the risk groups and in-hospital mortality but not with the incidence of VTE (52). The authors suggested that the Padua RAM is better used as a general co-morbidity and disease severity index score than a VTE RAM (52).

Impact Analysis of Risk Assessment Models

Stuck et al. identified impact studies (4). The authors found that three RAMs described in the systematic reviews by Barbar et al. (Padua RAM), Nendaz et al. (Geneva RAM) and Kucher et al., have been assessed in terms of thromboprophylaxis rates or clinical outcomes. The impact of the RAM by Barbar et al. (Padua RAM) was assessed in a single center study and was found to improve rates of adequate prophylaxis (36). The RAM described in the systematic reviews by Nendaz et al. (Geneva RAM) was included in an e-Alert system, as part of a multicentre trial, and showed that its use increased appropriate prophylaxis rates (41). Two single center studies tested the impact of the RAM described by Kucher et al. One was a randomised trial that included the RAM in a computer-alert program and showed an increase in the use of prophylaxis and a reduction in VTE rates among at-risk patients (53). The second study confirmed that implementing a computer alert program using the RAM may increase prophylaxis rates (54). No impact studies were conducted to assess the economic impact of the RAMs.

Discussion

Summary of findings

We conducted an overview of systematic reviews to identify RAMs for VTE and bleeding in hospitalized medical patients. We identified 15 unique RAMs for VTE, seven of which were derived from individual participant data and eight that were developed empirically using consensus approaches, risk factors identified from a literature review, and clinical expertise. The RAMs described in the systematic reviews by Caprini et al. (Caprini RAM), Nendaz et al. (Geneva RAM), Spyropoulos et al. (IMPROVE RAM), Kucher et al. and Barbar et al. (Padua RAM) have been externally validated. The RAMs described by Barbar et al. (Padua RAM), Nendaz et al. (Geneva RAM) and Kucher et al. have been evaluated in terms of thromboprophylaxis rates or clinical outcomes and have been reported to increase appropriate prophylaxis rates. However, their economic impact has not been assessed.

Findings in relation to the literature

Following the publication of the most recent systematic review by Stuck et al. in 2017 (4), additional validation and impact studies were conducted. One study used the Kucher RAM along with electronic alerts and performance audits and reported increased rates of thromboprophylaxis in high risk patients and decreased 90-day VTE rates without an observed increase in adverse events (55, 56). Also, although our overview of systematic reviews did not identify any impact assessment of the Caprini RAM, we did identify a single center study that used the Caprini RAM as part of a multifaceted quality

improvement initiative (57). The study reported increased VTE prophylaxis rates and a reduction in hospital acquired VTE rates with the use of the Caprini RAM (57). Another prospective comparative study that was not included in the systematic reviews was conducted to assess the performance of the Geneva, Padua and IMPROVE RAMs on thromboprophylaxis rates in acutely ill hospitalized medical patients (58). The study reported comparable discrimination abilities with a 90-day AUC of 0.71 for the Geneva RAM and an AUC of 0.70 for both the Padua and IMPROVE RAMs in patients not on thromboprophylaxis (58). The authors of the study highlighted that the IMPROVE RAM classified more patients as low risk (two-thirds of patients) compared to the Geneva RAM (one-third of patients), but with possibly lower sensitivity and greater VTE risks (58). Also, a secondary analysis of a cohort of acutely ill hospitalized medical patients participating in a cluster-randomized control trial: The Prevention of Venous Thromboembolism Disease in Emergency Departments (PREVENU) study was not included in the systematic reviews (59). This study aimed to assess the Caprini, IMPROVE and Padua RAMs and compared their performance to advanced age as a stand-alone predictor (59). The study reported poor discriminative ability of the RAMs to identify non-critically ill inpatients at risk of VTE and found that the RAMs did not perform better in comparison to risk assessment using advanced age as a sole predictor (59). Our search did not capture a systematic review reporting on bleeding RAMs in hospitalized medical patients. However, a primary study by Decousus et al. in 2011 reported on the development of the IMPROVE bleeding RAM for in-hospital bleeding risk in acutely ill

medical patients (31). Two studies externally validated the IMPROVE RAM and found similar results to the derivation effort where hospitalized medical patients with a score greater than seven were shown to have over a two-fold increased risk of any bleed or major bleed compared to those with a lower bleeding risk scores (60, 61).

Strengths

Our study has several strengths, including the systematic and rigorous methods, a robust search strategy, the use of broad inclusion criteria, and our duplicate and independent screening and data abstraction process. Another strength of our study is the applicability of our findings. The RAMs identified and the description of their clinical utility informed guideline developers. The RAMs can also aid health care practitioners and health care systems in selecting RAMs to optimize shared decision making and provide appropriate prophylactic management.

Limitations and Challenges

The limitations of this study result from the included studies themselves. Huang et al. applied language restrictions during the initial search (33) and Stuck et al. applied language restrictions during the full text evaluation (4). Stuck et al. conducted searches in only one database (4). These limitations may have led to missing relevant studies. Some of the studies that were missed in the overview of reviews include a study by Zakai et al. in 2014 in which the authors empirically derived the Medical Inpatients and

Thrombosis (MITH) RAM to assess risk of VTE in medical patients on admission (62). Another study that the overview of reviews did not capture was the IMPROVEDD RAM, where the variable D-dimer was added to the IMPROVE RAM and showed an enhanced VTE risk discrimination in hospitalized medical patients compared with the IMPROVE RAM (63). Also, we did not identify the external validation study by Greene et al. in 2016 was not captured. This study aimed to validate the Kucher, Padua, IMPROVE and Intermountain RAMs (64). The authors reported that all RAMs showed good calibration but uniformly poor discrimination (64).

Implications for practice

The RAMs identified in our study can be used to estimate baseline risks of future health outcomes in people with a given disease or health condition (1) and to aid health care practitioners in identifying an individual patient's risk of VTE based on their individual characteristics. Also, many of these RAMs can be readily embedded in clinical decision aids to individualize the population-based recommendations. However, numerous shortcomings have limited the interpretation and clinical utility of the developed RAMs. First, the inability to more accurately identify medically ill patients at low or high risk of VTE may lead to over-use or underuse of prophylaxis and increased adverse events such as bleeding or thrombosis (25). Second, the complexity of some of the current RAMs (due to the large number of risk factors, such as 39 variables in Caprini and 86 in the Full Logistic RAM) limit their use to computer-based calculations (37, 47). Third, the

variability in the derivation and validation methods of the RAMs limit their comparability. Fourth, in the two systematic reviews some RAMs were not found to be externally validated, limiting their use in clinical practice (43, 45). Also other RAMs have been validated in very specific medical subpopulations such as those with sepsis or cancer as noted in the Padua and Caprini RAMs, thus limiting the generalizability of their results to the general medical population (34, 52). Fifth, there is a limited number of prospective comparative studies that assess the impact of applying different RAMs in clinical practice on outcomes.

Implications for future research

In this study we provide the original and the update of the systematic reviews evaluating VTE and bleeding RAMs used in hospitalized medical patients that informed the ASH guidelines. Findings from the original search directed us to conduct several follow-up studies. First, our work led us to conduct a systematic review of prognostic studies to identify all potential risk factors for VTE and bleeding in hospitalized medical patients (16). Second, we assessed the certainty of the evidence of the identified risk factors using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (16). Third, we aimed to develop RAMs for VTE and bleeding that are accurate and usable in clinical practice (19). This was done by using the results of the systematic review and the clinical and methodological input of an expert panel (16, 19). The expert panel made judgements on whether to include, potentially include or

exclude the identified risk factors from the final RAMs by considering GRADE evidence to decision framework criteria using the Delphi method (19). Fourth, we standardized the definitions of the identified included and potentially included risk factors based on our systematic review to decrease variability in methods of measurement across settings and provide more clarity to health care professionals when evaluating patients' risks of VTE and bleeding (19).

Conclusion

We conducted an overview of systematic reviews of VTE RAMs in hospitalized medical patients to inform the 2018 ASH guidelines on VTE prophylaxis (5). Our findings can assist experts in selecting a RAM to integrate in their health care systems, although further effort should be made to enhance these existing RAMs. This will allow standardizing approach to estimating patients' risks of VTE and individualize population-based guideline recommendations for appropriate prevention strategies.

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Authorship contributions

Conception and design: AJD, EAA, HJS

Data acquisition: AJD, ABR, RZM, RC, IEI, SGK, AA, TL, RW, EAA, HJS

Data analysis: AJD, ABR, HJS

Interpretation of results: AJD, ABR, FAS, RZM, RC, IEI, KAB, AEB, MC, FD, SRK, SMR, NZ, AA, SGK, TL, WW, RW, AI, EAA, HJS

Manuscript drafting: AJD, ABR, HJS

Critically revision of the manuscript and approval of the final version: AJD, ABR, FAS, RZM, RC, IEI, KAB, AEB, MC, FD, SRK, SMR, NZ, AA, SGK, TL, WW, RW, AI, EAA, HJS

Disclosure of Conflicts of Interest

All authors were members of the 2018 ASH guideline panel, members of the overview of systematic review team, or both. Authors AJD, IEI, AI, EAA and HJS reported that they are members of the GRADE working group. AJD, FAS, MC, NAZ, AA, SGK, AI, EAA and HJS were authors on a manuscript that conceptualized and tested a novel approach to selecting prognostic factors for the development or update of a RAM that has been

accepted in the journal Blood Advances. HJS reported being co-chair of the ASH 2018 guidelines for prophylaxis for hospitalized and non-hospitalized medical patients and grant funding from the Centers for Disease Control (CDC) for the project on identifying and selecting VTE and bleeding prognostic factors for the development or update of a RAM using a novel approach. MC reported being a former board director (2013-17) of the American Heart Association and chairing the ASH 2018 guidelines for management of VTE: prophylaxis for hospitalized and non-hospitalized medical patients. FAS, ABR, KAB, AEB, FD, SRK, SMR and NAZ reported participating as panel members for the ASH 2018 guidelines for management of VTE: prophylaxis for hospitalized and non-hospitalized medical patients for which they disclosed their conflicts that are provided in the supplement of the published guideline. NAZ also reported receiving honoraria in 2017 from ASH for the Highlights of ASH 2017 meeting (Dallas, New York, Latin America). NAZ and MC reported intellectual conflicts as leads in the group that derived and validated the MITH RAM for VTE risk assessment in hospitalized medical patients.

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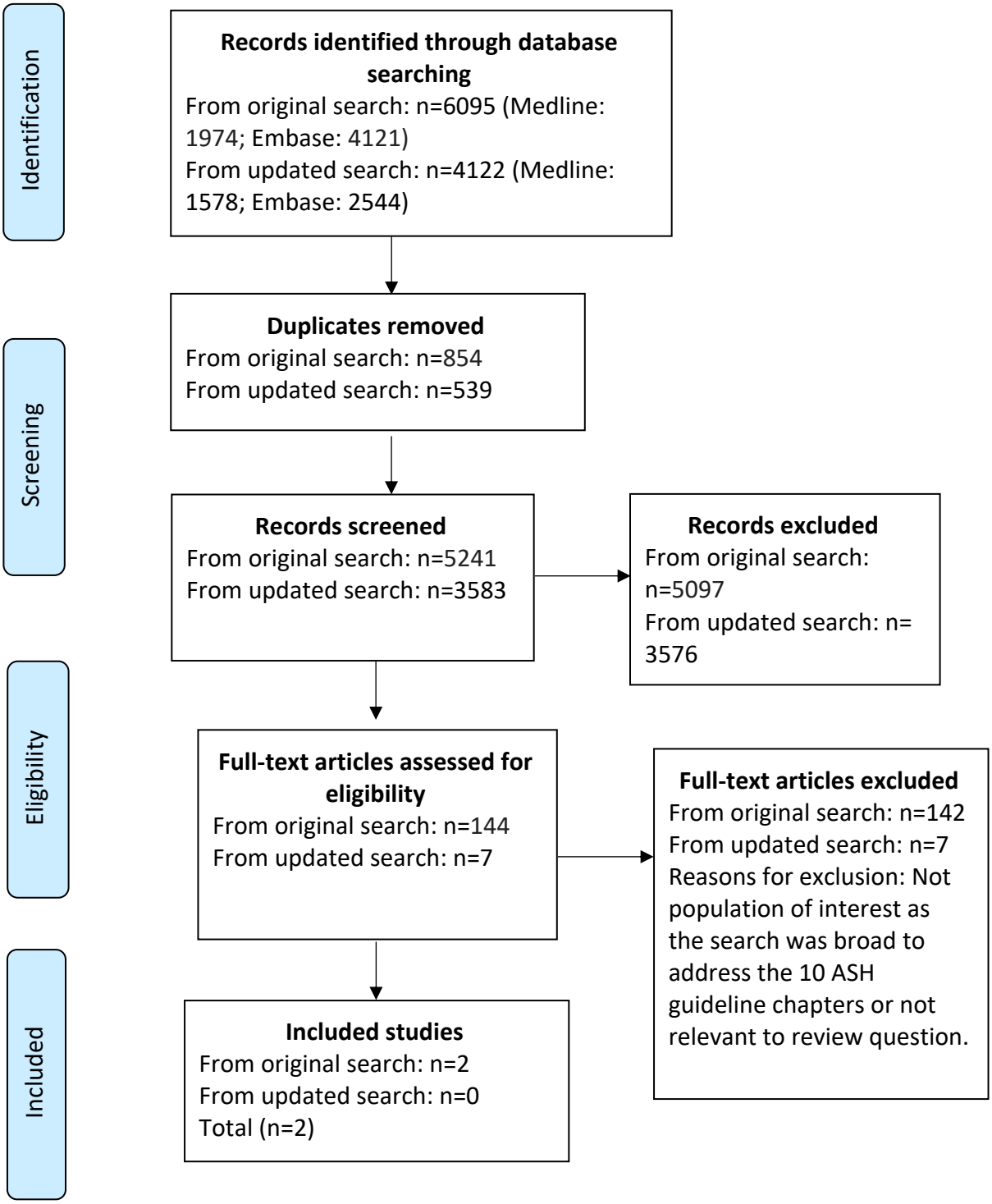
Figures

Figure 1. Prisma flow chart



Tables

Table 1. Systematic review characteristics

First Author, Year	Population	Outcome	Study Types	Quality assessment and grading	Statistical analysis	RAMs identified
Huang (2013) (33)	Hospitalized non-surgical patients (studies that focused primarily on children, pregnant women, psychiatric patients, surgical patients, or outpatients were excluded)	VTE (DVT/ PE); studies that only included patients with upper-extremity DVT were excluded	Prognostic model studies where the model was developed either by analyzing individual patient data or by expert consensus	Studies that developed RAMs based on individual patient data: modified Downs and Black checklist. Studies that developed RAMs based on expert consensus: modified Appraisal of Guidelines for Research and Evaluation (AGREE) instrument. The quality score was expressed as a percentage of the total assigned score divided by the total maximum score of applicable items.	Narrative synthesis. No meta-analysis was done due to heterogeneous studies. Reported odds ratios (ORs) or hazard ratios (HRs) of risk factors included in category-I RAMs. C-statistics reported (model discrimination on derivation and/or validation datasets).	<u>RAMs based on individual patient data:</u> Woller 2011 (Intermountain/4 element) Spyropoulos 2011 (IMPROVE) Rothberg 2011 (Multivariable model) Alikhan 2004 (MEDENOX) Weil-Engerer 2004 Yale 2005 <u>RAMs based on expert consensus:</u> Rocha 2007 McCaffrey 2007 Samama 2006 Cohen 2005 Caprini 2001 (Caprini)
Stuck (2017) (4)	Acutely ill medical patients (studies in non-medical, pediatric, pregnant,	VTE (DVT/ PE)	Prognostic model studies developed based on individual	Not conducted	Narrative synthesis. No meta-analysis was done.	<u>RAMs developed by derivation by identifying factors with predictive power:</u> 4-Element RAM

	or psychiatric patients were excluded)		patient data or consensus			IMPROVE-RAM (multi-center external validation) Multivariable model Full logistic model <u>RAMs generated empirically based on consensus approaches, published data, and clinical expertise:</u> Kucher RAM (multicenter external validation) Geneva RAM (multicenter external validation) Padua RAM (multi-center external validation) Caprini RAM

Table 2. Characteristics of the risk assessment models

Name of Risk Assessment Model	Number of risk factors	Risk Factors	Weighing points of risk factors	Defined cut-offs for risk groups
RAMs developed based on individual patient data				
MEDENOX RAM (35)	5	• Age, prior VTE, active cancer, acute infectious disease, chronic respiratory disease (primary diagnosis of COPD)	Not described	Not described
Weill Engerer RAM (46)	7	• Age, prior VTE, chronic edema of lower limbs, chronic heart failure, current lower limb paralysis, bed rest/immobilized, congestive heart failure	Not described	Not described
Yale RAM (48)	8	• Age, oral contraceptive/HRT, varicose veins, type II diabetes mellitus, nursing home, chemotherapy, corticosteroids, angina	Not described	Not described
IMPROVE RAM (45)	7	• Previous VTE • Known thrombophilia, Current lower-limb paralysis, Current cancer • Immobilized ≥7 days, ICU/CCU stay, Age >60 years	3 2 points each 1 point each	• According to Rosenberg et al. (42): 0–2 low risk, ≥3 high risk • According to Mahan et al. (39): 0–1 low risk, 2–3 intermediate risk, ≥4 high risk
Multivariable RAM (43)	13	• Age, length of stay, gender, primary diagnosis, cancer, inflammatory bowel disease, obesity, central venous catheter, inherited thrombophilia, steroid use, mechanical ventilation, active chemotherapy, and urinary catheters.	None	No cut-off available
4-Element RAM (47)	4	• Previous VTE, an order for bed rest, peripherally inserted central venous catheterization line, cancer diagnosis	1 point each	0 low risk ≥1 high risk

Full logistic RAM (47)	86	• Risk factors were not provided by systematic review; see reference for all risk factors	None	No cut-off available
RAMs developed based on consensus approaches, data from the literature and clinical expertise				
Caprini RAM (37)	39	• Stroke; Multiple trauma; Elective major lower extremity arthroplasty; Hip, pelvis or leg fracture; Acute spinal cord injury (paralysis) • Age (≥75 years); History of VTE; Positive Factor V Leiden; Positive prothrombin G20210A; Elevated serum homocysteine; Positive Lupus anticoagulant; Other congenital or acquired thrombophilia; Heparin-induced thrombocytopenia (HIT); Family history of VTE; Elevated anticardiolipin antibodies • Age (61–74 years); Central venous access; Arthroscopic surgery; Major surgery; Malignancy; Laparoscopic procedure ≥45 min; Patient confined to bed; Immobilizing plaster cast • Age (41–60 years); Acute myocardial infarction; Heart failure; Varicose veins; Obesity (BMI≥25); Inflammatory bowel disease; Sepsis; COPD or abnormal pulmonary function; Severe lung disease; Oral contraceptives or HRT; Pregnancy or postpartum; History of unexpected stillborn infant, recurrent spontaneous abortion (≥3), premature birth with toxemia or growth-restricted infant; Medical patient currently at bed rest; Minor • surgery planned; History of prior major surgery; Swollen legs	5 points each 3 points each 2 points each 1 point each	• According to Zhou HX et al. (50) and Zhou H et al. (49): 0–1 low risk; 2 intermediate risk; 3–4 high risk; >5 highest risk • According to Abdel-Razeq et al. (34): ≥2 Low risk; 3–4 moderate risk high; ≥5 high risk
Cohen RAM (38)	Not described	Not described	Not described	Not described
Samama RAM (44)	Not described	Not described	Not described	Not described
Rocha RAM (51)	Not described	Not described	Not described	Not described

McCaffrey RAM (40)	Not described	Not described	Not described	Not described
Kucher RAM (53)	8	• Cancer, Prior VTE, Hypercoagulability • Major surgery • Bed rest, Age >70 years, Obesity (BMI >30), Hormone replacement therapy/oral contraceptive pill	3 points each 2 points 1 point each	• According to Kucher et al. (53): 1–3 low risk; ≥4 points high risk • According to Woller et al. (47): 1–2 low risk, ≥3 high risk
Padua RAM (36)	11	• Active cancer, Previous VTE (with exclusion of superficial vein thrombosis), Reduced mobility, Known thrombophilia • Recent (≥1 month) trauma and/or surgery • Elderly age (≥70 years), Heart and/or respiratory failure, Acute myocardial infarction or ischaemic stroke, Acute infection and/or rheumatologic disorder, Obesity (BMI≥30), Ongoing hormonal treatment	3 points each 2 points 1 point each	<4 low risk ≥4 high risk
Geneva RAM (41)	19	• Cardiac failure, Respiratory failure, Recent stroke (<3 months), Recent myocardial infarction (<4 weeks), Acute infectious disease (including sepsis), Acute rheumatic disease, Active cancer, Myeloproliferative syndrome, Nephrotic syndrome, Prior VTE, Known hypercoagulable state • Immobilization (complete bed rest or inability to walk for >30 minutes/day) for >3 days, Recent travel >6 hours, Age >60 years, BMI >30, Chronic venous insufficiency, Pregnancy, Hormonal therapy, Dehydration (assessed subjectively by the treating physician)	2 points each 1 point each	1–2 low risk ≥ 3 high risk

Table 3. Characteristics of the studies describing the risk assessment models developed using individual patient data

RAM	First Author, Year (quality score by authors of SR)	Reference systematic review	Study design and study type (sample size)	Setting	Data source	Population (sample size)	Outcomes and methods of diagnosis	Follow-up time
MEDENOX RAM	Alikhan et al. 2004 (82%) (35)	Huang et al.	Double masked RCT- Derivation (1,102 enrolled, 866 without missing data)	Countries: 9 Sites: 60 Time: 1996-1998	Medical Records (MEDENOX study)	Age >75 years: 51.7; Male: 49.7%; Cancer: 13.6%; Major surgery within 3 months: 0%; % of VTE: 12%; % of PE: 4/102 (4%); In hospital VTE Prophylaxis: 288 (placebo; 287 enoxaparin 20 mg; 291 enoxaparin 40 mg)	DVT including below the knee DVT but not upper extremity DVT (diagnosis based on venography of the legs or ultrasonography); PE (diagnosis confirmed by lung scanning, pulmonary angiography, helical CT; or at autopsy); Anticoagulant/ thrombolytic medication use was considered in model	14 days since admission
Weill Engerer RAM	Weill-Engerer et al. 2004 (85%) (46)	Huang et al.	Prospective case control-Derivation (310:310)	Countries: 1 (France) Sites: 10 (university hospitals with long, intermediate, and short-term	Medical Records	Geriatric and high-risk patients. Mean age: 85.7 ± 7 years; Male: 23.5%; Cancer: 9%; Major surgery within 1 months: 4%; Upper limb DVT: ND; Unknown	Clinically confirmed DVT including below the knee DVT but not upper extremity DVT (diagnosis based on ray-scale and Doppler sonography or venography); Anticoagulant/	In hospital

				care facilities) Time: 16 months		site VTE: ND; In-hospital VTE Prophylaxis: ND	thrombolytic medication use was considered in model	
Yale RAM	Yale et al. 2005 (55%) (48)	Huang et al.	Case control-Derivation (190:190)	Countries: 1 (USA) Sites: multiple Time: 1995-2002	Electronic Medical Records	Medical patients discharged and re-hospitalized. Median age: ND; Male: ND; Cancer: ND; Major surgery within 3 months: 0%; Upper-limb DVT: ND; Unknown site VTE: ND; In-hospital VTE Prophylaxis: ND	DVT, location not described (not specified on diagnosis and definition); Anticoagulant/ thrombolytic medication use was considered in model	60 days
IMPROVE RAM	Spyropoulos et al. 2011 (86%) (45)	Huang et al. and Stuck et al.	Prospective cohort-Derivation (N=15156)	Countries: 12 Sites: 52 Time: 2002-2006	Medical records review (IMPROVE Study)	Median age: 68 years; Male: 50%; Cancer: 22%; Major surgery within 3 months: 0%; % of VTE: 184 (1.2%); % of PE: ND; In hospital VTE Prophylaxis: 44%	Symptomatic VTE excluding Upper extremity DVT, No description if below the knee DVT was included (diagnosis based on diagnosis test result and treatment information); Anticoagulant/ thrombolytic medication use was considered in model	92 days
	Mahan et al. 2014 (ND) (39)	Stuck et al.	Case control-External validation (ND)	Countries: ND Sites: 3 Time: ND	Not described	Not described	Not described	Not described

	Rosenberg et al. 2014 (ND) (42)	Stuck et al.	Retrospective study- External validation (ND)	Countries: ND Sites: 2 Time: ND	Not described	Not described	Not described	Not described
Multivariable RAM	Rothberg et al. 2011 (88%) (43)	Huang et al. and Stuck et al.	Retrospective cohort- Derivation and internal validation ((242,738: 194,198 [80 %] derivation set; 48,540 [20 %] validation set))	Country: 1 (USA) Sites: 374 Time: 2004–2005	Premier's Perspective database (measuring quality and healthcare utilization)	Age ≥ 50 years: 87; Male: 41%; Cancer: 14%; Major surgery before admission: ND; % VTE: 1,052 (0.4%); % of PE: ND; In-hospital VTE Prophylaxis: 30%	Symptomatic VTE including below the knee DVT, upper extremity DVT was excluded. (2nd diagnosis based on ICD-9-CM and confirmed with diagnosis test result and treatment information); Anticoagulant/ thrombolytic medication use was considered in model	30 days
4-Element RAM	Woller et al. 2011 (68%) (47)	Huang et al. and Stuck et al.	Retrospective cohort- Derivation (143,975 + 46,856)	Country: 1 (USA) Sites: 22 Time: 2000–2007 derivation; 2008–2009 validation	Intermountain healthcare administrative and EMR system	Mean age: 63 years; Male: 44 %; Cancer: 44 %; Major surgery within 30 days: 1 %; % of VTE: 3.7%; % of PE: ND	Symptomatic VTE including below the knee and upper extremity DVT (diagnosis based on ICD-9-CM); No description whether anticoagulant/thrombolytic medication use was considered in model	90 days post admission
Full logistic RAM		Stuck et al.						

Table 4. Characteristics of the studies describing the risk assessment models developed using consensus approaches

RAM	First Author, Year (quality score by authors of SR)	Reference systematic review	Study type	Literature search and Methods used	Target population (sample size)	Outcome	Model
Caprini RAM	Caprini et al. 2001 (64%) (37)	Huang et al.	Development	Literature search ND; Consensus	VTE Prophylaxis among medical and surgical patients	Symptomatic VTE; Diagnosis: ND, Varied among studies	Checklist with risk stratification score
	Abdel- Razeq et al. 2010 (ND) (34)	Stuck et al.	External validation	Validation cohort used	Medically ill hospitalized cancer patients (n=606)	VTE (location, definition and diagnosis in systematic review)	Checklist with risk stratification score
	Zhou et al. 2012 (ND) (50)	Stuck et al.	External validation	Validation cohort used	Hospitalized Chinese patients	VTE (location, definition and diagnosis ND in systematic review)	Checklist with risk stratification score
	Zhou et al. 2014 (ND) (49)	Stuck et al.	External validation	Validation cohort used	Hospitalized Chinese patients	VTE (location, definition and diagnosis ND in systematic review)	Checklist with risk stratification score
Cohen RAM	Cohen et al. 2005 (71%) (38)	Huang et al.	Development	Literature search ND (2004 = latest literature included); Consensus per literature review result	VTE prophylaxis Among acutely ill Medical patients in hospital	Symptomatic VTE Diagnosis: ND, varied among studies	Flow chart; No validation performed

Samama RAM	Samama et al. 2006 (63%) (44)	Huang et al.	Development	Literature search through 2002 (assess efficacy and effectiveness in combination with structured, quantitative techniques for incorporating the judgment of expert clinicians to produce appropriateness assessments for clinical conditions); RAND/UCLA appropriateness method to develop the risk matrix	VTE prophylaxis Among medical and surgical patients (pregnancy excluded)	Symptomatic VTE Diagnosis: ND, varied among studies	Low/moderate/high/ very high grid Case validation
Rocha RAM	Rocha et al. 2007 (77%) (51)	Huang et al.	Development	Systematic review search through 8/2004: RCT/cohort/case–control studies with at least 10 subjects evaluating risk factors or efficacy of prophylactic methods (LDUH, LMWH, mechanical) for VTE; Classification of level of evidence per AHA/ACC/ESC guidelines for the management of patients	VTE Prophylaxis among acutely ill medical patients in hospital	Symptomatic VTE; Diagnosis: ND, varied Among studies	Flow chart; no validation performed

McCaffrey RAM	McCaffrey et al. 2007 (48%) (40)	Huang et al.	Development	Literature search: 2000–2005 (OVID, ELSEVIER, CINAHL, Web of science); local hospitals and hospitals within the HCA network were asked to share DVT risk-assessment tools (total 15); Consensus per literature review result	VTE Prophylaxis among all hospitalized patients	Symptomatic DVT; Diagnosis: ND	Checklist with scores Case validation (72 cases; 72 controls) ANOVA test used to compare the risk scores in 2 groups. t test used for each individual measure Inter-rater reliability measured (3 nurses; 144 charts at different times)
Kucher RAM	Woller et al. 2011 (ND) (47)	Stuck et al.	External validation	Validation cohort used	Medical patients (n= 143975 (DC); n=46846 (VC))	VTE (location, definition and diagnosis ND in systematic review)	Risk stratification score
	Zhou et al. 2012 (ND) (50)	Stuck et al.	External validation	Validation cohort used	Hospitalized Chinese patients	VTE (location, definition and diagnosis ND in systematic review)	Risk stratification score
	Kucher et al. 2005 (ND) (53)	Stuck et al.	Development and Impact study	A single center randomized trial where a computer-alert program was implemented to identify hospitalized patients at risk of VTE and assess impact on VTE and prophylaxis rates.	Hospitalized patients	VTE	Computer-alert program

	Baroletti et al. 2008 (ND) (54)	Stuck et al.	Impact study	A prospective cohort study where electronic alerts were implemented to identify hospitalized patients at high risk of VTE not receiving prophylaxis	Hospitalized patients	VTE	Electronic alerts
Padua RAM	Barbar et al. 2010 (ND) (36)	Stuck et al.	Development	Empirically generated based on consensus approaches, published data, and clinical expertise.	Hospitalized medical patients	VTE (location, definition and diagnosis ND in systematic review)	Risk stratification score
	Zhou et al. 2012 (ND) (50)	Stuck et al.	External validation	Validation cohort used	Hospitalized Chinese patients	VTE (location, definition and diagnosis ND in systematic review)	Risk stratification score
	Vardi et al. 2013 (ND) (52)	Stuck et al.	External validation	Validation cohort used	Patients with sepsis admitted to internal medicine department	VTE (location, definition and diagnosis ND in systematic review)	Risk stratification score
	Zhou et al. 2014 (ND) (49)	Stuck et al.	External validation	Validation cohort used	Hospitalized Chinese patients	VTE (location, definition and diagnosis ND in systematic review)	Risk stratification score
	Nendaz et al. 2014 (ND) (41)	Stuck et al.	External validation	Validation cohort used to test the Padua prediction score that was developed through integration of additional empirically gained risk factors to the Kucher model.	Acutely ill medical patients (characteristics ND) (n=1478)	VTE (location, definition and diagnosis ND in systematic review)	Risk stratification score

	Rossetto et al. 2013 (ND) (65)	Stuck et al.	Impact study	Physician compliance using Padua RAM in preventing VTE	Hospitalized medical patients	VTE	Risk stratification score
Geneva RAM	Chopard et al. 2006 (Not described in the systematic reviews) (66)	-	Development	Not described in the systematic reviews	Not described in the systematic reviews	Not described in the systematic reviews	Not described in the systematic reviews
	Nendaz et al. 2014 (ND) (41)	Stuck et al.	External validation	Validation cohort used to test the Geneva risk score that was developed based on VTE prevention trials identified (search and search date ND) and recommendations from the ACCP guidelines	Acutely ill medical patients (characteristics ND) (n=1478)	VTE (location, definition and diagnosis ND in systematic review)	Risk stratification score; validated
	Nendaz et al. 2010 (ND) (67)	Stuck et al.	Impact study	A multi-centre trial that implemented an e-Alert system with integration of the Geneva RAM	Acutely ill medical patients	VTE	Electronic alerts and integrated RAMs

Table 5. Findings from comparative studies of risk assessment models identified in the systematic reviews

Comparative studies (number of centers)	Number of patients in study	RAM	AUC	Proportion of low-risk patients of VTE (%)	Overall VTE incidence at 3 months (%)	VTE incidence in low-risk patients (%)	VTE incidence in high-risk patients (%)
Woller et al. 2011 (22 centers) (47)	Derivation cohort (DC): 143975 Validation cohort (VC): 46846	Full logistic RAM	DC: 0.893 VC: 0.861	Not assessed	DC: 3.7% VC: 4.5%	Not assessed	Not assessed
		4 Element RAM	DC: 0.874 VC:0.843				
		Kucher RAM	DC: 0.781 VC: 0.756				
Zhou HX et al. 2012 (50)	Not described	Caprini RAM	Not described	Caprini was found to classify more VTE patients into high or highest risk groups compared to the Kucher and Padua RAMs			
		Kucher RAM					
		Padua RAM					
Zhou H et al. 2014 (49)	Not described	Caprini RAM	Not described	17.7%	Not described	Not described	Not described
		Padua RAM		60.9%			
Nendaz et al. 2014 (8 centers) (41)	Validation cohort (VC): 1478	Geneva RAM	Negative likelihood ratio to identify low risk patients who do not require thromboprophylaxis: 0.28	35%	2.3%	0.6%	3.25
		Padua RAM	Negative likelihood ratio to identify low risk patients who do not require thromboprophylaxis: 0.51	52%	2.3%	1.1%	3.5%

Appendices

Supplemental Table 1. Search Strategies (Medline and Embase)

Medline

Search name: z - Prognostic SR_Medline2

OVERVIEW	
Interface:	Ovid
Database:	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Date of Search:	01 June 2017
Study Types:	Systematic reviews
Limits:	Publication date: 2005- June 2017 Update: June 2017- January 2020

Search Strategy: search terms (number of results)	
Prognosis filter- HIRU:	
1	prognosis.sh. (397000)
2	diagnosed.tw. (400740)
3	cohort:.mp. (419996)
4	predictor:.tw. (252945)
5	death.tw. (518182)
6	exp models, statistical/ (306458)
7	1 or 2 or 3 or 4 or 5 or 6 (1947248)
8	predict:.tw. (1085985)
9	validat:.mp. (356651)
10	develop.tw. (392257)
11	8 or 9 or 10 (1700708)
12	7 or 11 (3161420)
Venous thromboembolism block:	
13	exp Thromboembolism/ or exp Venous Thromboembolism/ (47106)
14	exp Pulmonary Embolism/ (33624)
15	exp Venous Thrombosis/ (47911)
16	Thrombophlebitis/ (21345)
17	(DVT or VTE or PE).mp. (39189)
18	((Pulmon$ or vein or venous or lung) adj (Emboli$ or thromb$)).mp. (91578)
19	(thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).mp. (323610)
20	(((deep or thromb* or stasis) adj2 (vein* or venous)) or (blood flow stasis or blood clot)).mp. (66788)

21 or/13-20 (364914)
Systematic review filter:
22 meta-analysis/ (62640)
23 meta-analysis as topic/ (14603)
24 (meta analy* or metanaly* or metaanaly*).ti,ab. (87979)
25 (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. (30069)
26 ((systematic* or evidence*) adj2 (review* or overview*)).ti,ab. (101913)
27 (search strategy or search criteria or systematic search or study selection or data extraction).ab. (32680)
28 (search* adj4 literature).ab. (36249)
29 (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. (116019)
30 ((pool* or combined) adj2 (data or trials or studies or results)).ab. (37750)
31 cochrane.jw. (12026)
32 or/22-31 (280243)
33 animals/ not humans/ (4171365)
34 exp Animals, Laboratory/ (760821)
35 exp Animal Experimentation/ (7815)
36 exp Models, Animal/ (455619)
37 exp Rodentia/ (2838894)
38 (rat or rats or mouse or mice).ti. (1180410)
39 or/33-38 (4919140)
40 32 not 39 (267527)
41 12 and 21 (70296)
42 40 and 41 (2553)
43 limit 42 to yr="2005 -Current" (1974)
Records Retrieved: 1974

Embase

Search name: z - Prognostic SR_Embase2

OVERVIEW	
Interface:	Ovid
Database:	Embase
Date of Search:	01 June 2017
Study Types:	Systematic reviews
Limits:	Publication date: 2005- June 2017
	Update: June 2017- January 2020
Search Strategy: search terms (number of results)	
Prognosis filter- HIRU:	
1 follow-up.mp. (1343268)	

2 prognos:.tw. (600610)
3 ep.fs. (949227)
4 1 or 2 or 3 (2666921)
5 validat:.mp. (503101)
6 index.tw. (714827)
7 model.tw. (1782605)
8 5 or 6 or 7 (2794860)
9 4 or 8 (5133098)

Venous thromboembolism block:

10 exp vein thrombosis/ (99801)
11 exp Venous Thromboembolism/ (109897)
12 exp 'lung embolism'/ (69215)
13 Thrombophlebitis/ (15894)
14 (PE or DVT or VTE).mp. (61367)
15 ((Pulmon$ or vein or venous or lung) adj (Emboli$ or thromb$)).mp. (164492)
16 (thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).mp. (521335)
17 (((deep or thromb* or stasis) adj2 (vein* or venous)) or (blood flow stasis or blood clot)).mp. (156426)
18 or/10-17 (590373)

Systematic review filter:

19 systematic review/ (103322)
20 meta-analysis/ (105521)
21 (meta analy* or metanaly* or metaanaly*).ti,ab. (116198)
22 (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. (35044)
23 ((systematic* or evidence*) adj2 (review* or overview*)).ti,ab. (125994)
24 (search strategy or search criteria or systematic search or study selection or data extraction).ab. (38071)
25 (search* adj4 literature).ab. (45664)
26 (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. (143490)
27 ((pool* or combined) adj2 (data or trials or studies or results)).ab. (48665)
28 cochrane.jw. (12685)
29 or/19-28 (375803)
30 animals/ not humans/ (1150971)
31 nonhuman/ (4712149)
32 exp Animal Experiment/ (1813496)
33 exp Experimental Animal/ (498588)
34 animal model/ (859900)
35 exp Rodent/ (2975235)
36 (rat or rats or mouse or mice).ti. (1267418)
37 30 or 31 or 32 or 33 or 34 or 35 or 36 (6659021)

38	29 not 37 (339489)
39	9 and 18 (157148)
40	38 and 39 (5531)
41	limit 40 to yr="2005 -Current" (4474)
42	limit 41 to Embase (4121)
Records Retrieved: 4121	

Supplemental Table 2. Risk of bias assessments using ROBIS for systematic reviews of RAM studies

	Phase 2				Phase 3
First Author, Year	**Domain 1: Study eligibility criteria**	**Domain 2: Identification and selection of studies**	**Domain 3: Data collection and study appraisal**	**Domain 4: Synthesis and findings**	**Risk of Bias in review**
Huang (2013)	Low risk	High risk	Low risk	Low risk	Low risk
Stuck (2017)	Low risk	High risk	High risk	High risk	High risk

*****Despite the high risk of bias in Domain 2, we noted that Huang et al. had captured all studies within its search date, which was from inception through May 2011, despite limitations. Therefore, we judged that review overall to be at low risk of bias.

CHAPTER 3. PROGNOSTIC FACTORS FOR VTE AND BLEEDING IN HOSPITALIZED MEDICAL PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Prognostic factors for VTE and Bleeding in Hospitalized Medical Patients: a systematic review and meta-analysis

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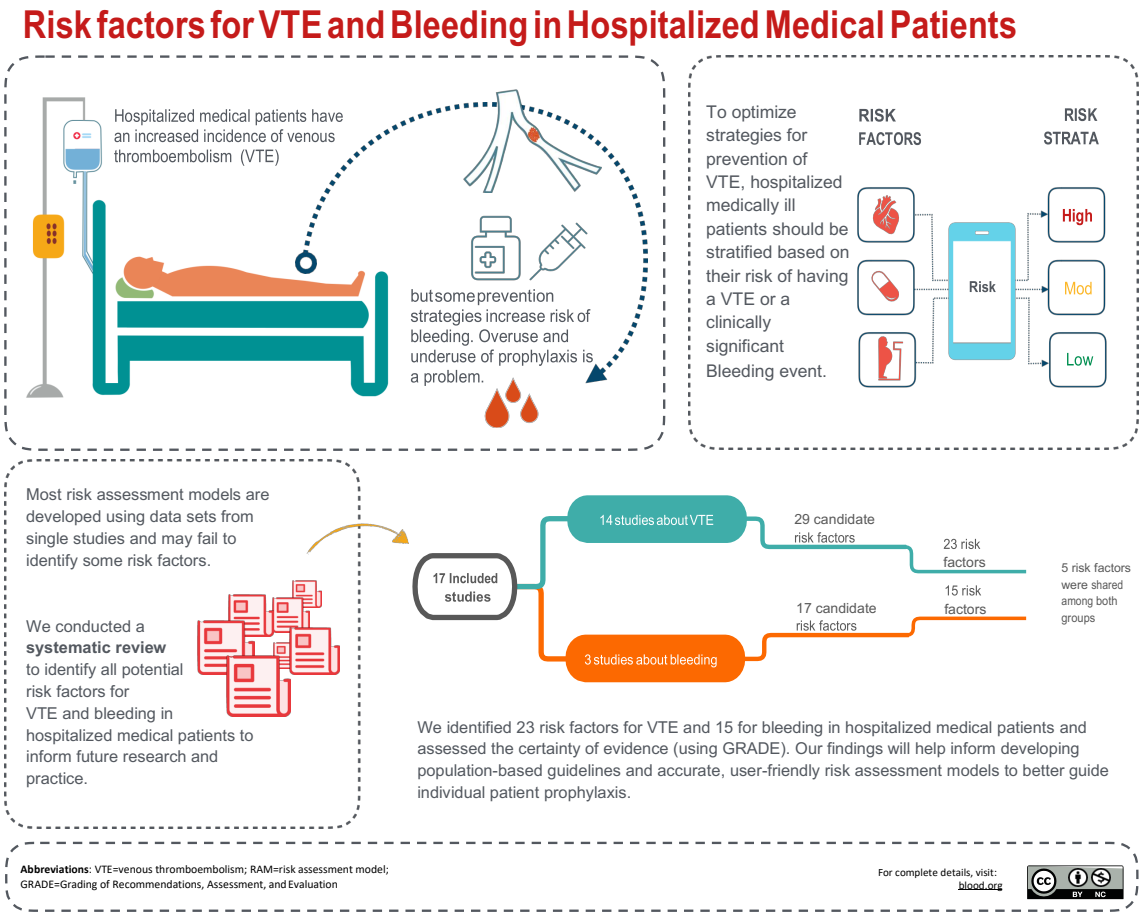
Key points

1. Using a systematic approach, we identified 23 prognostic factors for venous thromboembolism (VTE) and 15 for bleeding.
2. We identified several prognostic factors for VTE and bleeding that are not considered in most of the widely used risk assessment models.

Visual abstract



Abstract

There may be many predictors of venous thromboembolism (VTE) and bleeding in hospitalized medical patients, but until now, systematic reviews and assessments of the certainty of the evidence have not been published. We conducted a systematic review to identify prognostic factors for VTE and bleeding in hospitalized medical patients and searched Medline and EMBASE from inception through May 2018. We considered studies that identified potential prognostic factors for VTE and bleeding in hospitalized adult medical patients. Reviewers extracted data in duplicate and independently and assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Of 69,410 citations, we included 17 studies; 14 that reported on VTE and three that reported on bleeding. For VTE, moderate certainty evidence shows a probable association with older age; elevated CRP, D-dimer and fibrinogen levels; tachycardia; thrombocytosis; leukocytosis; fever; leg edema; lower Barthel Index score; immobility; paresis; previous history of VTE; thrombophilia; malignancy; critical illness; and infections. For bleeding, moderate certainty evidence shows a probable association with older age; sex, anemia, obesity, low hemoglobin, gastroduodenal ulcers, rehospitalization, critical illness, thrombocytopenia, blood dyscrasia, hepatic disease, renal failure, antithrombotic medication and central venous catheter (CVC). Elevated CRP, a lower Barthel Index, history of malignancy and tachycardia are not included in most VTE risk assessment

models (RAMs). This study informs risk prediction in the management of hospitalized medical patients for VTE and bleeding; it also informs guidelines for VTE prevention and future research.

Keywords: risk assessment model, prognosis, venous thromboembolism, bleeding, hospitalized medical patients, GRADE.

Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), has an annual incidence of approximately 1 per 1000 in adult populations (5, 22). VTE is a major burden in hospitalized medical patients. Medical patients can be classified as having acute, critical or chronic medical illness and their risk for both VTE and bleeding may depend on the severity of their medical illness. The incidence of VTE in hospitalized acutely ill medical patients detected by screening is up to 14.9% (68). Over 50-70% of symptomatic VTE and 70-80% of fatal PE occur in acute medically ill patients (45, 69-71).

The risk of hospital acquired VTE is reduced by using pharmacological and non-pharmacological interventions, but these interventions are not without potential patient harms. Risk Assessment Models (RAM) have been employed in hospitalized medically ill patients to stratify the different subsets of patients by their risk of having a VTE or clinically significant bleeding event (31). This stratification may then support optimized management for the prevention of either outcome (72). A RAM is a formal combination of multiple predictors from which risks of a specific endpoint can be calculated for individuals. The value of using RAMs include generation of specific baseline risks to inform recommendations for a 'strata of patients'; and calculation of a predicted risk of an outcome for an individual patient (e.g., VTE or bleeding) based on patient's characteristics (i.e., the prognostic factors). Implementation of RAMs in the field of VTE

prevention can be accomplished by embedding them in clinical encounters or decision aids to individualize the use of guideline recommendations. However, this is variably done in current practice (68).

Most RAMs are developed using data registries that are not based on a systematic review of all potential prognostic factors (17). However, guiding principles for developing RAMs describe the importance of identifying prognostic factors through systematic reviews (17). We identified only one systematic review conducted 11 years ago that evaluated VTE as an outcome in medical patients, but the effect sizes of the prognostic factors were not meta-analyzed, and bleeding risk, critical for balancing benefits and harms in these patients, was not included as an outcome (51).

Therefore, our aim was to conduct a systematic review of prognostic factors for VTE and bleeding in hospitalized medical patients that may inform management, future guideline recommendations and the development of RAMs in hospitalized medical patients.

Methods

We conducted a systematic review using Cochrane methodology to identify studies that reported on prognostic factors for VTE and bleeding in hospitalized medical patients (73). We developed a protocol for this review, which was reviewed and revised by the

co-authors, but we did not register it because of confidentiality clauses in the research contract.

Data sources and searches

We searched Medline and EMBASE from inception through May 2018 with the assistance of an information scientist. Supplemental Table 1 provides detailed descriptions of the search strategy. The search included both MesH terms and text-word terms. It combined VTE-related terms with primary prevention terms and two search blocks defining prognosis and prediction guide filters. We used no language restrictions or time limits.

Study selection

Four teams of two reviewers participated in training and calibration exercises prior to starting the screening processes. Teams of two reviewers screened independently and in duplicate the titles and abstracts of all the retrieved citations. They then retrieved the full texts of all citations judged as potentially eligible by at least one of the reviewers on each team. The reviewers screened the full texts independently and in duplicate and compared results. A third senior reviewer resolved disagreements when necessary. Reviewers used a standardized screening form and conducted calibration exercises before the screening process. The eligibility criteria for study selection entailed the following characteristics:

Population: We included studies that evaluated adult medical patients who were acutely, critically or chronically ill. We also included studies in which the population included non-medical patients or medical patients with a recent history of surgery or trauma if the final regression model adjusted for these factors. We included studies if less than 10% of the population were on thromboprophylaxis or if the statistical analysis adjusted for the use of thromboprophylaxis. Thromboprophylaxis included the use of anticoagulation therapy (i.e. warfarin, low molecular weight heparin and unfractionated heparin), antiplatelet therapy (i.e. aspirin), or mechanical prophylaxis (i.e. elastic stockings or intermittent pneumatic compression).

We excluded studies if the population did not reflect the general population of interest such as studies that only looked at selected types of cancer patients (74, 75). We defined acutely ill medical patients as patients hospitalized for a medical illness including heart failure, respiratory insufficiency, stroke, and infectious or inflammatory diseases requiring urgent care (5). Critically ill patients were those suffering from an immediately life-threatening condition admitted to an intensive or critical care unit (5). Chronically ill medical patients included those with acute exacerbations of chronic medical conditions who required hospitalization (5).

Exposure: We investigated all prognostic factors reported in individual studies.

Comparisons: We investigated the absence or different levels of the prognostic factor.

Outcomes: Studies had to report on the outcomes VTE or bleeding. VTE was defined as any symptomatic or asymptomatic DVT or PE within 90 days post discharge. Bleeding included major or non-major but clinically significant bleeding within 90 days post discharge (31).

Setting: Studies that included patients who were admitted to a non-surgical inpatient ward.

Type of studies: We included prognostic factor and risk assessment model studies that are based on typologies of prognosis proposed by Iorio and colleagues (76), founded on the PROGnosis RESearch Strategy (PROGRESS) Group framework (77).

Data extraction

Two reviewers abstracted data independently and in duplicate from all eligible studies using standardized forms. Reviewers compared and discussed results and consulted a third reviewer in case of any disagreement. We conducted calibration exercises and piloting of all forms prior to the start of the data abstraction process. All eligible studies were published in English.

For all identified studies, RAMs and prognostic factor studies, the reviewers abstracted data on the following characteristics:

- Study context (e.g. country, year of publication)

- Type of prediction model study (development, validation, impact)
- Study design (e.g. cohort or case control; duration of follow up)
- Population and their demographics (e.g. sample size, age, number of centers, administration of prophylaxis and what type)
- Outcomes (VTE, bleeding)
- Prognostic factors, definitions, and measurement methods (including thresholds used for continuous predictors)
- Measures of association (e.g. odds ratio (OR), risk ratio (RR), hazard ratio (HR))

Quality assessment

Risk of Bias Assessment

We assessed the risk of bias in the included studies using the Prediction study Risk Of Bias Assessment Tool (PROBAST) for RAM studies (78) and the Quality in Prognosis Studies tool (QUIPS) for prognostic factor studies (79-81).

Synthesis of Findings and Certainty of Evidence Assessment

We presented the results of the included studies including the individual prognostic factors in both tabular and narrative formats. We also described the identified prognostic factor studies and the measure of association with the outcomes of interest. We performed an assessment of the certainty of evidence for each of the prognostic

factors per outcome based on the GRADE approach (18). The approach considers the following domains: risk of bias, indirectness, inconsistency, imprecision, and publication bias. We developed evidence profiles and rated the overall certainty of evidence as high, moderate, low or very low depending on the grading of the individual domains (18). We narratively described the strength of the association using the terms “there is”, “there probably is” or “there may be” depending on whether the quality of the evidence was “high”, “moderate” or “low/very low” respectively.

Data synthesis and analysis

We standardized the units of measurement for each prognostic factor, unifying the direction of the predictors, adjusting the weights of the studies and calculating crude effect estimates when not provided (82). When possible, we meta-analyzed all prognostic factors associated with the outcomes VTE and bleeding that were reported by more than one study. We then presented the effect estimate as ORs and their corresponding 95% confidence intervals (CI). In studies that reported the measure of association as an HR or RR, we converted them to ORs using the baseline risk (incidence of those not on prophylaxis having VTE or bleeding out of the total sample) reported in the studies (83, 84). We meta-analyzed associations using the generic inverse variance-based method to produce an overall measure of association. We used the crude effect estimates when the adjusted estimates were not provided. We explored consistency of the associations between our meta-analyzed results and studies reporting the same

predictors that could not be pooled. All analyses used random-effect models applying the prognosis module in Review Manager version 5.3 (85).

Results

Figure 1 is a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart. Our search identified 69,410 citations of which we included 807 studies for full text assessment. Seventeen studies fulfilled the inclusion criteria for evaluating VTE or bleeding outcomes or both (7,8, 25-39).

Description of included studies

Table 1 describes the characteristics of the included studies reporting on the outcomes VTE and/ or bleeding. Eight studies were prognostic factor studies; four were prognostic model development studies and five were external validation studies. Five studies were retrospective case control studies (39, 42, 62, 86, 87), two of which were multicenter (39, 42); five were retrospective cohorts (43, 88-91), three of which were multicenter (43, 89, 90). Seven studies were prospective cohorts (31, 45, 92-96), four of which were multicenter (31, 45, 93, 96). The included studies were conducted in the United States (n = 9), China (n = 3), Canada (n = 2), United Kingdom (n = 1), Poland (n = 1) and Japan (n = 1). Out of the 14 included studies for VTE (defined as proximal DVT or PE), nine reported on symptomatic VTE only (7, 25-31, 34). The other five studies reported on both

symptomatic and asymptomatic VTE (35-39). The follow up time was up to three months in 12 out of 14 studies reporting on VTE. The other two studies, Zhou et al. (39, 42, 62, 86, 87) and Yi et al., (39, 42, 62, 86, 87) had a follow-up time of six months and one year respectively, but also reported the occurrence of VTE during hospitalization. In accordance with our protocol we used the incidence of VTE during hospitalization from those studies. The three studies that reported on bleeding (major or clinically relevant) had a follow-up time up to one month (31, 90, 91). Of the 14 studies reporting on VTE, 12 studies included patients who received thromboprophylaxis in 0.4% to 67% of the patients. Of those, two studies (87, 89, 90, 92, 93) included less than 10% of patients on thromboprophylaxis and 10 studies adjusted for prophylaxis in their statistical analysis (87, 89, 90, 92, 93). As for bleeding, all three studies included prophylaxis use in 9 to 70%, that was accounted for in their analysis (31, 90, 91).

Risk of bias assessment

Risk of bias was serious across all identified studies, each presenting risk of bias in at least one domain or item (Tables 2 and 3). Among the 17 included studies, 10 studies were retrospective, which may have introduced classification bias (39, 42, 43, 62, 86-91). Seven of the eight prognostic factor studies only included variables significant in bivariable analysis in their final regression model and did not present any data for nonsignificant predictors in their adjusted analysis (88, 90, 91, 93-96). Two of the eight prognostic factor studies (90, 91); and four of the nine prognostic model development or

validation studies did not have a clear description of appropriate outcome measurement (42, 62, 86, 87). We detected no evidence of publication bias through visual assessment of asymmetry of the funnel plot for each pooled predictor in those that included at least 10 studies (Tables 2 and 3). Supplemental Table 2 provides the detailed judgements for each of the risk of bias domain criteria.

Prognostic factors for VTE in hospitalized medical patients

The studies investigated 29 candidate prognostic factors for VTE from the 14 studies including 151,714 patients. Table 2 provides the evidence profile for VTE related prognostic factors. Supplemental Figure 1 provides the forest plots of the meta-analyses of each of the prognostic factors.

Demographic factors

We found moderate certainty evidence that there is probably an association between risk of any VTE and age ≥60 (OR of 1.34; 95%CI: 1.17-1.55) (39, 42, 43, 45, 62, 87, 89, 92-94, 96); and that there is probably little to no association between risk of any VTE and sex (males compared to females) (OR 1.03; 95%CI: 0.80-1.33) (43, 62, 92-94).

Functional factors

There was moderate certainty evidence for a probable association between risk of any VTE and lower Barthel Index scores (BI ≤9) (OR 8.30; 95% CI: 2.70-25.52) (94); immobility

defined as confinement to bed for >72h or >7days or bedridden or non-ambulatory (OR 3.17; 95%CI: 2.18-4.62) (39, 42, 45, 86, 87, 89, 94, 96); and paresis (OR 2.97; 95%CI: 1.20-7.36) (39, 42, 45, 94).

Medical illness and patient history factors

We identified moderate certainty evidence for an association between risk of any VTE and history of VTE (OR 6.08; 95%CI: 3.71-9.97) (39, 42, 45, 62, 87-89, 93); thrombophilia defined as familial or acquired disorder of the hemostatic system (OR 5.88; 95%CI: 2.80-12.35) (39, 42, 43, 45, 87); history of malignancy (OR 3.20; 95%CI: 2.14-4.79) (42); active malignancy defined as the presence of cancer on admission or within the past year (OR 2.65; 95%CI: 1.79-3.91) (39, 43, 45, 62, 86, 88, 89, 93, 94); critical illness defined as intensive care unit (ICU) or coronary care unit (CCU) stay, or need for resuscitation (OR 1.65; 95%CI: 1.39-1.95) (39, 42, 43, 45, 62, 87, 93); and infections including cellulitis, pneumonia and sepsis (OR 1.48; 95%CI: 1.16-1.89) (62, 86, 87, 89, 93).

We found low certainty evidence that there may be an association between risk of any VTE and history of heart failure (OR of 2.68; 95%CI: 1.11-6.44) (62, 87, 92); autoimmune diseases including rheumatological diseases and inflammatory diseases (OR 2.33; 95%CI: 1.13-4.83) (43, 89, 93, 96); central venous catheter (CVC) use (OR 2.05; 95%CI: 0.74-5.65) (43, 89); and severe stroke defined as acute ischemic stroke (OR 1.79; 95%CI: 0.77-4.18) (87, 89, 90, 92, 93). The findings for severe stroke when assessed using a diagnostic tool, the National institute of Health Stroke Scale (NIHSS), were consistent with our results

(table 2)(92). We also identified low certainty evidence that there may be an association between risk of any VTE and current tobacco use (OR 1.59; 95%CI: 0.28-9.03); however, there may be little to no association between risk of any VTE and previous tobacco use (OR 0.97; 95%CI: 0.24-3.92).

Furthermore, we identified low certainty evidence that there may be little to no association between risk of any VTE and respiratory failure (OR 1.04; 95% CI: 0.69-1.58); coronary artery disease (CAD) (OR 1.01; 95%CI: 0.33-3.09); acute heart failure (OR 0.82; 95%CI: 0.42-1.60 (89, 93); and hormone use (OR 0.8; 95%CI: 0.36-1.78) (87, 89, 93, 94).

We found very low certainty evidence that there may be little to no association between risk of any VTE and chronic renal failure (OR 0.76; 95%CI: 0.18-3.18) (93).

Laboratory and physical examination factors

There is moderate certainty evidence of an association between risk of any VTE and C-reactive protein (CRP) >10mg/L (OR 10.10; 95% CI: 1.93-52.85) (92); and D-dimer >500ng/mL at baseline (OR 2.46; 95%CI: 1.19-5.10) (93). The findings for D-dimer concentration when assessed as a continuous variable were consistent with our results (Table 2) (96). Also, there is probably an association between risk of any VTE and elevated heart rate (>100 beats per minute) (OR 2.48; 95%CI: 1.66-3.71) (62); thrombocytosis (platelet count >350x10^ 9/L) (OR 2.16; 95%CI: 1.40-3.35) (62, 86); leukocytosis (white blood count (WBC) ≥11x10^ 9/L) (OR 1.91; 95% CI: 1.24-2.94) (62);

fever (body temperature >38-38.5°C) (OR 1.88; 95%CI: 1.10-3.21) (62, 86); leg edema (OR 1.88; 95%CI: 1.23-2.90) (86, 89) and elevated fibrinogen levels (>400 mg/dL) (OR 0.18; 95% CI: 0.04-0.81) (92).

We identified low certainty evidence that there may be an association between risk of any VTE and varicose veins (OR 1.53; 95%CI: 0.85-2.76) (87, 89); and obesity (BMI >30 kg/m2) (OR 1.34; 95%CI: 0.94-1.91) (43, 62, 87, 89, 93).

Additional analyses

We performed a sensitivity analysis, including studies that reported on immobility, to compare the association between immobility >72 hours and >7 days with risk of VTE. We found similar effect estimates for both categories with a slightly stronger association between immobility, defined as bed rest for >7 days, and risk of VTE (OR 3.67; 95%CI 0.85-15.93) compared to immobility, defined as bed rest for >72 hours, and risk of VTE (OR 3.18; 95%CI 1.10-9.16).

We also conducted a sensitivity analysis, including studies that reported on symptomatic VTE only, to evaluate the influence of the studies that reported on both symptomatic and asymptomatic VTE. The results of the sensitivity analysis showed similar effect estimates across prognostic factors except for CAD. The association between CAD and risk of symptomatic VTE was somewhat stronger in the sensitivity analysis of the nine

studies (OR 2.02; 95%CI 0.32-12.64), compared to little to no association with risk of VTE in the primary analysis (OR 1.01; 95%CI 0.33-3.09; supplemental Table 4).

Prognostic factors for bleeding in hospitalized medical patients

Three studies including 160,142 patients investigated 17 candidate prognostic factors for bleeding. Table 3 provides the evidence profile for bleeding related prognostic factors. Supplemental Figure 2 provides the forest plots of the meta-analyses of each of the prognostic factors.

Demographic factors

We found moderate certainty evidence that there is probably an association between risk of bleeding and age ≥ 65 (OR 1.95; 95%CI: 1.59-2.38) (31, 90); and sex (males compared to females) (OR 1.27; 95%CI: 1.09-1.47) (31, 90).

Medical illness and patient history factors

There was moderate certainty evidence of a probable association between risk of bleeding and gastroduodenal ulcers (OR of 2.74; 95%CI: 1.42-5.26) (31, 90); rehospitalization (OR 2.39; 95%CI: 2.25- 2.54) (90); critical illness including ICU or CCU stay (OR 2.10; 95%CI: 1.42-3.11) (31); and thrombocytopenia (OR 1.79; 95%CI 0.97-3.29) (31, 90, 91). When cut-offs for thrombocytopenia were assessed separately, results showed that there probably is a greater magnitude of association between risk of

bleeding and platelet count <50 x109 /L compared to a platelet count ≥50 x109 /L (OR 3.37; 95%CI: 1.84-6.18) (26); whereas a smaller magnitude of association between risk of bleeding and platelet count <150 x109 /L compared to platelet count ≥150 x109 /L (OR 1.30; 95%CI: 0.92-1.82) (30, 32). We also found moderate certainty evidence that there is probably an association between risk of bleeding and blood dyscrasia, defined as the presence of any bleeding disorders on admission (OR 1.70; 95%CI: 1.60- 1.81) (90); hepatic disease (OR 1.53; 95%CI: 1.09-2.15) (31, 90); and renal failure (OR 1.43; 95%CI: 1.06-1.93) (31, 90). One study assessed renal failure by severity and results showed that there probably is a greater magnitude of association between risk of bleeding and severe renal failure (glomerular filtration rate (GFR), <30 mL/min/m^2) compared to no severe renal failure (OR 2.14; 95%CI: 1.22-3.75) (31); and a smaller magnitude of association between risk of bleeding and moderate renal failure (GFR, 30-59 mL/min/m^2) compared to no moderate renal failure (OR 1.37; 95%CI: 0.84-2.23) (31). We also identified moderate certainty evidence that there is probably an association between risk of bleeding and CVC use (OR 1.37; 95%CI: 0.83-2.26) (31, 90); and antithrombotic medication use (OR 1.28; 95%CI: 1.01-1.64) (31, 90).

We found moderate certainty evidence that there is probably little to no association between risk of bleeding and hormone use defined as estrogen intake (OR 0.95; 95%CI: 0.82- 1.10) (90).

Low quality evidence exists showing that there may be an association between risk of bleeding and autoimmune disease (OR 1.30; 95%CI: 0.77-2.19) (31, 90). However, we identified low certainty evidence that there may be little to no association between risk of bleeding and malignancy (OR 1.08; 95%CI: 0.42-2.77) (31, 90).

Laboratory and physical examination factors

There is moderate certainty evidence of a probable an association between risk of bleeding and anemia as the reason for admission (OR 5.15; 95%CI: 2.45- 10.81) (91); morbid obesity (BMI ≥40 kg/m^2) (OR 3.08; 95%CI: 1.35- 7.02) (91); and low hemoglobin (<13 gm/dl for males and <11.5 gm/dl for females) (OR 2.33; 95%CI: 1.04- 5.22) (91).

Discussion

Summary of findings

We evaluated prognostic factors for VTE and bleeding in hospitalized medical patients. We identified 23 prognostic factors for VTE and 15 for bleeding, some supported by moderate certainty of the evidence. Age, critical illness, CVC use, and autoimmune disease were prognostic for both outcomes. Obesity (BMI>30 kg/m2) and morbid obesity (BMI>40 kg/m2) were associated with VTE and bleeding, respectively. However, only age, critical illness and autoimmune disease had the same quality of evidence for

the two outcomes. This study is unique in many aspects including its comprehensiveness, novelty in its findings and transparent approach.

Strengths

Methodologically, our study benefits from the rigorous methods, breadth of our search, our duplicate and independent screening, data abstraction process, and our assessment of the certainty of evidence using a structured framework. Also, we conducted a sensitivity analyses to compare different duration cut-offs for immobility and to address differences in type of outcome. Other strengths include the involvement of a number of content and methodological experts.

Limitations and challenges

A potential limitation in terms of the search strategy was the focus on prevention which we did to restrict the rather large number of citations that we identified in our searches and because we believed that we would not miss relevant studies. To confirm this, we checked a large random sample (n=3000) of citations obtained from a search not including a restriction to the topic of prevention. We did not identify any study that would have fulfilled the inclusion criteria and, therefore, our original search was unlikely to have missed eligible studies. Also, time bias may be a potential limitation, as we identified some of the prognostic factors from older studies. This may overestimate VTE

events when considering overall trends in the reduction of VTE events in hospitalized medical patients over time.

Potential limitations of the included studies relate to the inconsistency and variability across eligibility criteria in the original studies and variability in study design, study type, sample size, and definitions of the prognostic factors. Other challenges include inconsistency in methods of measurement employed across studies and contamination of the population with non-medical hospitalized patients.

Implications for practice

Our study identified candidate prognostic factors for VTE and bleeding that have been considered in the analysis of some developed and widely used RAMs in daily practice such as Caprini, IMPROVE VTE, IMPROVE bleed, and PADUA models (36, 37, 45, 97). However, some factors that we identified as having a probable association with VTE, based on our meta-analyzed results, were not included or considered in the development of most of the RAMs such as elevated CRP >10mg/l (OR 10.10), lower BI scores (BI $\leq$9) (OR 8.30), history of malignancy (OR 3.20) and tachycardia (>100 beats/min) (OR 2.48). In addition, we found that an elevated fibrinogen level was inversely associated with DVT risk in patients with early stroke (92). This observation was opposite to the finding that elevated CRP, another acute phase prognostic factor, showed an association with DVT risk. The authors speculated that this finding may be a

result of fibrinogen depletion due to active clot formation (92). We believe that such reverse causation, given the study design, may be plausible. However, given the small sample size the finding warrants further investigations in future primary studies. In terms of bleeding, the candidate prognostic factor antithrombotic use showed mixed results in the different studies and was only included in one final model (90). However we identified a probable association with the outcome when the individual results were meta-analyzed (31, 39, 91). This may be due to the limitation of the databases used that may not include all potential prognostic factors. Another reason that may have limited their findings is the methods used in the development of RAMs for the multivariate analysis such as automated procedures (e.g. backward or forward) used for prognostic factor selection, or selection of factors based on statistical significance at the univariate analysis stage. Therefore the findings in our study ensure the consideration of all identified potential prognostic factors in the literature during the development of a RAM; a better assessment of the databases being used; and the comprehensiveness of the factors included in the databases. Studies in this systematic review included patients that received thromboprophylaxis which may have altered the risk estimates. However, we controlled for the use of thromboprophylaxis in several ways. We selected studies only if they included a small fraction of patients on thromboprophylaxis (less than 10%) or if they controlled for it in the statistical analysis. Beyond that, given the general assumption that the relative risk related to a prognostic factor remains largely unaffected by administration of thromboprophylaxis (while the baseline risk of course

might change), we used relative estimates of the risk. This assumption is supported by the observation that in several studies the relative estimates of risk were not influenced by adjustment for prophylaxis use in the statistical analyses. We believe that these measures should address the influence of thromboprophylaxis on the prognostic factor we addressed herein.

Implications for future research

Research may be needed to re-evaluate existing RAMs, as the developers of the models may not have been able to use the variables we identified, given limitations in the existing databases. However, a full development or improvement of a RAM that supports clinical practice requires further investigation of all prognostic factors we identified in our study.

Conclusion

In this systematic review, we identified all reported relevant prognostic factors for VTE and bleeding in hospitalized medical patients. Some of these factors are not part of current risk prediction for VTE and bleeding in hospitalized medical patients. Our findings will help inform experts in developing population-based guidelines and accurate, user-friendly RAMs to better guide individual patient prophylactic management.

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Authorship contributions

Conception and design: AJD, HJS

Data acquisition: AJD, SGK, RC, IEI, FG, MR, AA, RZM, HJS

Data analysis: AJD, MR, LM, HJS

Interpretation of results: AJD, SGK, IEI, MC, MKG, LM, FAS, ACS, MBS, SW, NAZ, FG, MR, AA, RZM, AI, EAA, HJS

Manuscript drafting: AJD, HJS

Critical revision of the manuscript and approval of the final version: AJD, SGK, RC, IEI, MC, MKG, LM, FAS, ACS, MBS, SW, NAZ, FG, MR, AA, RZM, AI, EAA, HJS

Disclosure of Conflicts of Interest

Authors AD, IEI, AI, EAA, HJS reported that they are members of the GRADE working group. ACS reported receiving remuneration for consulting work for Bayer, Janssen,

Portola and research support grants from Boehringer Ingelheim, Janssen, Centre for Medicare and Medicaid services. ACS also reported intellectual conflict as the lead in the group that derived and validated the IMPROVE VTE tool for venous thromboembolism (VTE) risk assessment in hospitalized medical patients. MBS reported receiving remuneration for consulting work for Bayer, Janssen, Pfizer and Portola and research support grants from Boehringer-Ingelheim, Janssen, Portola and Roche. MC reported being a former board director (2013-17) of the American Heart Association and chairing the American Society of Hematology (ASH) 2018 guidelines for management of VTE: prophylaxis for hospitalized and non-hospitalized medical patients. FAS and NAZ reported participating as panel members for the ASH 2018 guidelines for management of VTE: prophylaxis for hospitalized and non-hospitalized medical patients. NAZ also reported receiving honoraria in 2017 from ASH for the Highlights of ASH 2017 (Dallas, New York, Latin America). LM, MKG and SW declared having no competing interests. HJS reported being co-chair of the American Society of Hematology (ASH) 2018 guidelines for management of VTE: prophylaxis for hospitalized and non-hospitalized medical patients and grant funding from the CDC for this study.

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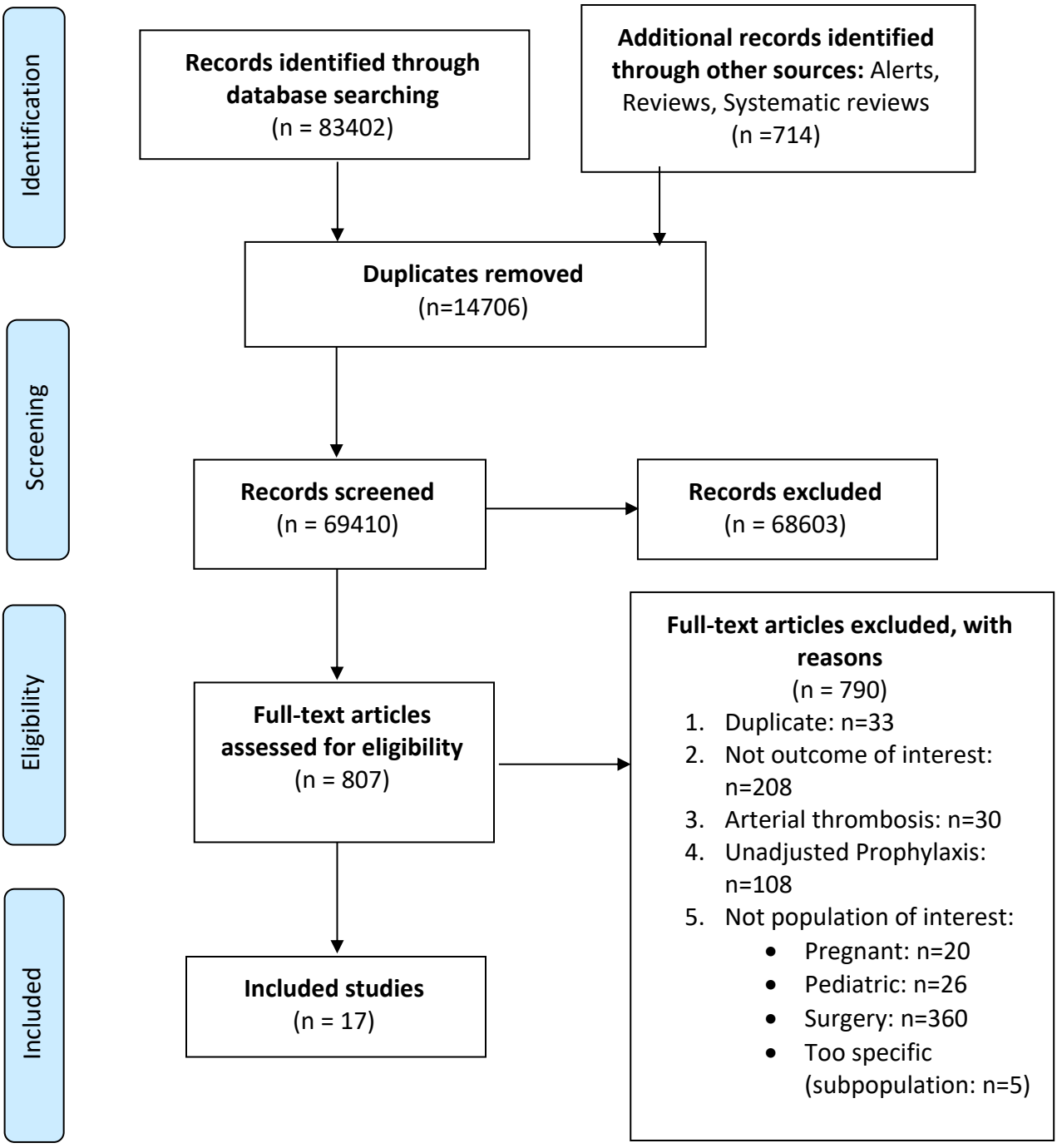
Figures

Figure 1. Prisma flow chart



Tables

Table 1. Study characteristics

First Author, Year (Country)	Population (sample size)	Time Frame (year)	Age Mean (SD)*	Study type (Number of centers and study design)	Prophylaxis (%)	Outcome (number of events)	Diagnostic methods	Follow-up time	Variables in Multivariate logistic regression when applicable
Venous thromboembolism									
Spyropoulos 2011 (U.S.) (45)	Acutely ill medical patients (N=15156)	2002-2006	68(52-79)*	Prognostic model development (Multi-center prospective cohort)	VTE prophylaxis (adjusted-dose warfarin, elastic stockings, low-molecular-weight heparin, unfractionated heparin, intermittent pneumatic compression, and aspirin): 44% The model was adjusted for VTE prophylaxis	Any symptomatic VTE (lower extremity DVT, and PE) (n=184)	Clinically observed VTE DVT verified by positive venogram or compression ultrasonography test.) PE verified by positive lung scan, pulmonary angiogram, or spiral CT scan.) Fatal PE was defined as PE diagnosed by autopsy or, in the absence of autopsy, when PE was	92 days	IMPROVE RAM related factors: Age >60; Prior cancer; Prior VTE; ICU/CCU stay; Lower limb paralysis; Immobility; Known thrombophilia

							considered the most likely cause of death.		
Mahan 2014 (Canada) (39)	Acute medical patients (N=417: VTE cases: 139 and non VTE controls: 278)	2005-2011	cases: 68; controls:65	External validation (Multi-center retrospective Case control)	VTE prophylaxis: 0%	Any symptomatic VTE (lower extremity DVT, and PE) (n=139)	PE verified by a positive pulmonary angiogram, spiral computed tomography, high probability ventilation / perfusion scan, or at autopsy) Lower extremity DVT verified by positive compression ultrasonography, computed tomography, magnetic resonance imaging, or at autopsy.	92 days	IMPROVE RAM related factors: Previous VTE; Known thrombophilia ; Lower limb paralysis; Current cancer; Immobilization >=7; ICU/CCU stay; age >60
Rosenberg 2014 (U.S.) (42)	Medical Patients (N=539: VTE cases: 135 and non VTE controls: 404)	2009-2013	67	External validation (Multi-center retrospective Case-control)	Any prophylaxis in VTE cases: 49% (of those 44% pharmacological VTE and 5% mechanical) Any prophylaxis in non VTE controls: 45 % (of those 40% pharmacological VTE and 5% mechanical)	Any symptomatic VTE (n=135)	VTE events identified using ICD-9 codes	within 90 days following the index admission	IMPROVE RAM related factors: same as those in the Spyropoulos 2011 study above

					The results were essentially unchanged when the cases and controls were stratified into groups that received VTE prophylaxis, including pharmacological prophylaxis during hospitalization and those that did not.				
Zakai 2013 (U.S.) (62)	Patients admitted to medical services (N=900: VTE cases: 299; and non VTE controls: 601)	2002-2009	cases: 63(17); controls:66 (15)	Prognostic model development (Single center retrospective Case-control)	Pharmacological prophylaxis in VTE cases: 64.6% and in non VTE controls: 62.2% Mechanical prophylaxis in VTE cases: 31.8 % and in non VTE controls: 27.6% The model was adjusted for both mechanical and pharmacological prophylaxis	Any symptomatic VTE (upper and lower extremity DVT and PE) (n=299)	VTE events identified using ICD-9 VTE discharge codes. Codes confirmed by clinician review. Records were reviewed by a research nurse and all hospital acquired VTE cases and 20% of non-cases were reviewed by a physician.	Discharge or transfer from medical service	Venous thrombosis prophylaxis (mechanical; pharmacologic); demographics (age, sex, BMI); past medical history (myocardial infarction, COPD, diabetes, chronic kidney disease);

									conditions active on admission (fever, COPD, pneumonia, any infection).
Zakai 2004 (U.S.) (86)	Medical patients (N=188: VTE cases: 65 and non VTE controls: 123)	2000-2002	68	External validation (Single center retrospective case-control)	VTE prophylaxis (including warfarin, unfractionated heparin, low molecular weight heparin or intermittent pneumatic compression devices) : in VTE cases:59%; and non VTE controls 47% The model was adjusted for prophylaxis	Any symptomatic VTE (upper and lower extremity DVT and PE) (n=65)	VTE events identified using ICD-9 VTE discharge codes.	LOS case: 16 (10-28); controls: 6 (4-10)	Trauma last 3 months; active cancer past year; admission fever; leg edema on admission; immobility >72 h; bacterial infection (cellulitis, pneumonia, sepsis, other); platelet count >350 x 10^9 /L; use of VTE prophylaxis
Zhou 2018 (China) (87)	Medically ill patients (N=1804: VTE cases: 902 and	2013-2016	Cases : 60 (17); Controls:	External validation (Single center retrospectiv	Any prophylaxis: in VTE Cases: 4.1% and in non VTE Controls: 6.1%	Any symptomatic VTE (defined	DVT verified by positive compression ultrasonography and/or contrast venography.	6 months after discharge	Caprini RAM factors* Padua RAM factors**

	non VTE controls: 902)		57 (17)	e Case-control)	VTE prophylaxis included any mechanical use (intermittent pneumatic compression devices or sole vein pump) or pharmacological use (unfractionated heparin, low-molecular-weight heparin, warfarin, fondaparinux sodium, etc.) The model was adjusted for VTE prophylaxis	as DVT or PE) (n=902)	PE verified by positive pulmonary angiogram, spiral computed tomography, high probability ventilation/ perfusion scanning, or autopsy		
Barclay 2013 (U.S.) (88)	Chronic Liver disease (N=1581)	2008-2011	51(11)	Prognostic Factor (Single center retrospective cohort)	Pharmacological VTE prophylaxis: 24.8% (Unfractionated heparin: 9.7%; low molecular weight heparin: 88.0%; or both: 2.3%) The model was adjusted for pharmacological prophylaxis	Any symptomatic VTE (including DVT, PE or portal vein thrombosis-PVT) (n=23)	VTE event identified in the medical record. VTE confirmed with radiologic testing.	4-7 days	VTE prophylaxis Active malignancy Trauma or surgery during hospitalization History of VTE

Grant 2016 (U.S.) (89)	Hospitalized medical patients (N=63548)	2011-2014	66	External validation (Multi-center retrospective cohort)	Pharmacological VTE prophylaxis: 60.9% The model was adjusted for the pharmacological prophylaxis	Any symptomatic VTE (defined as proximal upper- or proximal lower-extremity DVT and PE) (n=670)	VTE was clinically suspected. VTE was Image confirmed. Majority of events were identified by medical record review, 44 (6.6%) of the events were confirmed via telephone follow-up.	90 days	Caprini RAM factors*
Rothberg 2011 (U.S.) (43)	Medical Patients (N=46503)	2004 - 2005	NR	Prognostic model development (Multi-center retrospective cohort)	Pharmacological VTE prophylaxis: 30% There was no difference in the model estimates for the factors when the model was adjusted for prophylaxis	Any symptomatic VTE (n=1052)	VTE verified by lower extremity ultrasound, venography, CT angiogram, ventilation-perfusion scan, or pulmonary angiogram) on hospital day 3 or later Secondary diagnosis of VTE provided using ICD-9 diagnoses	30 days	Any prophylaxis; female; length of stay >=6 days; age (18-49; 50-64, >65); primary diagnosis (pneumonia, COPD, stroke, congestive heart failure, urinary tract infection, respiratory

									failure, septicemia) Comorbidities (inflammatory bowel disease, obesity, inherited thrombophilia); cancer (18-49 years, 50-64 years, >65 years) Treatments (CVC, mechanical ventilation, urinary catheter, chemotherapy , steroids)
Bembenek 2011 (Poland) (92)	Early stroke patients (N=299)	2007-2009	75(64-82)*	Prognostic factor (Single center prospective cohort)	Oral anticoagulation: 7.1% The model was not adjusted for oral anticoagulation but less than 10% of the included patients received prophylaxis.	Any symptomatic or asymptomatic DVT (n=9; 7 of which were distal)	The first ultrasonographic examination was performed within the first 7 days and then 8–10 after stroke onset by a trained physician blinded to patients' baseline health status in order	3rd and 9th day after stroke	Age (for each additional 10 years); female; hypertension; congestive heart failure; atrial fibrillation; diabetes;

							to identify patients in whom DVT occurred early in the course of stroke.		smoking status (current and previous); prestrike disability (mRS 0-1 pt and mRS 0-2 pts); stroke severity (each additional 4 pts. NIHSS, NIHSS >7 pts, NIHSS >14 pts); decreased consciousness (>=1 pt. in NIHSS, >=2 pts. in NIHSS); inflammatory markers (CRP >10mg/l, fibrinogen >4 mg/dl)
Fan 2011 (China) (93)	Acutely ill medical patients (N=458)	2006-2007	77(7)	Prognostic factor (Multi-center prospective cohort)	Pharmacological VTE prophylaxis: 0% Mechanical VTE prophylaxis (graduated compression stockings): 0.4%	Any symptomatic or asymptomatic	VTE verified by compression ultrasonography at enrollment and 3-week follow-up	90 day follow-up for symptomatic and 3 weeks	Univariate model with results provided; a multivariate analysis was

					The model was not adjusted for the mechanical thromboprophylaxis	VTE (DVT or PE) (n=45; 30 symptomatic and 15 asymptomatic)	Symptomatic cases were all screened by lower limb color duplex ultrasonography.	for asymptomatic	conducted but results of each factor were not reported
Kelly 2004 (United Kingdom) (94)	Acute Ischemic stroke (N=102)	NR	70(12)	Prognostic factor (Single center prospective cohort)	VTE prophylaxis: 0%	Any symptomatic or asymptomatic VTE (defined as proximal DVT or PE) (n=41)	Patients were assessed weekly for clinical evidence of VTE. New increases in calf circumference from initial assessment of >=3 cm (based on Well scoring system), local pain or tenderness for DVT, and oxygen saturations <=92% and/or respiratory rate >20/min in an otherwise patient asymptomatic for PE. VTE was classified as "unrecognized clinical" if associated with the aforementioned signs or symptoms	21 days	Age >70; barthel index score <=9; total anterior circulation infarcts; malignancy; atrial fibrillation

							that went unrecognized by the attending team. Magnetic resonance direct thrombus imaging was performed. If DVT was identified, thoracic imaging was performed to detect PE. All scans were reviewed independently by two reviewers who reached a consensus. Clinical events diagnosed conventionally and data from post-mortem examinations were included		
Ota 2009 (Japan) (95)	Congestive Heart Failure (N=161)	2003-2008	69.3(10.8)	Prognostic factor (Single center prospective cohort)	Anticoagulant therapy in DVT Cases: 38.9% and in the non-DVT 44.1% Antiplatelet therapy in DVT cases: 66.7% and in the non DVT: 62.9%	Any symptomatic or asymptomatic DVT (no PE was	DVT verified by standardized ultrasound criterion of venous no compressibility. PE verified by pulmonary angiography	11.8±11.5 days	NYHA functional class; poor IVC collapsibility; no anticoagulation therapy

					The model was adjusted for anticoagulant therapy	detected) (n=18)			
Yi 2012 (China) (96)	Acute stroke patients (N=1380)	2009-2010	69.8(11.6)	Prognostic factor (Multi-center prospective cohort)	Pharmacological VTE prophylaxis with warfarin or LMWH: 15% The model was adjusted for prophylaxis	Any symptomatic or asymptomatic VTE (Any PE and any DVT) (n=62; 32 symptomatic DVT and 30 asymptomatic DVT)	DVT verified by VDU, venous angiography or venous CTA examination PE verified by chest CTA or pulmonary angiography	12 months	<u>For PE as an outcome:</u> Age >=70; bed ridden; incidence of DVT <u>For DVT as an outcome:</u> Age >=70; bed ridden; wells score >=2; NIHSS score of lower limbs >=3; BI score; rehabilitative therapy; anticoagulant therapy; concentration of D-dimer evaluated at admission.
Bleeding									
Decousus 2011 (Canada) (31)	Acutely ill medical patients (N=15,156)	2002-2006	68.2 (51.8-78.9) *	Prognostic model development (Multi-	Pharmacological VTE prophylaxis: 48% (Low-molecular-weight heparin: 38.4%;	Major or clinically relevant Bleeding	Major bleeding was defined as a bleeding event contributing to death, clinically overt	14 days	Active gastroduodenal ulcer; bleeding in 3

				center prospective cohort)	Unfractionated heparin: 11.1%; Aspirin: 0.7%) Mechanical VTE prophylaxis: 9% (Elastic stockings: 5.4%; Intermittent pneumatic compression: 3.8%) There were no differences in the estimates of associations when the model was adjusted for pharmacologic prophylaxis use.	(n=230; 83 major and 147 nonmajor but clinically relevant bleeding)	bleeding associated with a fall in hemoglobin level of >=2 g/dL or leading to transfusion of at least 2 units of packed RBCs, or bleeding within a critical organ (including intracranial, retroperitoneal, intraocular, adrenal gland, spinal, or pericardial bleeding). Nonmajor but clinically relevant bleeding was defined as overt gastrointestinal bleeding (except for insignificant hemorrhoidal bleeding), gross hematuria (macroscopic and lasting longer than 24 h), substantial epistaxis that required intervention		months before admission; platelet count <50 x 10^9 cells/L; age >=85 vs <40; hepatic failure; severe renal failure GFR <30 vs >=60 mL/min/m^2; ICU/CCU; central venous catheter; rheumatic disease; current cancer; age 40-84 vs <40 years; male sex; moderate renal failure GFR 30-59 vs >=60 mL/min/m^2

							and was recurrent and/or lasted at least 5 min; extensive hematoma or bruising (>5 cm in diameter), intraarticular bleeding (documented by aspiration), menorrhagia or metrorrhagia (increased quantity or duration), or other bleeding important enough to be recorded on the hospital chart.		
Mahan 2013 (U.S.) (90)	Medical Patients (N=327,578)	2005-2009	69	Prognostic factor (Multi-center retrospective cohort)	All antithrombotic agent use: 9.4% Anticoagulants: 3.9% (warfarin: 3.6%; enoxaparin: 0.4%; heparin: 0.1% and other <0.0%) Antiplatelets: 5.7% (clopidogrel: 4.6%; aspirin-dipyridamole:0.9%); other: 0.3%)	Major or clinically relevant bleeding (n=29264; 5951 major and 23313 minor bleeding)	Bleeding events were identified through the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes.	Within 30 days after hospitalization	Age (40-54, 55-64, 65-74, >=75); male; pre-index risk factors (insufficient renal function, cancer, rheumatoid arthritis, gastroduodenal ulcer, blood

					Anticoagulants and antiplatelets: 0.2% The model was adjusted for antithrombotic use				dyscrasias, thrombocytopenia, liver disease, central venous catheter, thromboembolic stroke, estrogen use); post-index risk factors (post-discharge antithrombotic meds use, rehospitalization, length of stay (2 days, 3-5 days, >=6 days)
Patell 2017 (U.S.) (91)	Cancer Patients (N=3358)	2012-2014	62(19-98)*	Prognostic factor (Single center retrospective cohort)	Antiplatelets: 14% Anticoagulants: 67% Antiplatelet agents on day of admission were not found to be statistically significant in univariate analysis so were not added to multivariate regression analysis mode	Major or clinically relevant bleeding (n=69; 51 major and 18 nonmajor but clinically	Bleeding was assessed using the International Society on Thrombosis Hemostasis definitions of major bleeding and clinically relevant nonmajor bleeding Bleeding events were identified from	Median length of stay was 5 days (range, 0–152) days.	Reason for admission (anemia); BMI >=40; cancer site: GI; low hemoglobin (<13 gm/dl for males and <11.5 for females); low

					Anticoagulation exposure on admission was noted to be associated with a decreased risk of bleeding (OR 0.5, 95% CI 0.3–0.8, P = 0.004) although this was not significant in multivariable analysis (but the model adjusted for it)	relevant bleeding)	discharge summaries of admissions being studied. To obtain details of event, documentation including diagnostic tests (imaging and procedures) as well as clinical notes was used. All bleeding events were confirmed manually by two investigators (RP and AG, third year internal medicine residents at the time of study). When unclear, individual cases were cross-reviewed, discussed and included if both agreed. Of note no separate training was performed and no coding was used to extract bleeding information.		platelets (<150,000 /µl)

- **Caprini factors*: Stroke**; acute spinal cord injury or paralysis (<1 month); hip, pelvis, or leg fracture (<1 month); multiple trauma (<1 month); age >=75); history of VTE; family history of VTE; history of thrombophilia; heparin induced thrombocytopenia; age (41-60); age (61-74); positive history of cancer; immobilizing plaster cast; congestive heart failure; COPD or pulmonary function; inflammatory bowel disease; severe long disease (including pneumonia); acute myocardial infarction; sepsis (<1 month); surgery (<1 month); postpartum (<1 month); history of unexpected stillborn infant, recurrent spontaneous abortion (>=3) or premature birth; varicose veins; BMI >25 Kg/m2; swollen legs (current); central venous catheter present on admission; immobile/ not ambulating; hormone replacement therapy or oral contraceptives.
- **Padua factors****: Active cancer; previous VTE; reduced mobility; known thrombophilia; recent trauma and /or surgery; elderly age; heart and /or respiratory failure; acute myocardial infarction or ischemic stroke; acute infection and/ or rheumatologic disorder; obesity; ongoing hormone treatment, VTE prophylaxis.

Table 2. Evidence profile for VTE related prognostic factors

Question: Prognostic factors for medical patients

Outcome: VTE

Setting: Inpatient

Bibliography: see below

№ of studies	Certainty assessment domains						Overall certainty in the evidence about this prognostic factor	Relative effect (95% CI)
	Study design	Risk of Bias	Indirect	Inconsistent	Imprecise	Publication bias		
Age (>60 compared to <60) (39, 42, 43, 45, 62, 87, 89, 94, 96)								
9 [g]	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.34 (95%CI 1.17-1.55)
Sex (male compared to female) (43, 62, 92-94)								
5	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.03 (95%CI: 0.80-1.33)
C- Reactive protein (CRP) (CRP >10mg/l compared to CRP <10mg/l) (92)								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 10.10 (95%CI 1.93-52.85)
D-Dimer (>500ng/mL at baseline compared to <500ng/mL at baseline; and increase compared to no increase) (93, 96)								
2	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	Categorical: OR 2.46 (95%CI 1.19-5.10)

								Continuous: OR 3.45 (95%CI 2.01-5.92)
Heart rate (elevated >100 beats per minute compared to non-elevated <100 beats per minute) (62)								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 2.48 (95%CI 1.66-3.71)
Thrombocytosis (platelet count >350x10*9/L compared to platelet count <350x10*9/L) (62, 86)								
2	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 2.16 (95%CI 1.40-3.35)
Leukocytosis (WBC ≥11x109/L compared to WBC <11x109/L) (62)								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.91 (95%CI 1.24-2.94)
Fever (body temperature >38-38.5°C compared to body temperature <38-38.5°C) (62, 86)								
2	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.88 (95%CI 1.10-3.21)
Leg edema (presence compared to absence) (86, 89)								
2	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.88 (95%CI 1.23-2.90)
Varicose veins (presence compared to absence) (87, 89)								
2	Observational	Serious [a]	Not serious	Not serious	Serious [b]	Undetected	⊕⊕◯◯ LOW	OR 1.53 (95%CI 0.85-2.76)
Obesity (obesity with BMI >30 kg/m^2 compared to no obesity) (43, 62, 87)								
3	Observational	Serious [a]	Not serious	Not serious	Serious [b]	Undetected	⊕⊕◯◯ LOW	OR 1.34 (95%CI 0.94-1.91)
Fibrinogen levels (elevated levels >400 mg/dl) compared to no elevated levels) (92)								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 0.18 (95%CI 0.04-0.81)

Barthel Index (BI) score (BI ≤9 compared to BI >9) (94, 96)								
2	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 8.30 (95%CI 2.70-25.52)
Immobility: defined as confinement to bed for >72h or >7days or bedridden or non-ambulatory (yes compared to no) (42, 45, 62, 86, 87, 89, 94, 96)								
8	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 3.17 (95%CI 2.18-4.62)
Paresis (yes compared to no) (39, 42, 45, 94)								
4	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 2.97 (95%CI 1.20-7.36)
Previous VTE (yes compared to no) (39, 42, 45, 62, 87-89, 93)								
8	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 6.08 (95%CI 3.71-9.97).
Thrombophilia (familial or acquired disorder of the hemostatic system) (yes compared to no) (39, 42, 43, 45, 87)								
5	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 5.88 (95%CI 2.80-12.35)
Malignancy (active malignancy (defined as the presence of cancer on admission or within the past year) compared to no active malignancy; and past history compared to no past history of malignancy) (39, 42, 43, 45, 62, 86, 88, 89, 93, 94)								
10	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	Active cancer: OR 2.65 (95%CI 1.79-3.91) Past history of cancer: OR 3.20 (95%CI 2.14-4.79)
Critical illness: defined as intensive care unit (ICU) or coronary care unit (CCU) stay, or need for resuscitation (yes compared to no) (39, 42, 43, 45, 62, 87, 93)								
7	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.65 (95%CI 1.39-1.95)
Infections: including cellulitis, pneumonia and sepsis (yes compared to no) (86, 89)								

5	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	Any infection: OR 1.48 (95%CI 1.16-1.89) a) Acute infection: OR 1.59 (95%CI 1.23-2.06 b) Sepsis: OR 1.07 (95%CI 0.70-1.62)
Heart failure (HF) (acute HF compared to no acute HF; history of HF compared to no history of HF) (86, 87, 89, 92, 93)								
5	Observational	Serious	Not serious	Not serious	Serious [b]	Undetected	⊕⊕◯◯ LOW	Acute heart failure: OR 0.82 (95%CI 0.42-1.60) History of heart failure: OR 2.68 (95%CI 1.11-6.44)
Autoimmune disease: including rheumatological diseases and inflammatory diseases (yes compared to no) (43, 62, 87, 89)								
4	Observational	Serious [a]	Not serious	Serious	Not serious	Undetected	⊕⊕◯◯ LOW	OR 2.33 (95%CI 1.13-4.83)
Central venous catheters (CVC) (presence compared to absence) (43, 89)								
2	Observational	Serious	Not serious	Serious [d]	Not serious	Undetected	⊕⊕◯◯ LOW	OR 2.05 (95%CI 0.74-5.65)
Severe stroke: defined as acute ischemic stroke (yes compared to no) (87, 89, 90, 93)								
4	Observational	Serious [a]	Not serious	Not serious	Serious [b]	Undetected	⊕⊕◯◯ LOW	Acute ischemic stroke: OR 1.79 (95%CI 0.77-4.18) When stroke was assessed in terms of the NIH Stroke Scale (NIHSS), we found consistent results [f].
Tobacco (current use compared to no current use; previous use compared to no previous use) (92)								
1	Observational	Serious	Not serious	Not serious	Serious [b]	Undetected	⊕⊕◯◯ LOW	Current tobacco use: OR 1.59 (95%CI 0.28-9.03) Previous tobacco use: OR 0.97 (0.24-3.92)
Hormone use: defined as estrogen intake (yes compared to no) (89)								

1	Observational	Serious	Not serious	Not serious	Serious [b]	Undetected	⊕⊕◯◯ LOW	OR 0.80 (95%CI 0.36-1.78).
Renal failure [w] (yes compared to no) (93)								
1	Observational	Serious [c]	Not serious	Not serious	Very Serious [b, e]	Undetected	⊕◯◯◯ VERY LOW	OR 0.76 (95%CI 0.18-3.18)
Respiratory failure (yes compared to no) (62, 87, 89, 93)								
4	Observational	Serious [a]	Not serious	Not serious	Serious [b]	Undetected	⊕⊕◯◯ LOW	Any respiratory failure: OR 1.04 (95% 0.69-1.58). a) acute respiratory failure: OR 1.18 (95%CI 0.76-1.84) b) chronic respiratory failure: OR 0.58 (95% 0.30-1.10).
Coronary artery disease (CAD) (yes compared to no) (87, 89, 93, 94)								
4	Observational	Serious [a]	Not serious	Serious [d]	Not serious	Undetected	⊕⊕◯◯ LOW	OR 1.01 (95%CI 0.33-3.09)

Explanations

a. Certainty in evidence was downgraded for risk of bias given a follow-up time of more than three months in the included studies that may cause an overestimation of the magnitude of the association (Zhou 2018: 6 months after discharge and Yi 2012: 12 months after discharge)
b. Certainty in evidence was downgraded for imprecision given the confidence interval suggests that there may be no association.
c. Certainty in evidence was downgraded for risk of bias given that a results of each prognostic factor in the multivariate analysis were not reported and therefore we had to rely on the unadjusted measures of association. Also, the multivariate analysis only included factors statistically significant in the univariate analysis.
d. Certainty in evidence was downgraded for inconsistency but not imprecision given the inconsistency is the likely cause for the imprecision.
e. Certainty in evidence was downgraded for imprecision given the small number of events (n=32)

f. Bembenek 2012 assessed the severity of a stroke experienced by an individual by using the NIH Stroke Scale (NIHSS), a diagnostic tool, results showed consistent results with the meta-analysis that severe stroke may result in an increase in risk of any DVT (OR 2.11; 95%CI: 0.50-8.90) for NIHSS >7 compared with a NIHSS score <7. Also, severe stroke may result in an increase in risk of any DVT (OR 1.34; 95%CI: 0.25-7.18) for NIHSS > 14 compared with a NIHSS < 14 (92). When NIHSS was assessed continuously, results showed that severe stroke may result in an increase in risk of any DVT (OR 1.21; 95%CI: 0.86-1.70) for each additional 4 points on the NIHSS scale.

g. Fan et al., (36) with 458 patients older than 60 years of which 45 patients had any VTE, presented age as a continuous variable and showed no association between age and any VTE with an OR of 1.03 (95%CI 0.98-1.08). Another study by Bembenek et al., with 299 patients of which 9 had any DVT, 7 of which were distal, presented age per 10 year increase and showed a decrease in risk per 10 year increase in age with any DVT with an OR of 0.64 (95%CI 0.33-1.24).

Table 3. Evidence profile for the Bleeding related prognostic factors

Question: Prognostic factors for medical patients

Outcome: Bleeding

Setting: Inpatient

Bibliography: see below

№ of studies	**Certainty assessment domains**						**Overall certainty in the evidence about this prognostic factor**	**Relative effect (95% CI)**
	Study design	**Risk of Bias**	**Indirect**	**Inconsistent**	**Imprecise**	**Publication bias**		
Age (≥65 compared to <65) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Not serious	Undetected	⨁⨁⨁◯ MODERATE	Age ≥ 65: OR: 1.95 (95CI% 1.59-2.38)
Sex (male compared to female) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Not serious	Undetected	⨁⨁⨁◯ MODERATE	OR 1.27 (95%CI 1.09-1.47).
Anemia as a reason for admission (presence compared to absence) (91)								
1	Observational	Serious [c]	Not serious	Not serious	Not serious	Undetected	⨁⨁⨁◯ MODERATE	OR 5.15 (95%CI 2.45-10.81)
Morbid obesity (BMI ≥40 kg/m2 compared to BMI < <40 kg/m2) (91)								
1	Observational	Serious [c]	Not serious	Not serious	Not serious	Undetected	⨁⨁⨁◯ MODERATE	OR 3.08 (95%CI 1.35-7.02)

Low hemoglobin: defined as <13 gm/dl for males and <11.5 gm/dl for females (yes compared to no) (91)								
1	Observational	Serious [c]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 2.33 (95%CI 1.04-5.22)
Gastroduodenal ulcers (yes compared to no) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 2.74 (95%CI 1.42-5.26)
Rehospitalisation (yes compared to no) (90)								
1	Observational	Serious [b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 2.39 (95% 2.25-2.54)
Critical illness (yes compared to no) (31)								
1	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 2.10 (95%CI 1.42-3.11).
Thrombocytopenia (yes compared to no) (31, 90, 91)								
3	Observational	Serious [a,b,c]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	All: OR 1.79 (95%CI 0.97-3.29) a) <50 x109 /L: OR 3.37 (95%CI 1.84-6.18) b) <150 x109 /L :OR 1.30 (95%CI 0.92-1.82)
Blood dyscrasia defined as the presence of any bleeding disorders on admission (presence compared to absence) (90)								
1	Observational	Serious [b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.70 (95%CI 1.60-1.81)
Hepatic disease (yes compared to no) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.53 (95%CI 1.09-2.15)
Renal failure (yes compared to no) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	Total: OR 1.43 (95%CI 1.06-1.93) Any renal failure (RF): OR 1.23 (95%CI 0.92-1.65).

								Moderate RF (GFR30-59 mL/min/m^2): OR 1.37(95%CI 0.84-2.23) Severe RF (GFR<30 mL/min/m^2): OR 2.14 (95%CI 1.22-3.75)
Antithrombotic medication (yes compared to no) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.28 (95%CI 1.01-1.64)
Central venous catheters (yes compared to no) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	1.37 (95%CI 0.83-2.26)
Autoimmune disease (yes compared to no) (31)								
2	Observational	Serious [a]	Not serious	Not serious	Serious [d]	Undetected	⊕⊕◯◯ LOW	OR 1.30 (95%CI 0.77-2.19)
Hormone use: defined as estrogen intake (yes compared to no) (90)								
1	Observational	Serious [b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 0.95 (95%CI 0.82-1.10)
Malignancy (yes compared to no) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Serious [d]	Undetected	⊕⊕◯◯ LOW	OR 1.08 (95%CI 0.42-2.77).

Explanations

a. Certainty in evidence was downgraded for risk of bias given patients were enrolled both prospectively and retrospectively in the Decousus et al. study. The retrospective enrollment of patients may have introduced classification bias.

b. Certainty in evidence was downgraded for risk of bias given the authors evaluated bleeding risk in medical patients after hospitalisation, that may overestimate the magnitude of the association. This is possibly due to patients being discharged on thromboprophylaxis without proper risk stratification for bleeding placing unmonitored patients at a higher risk of having a bleeding event.

c. Certainty in evidence was downgraded for risk of bias given the population is specific to hospitalized cancer patients that are at a higher risk of VTE and may be given thromboprophylaxis placing them at a higher risk of having a bleeding event. This in turn may overestimate the magnitude of the association.

d. Certainty in evidence was downgraded for imprecision given the confidence interval suggests that there may be no association

Appendices

Supplemental Table 1. Search Strategies (Medline and Embase)

Medline

Search name: z - Prognostic SR_Medline2

OVERVIEW	
Interface:	Ovid
Database:	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Date of Search:	28 October 2017- alerts till May 2018
Study Types:	All
Limits:	Publication date: No limit
Search Strategy: search terms (number of results)	
VTE Block:	
1 Primary Prevention/ (17503)	
2 Venous Thrombosis/pc [Prevention & Control] (4385)	
3 Venous Thromboembolism/pc [Prevention & Control] (3582)	
4 Pulmonary Embolism/pc [Prevention & Control] (4886)	
5 Prevent*.mp. (1332101)	
6 Thromboprophylax*.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, synonyms] (4072)	
7 Prophylax*.mp. (104027)	
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (1405763)	

9 exp Venous Thromboembolism/ or exp Thromboembolism/ (53573)
10 exp Pulmonary Embolism/ (37750)
11 exp Venous Thrombosis/ (53428)
12 Thrombophlebitis/ (22521)
13 (DVT or VTE or PE).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, synonyms] (48782)
14 ((Pulmon* or vein or venous or lung) adj (Emboli* or thromb*)).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, synonyms] (107521)
15 (thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).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, synonyms] (377373)
16 (((deep or thromb* or stasis) adj2 (vein* or venous)) or (blood flow stasis or blood clot)).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, synonyms] (79440)
17 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (425979)
18 8 and 17 (55938)

Prognosis filter:
19 Incidence.sh. (240248)
20 exp Mortality/ (359024)
21 Follow-Up Studies.sh. (628038)
22 Prognos:.tw. (524700)
23 Predict:.tw. (1363351)
24 Course:.tw. (580752)
25 19 or 20 or 21 or 22 or 23 or 24 (3152981)
26 18 and 25 (11256)

Clinical prediction guide filter:
27 predict:.mp. (1444321)
28 scor:.tw. (814052)
29 observ:.mp. (3283307)
30 27 or 28 or 29 (5007508)
31 18 and 30 (11822)
32 26 or 31 (17981)
Records Retrieved: 17981

Embase

Search name: z - Prognostic SR_Embase2

OVERVIEW	
Interface:	Ovid
Database:	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Date of Search:	28 October 2017- alerts till May 2018
Study Types:	
Limits:	Publication date: No limit
Search Strategy: search terms (number of results)	
VTE Block:	
1 Primary Prevention/ (35278)	
2 Venous Thrombosis/pc [Prevention & Control] (785)	
3 Venous Thromboembolism/pc [Prevention & Control] (7088)	
4 Pulmonary Embolism/pc [Prevention & Control] (1752)	
5 Prevent*.mp. (2477729)	
6 Thromboprophylax*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (6379)	

7 Prophylax*.mp. (195774)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2548335)
9 exp Venous Thromboembolism/ or exp Thromboembolism/ (433469)
10 exp Pulmonary Embolism/ (80922)
11 exp Venous Thrombosis/ (114178)
12 Thrombophlebitis/ (15800)
13 (DVT or VTE or PE).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (144215)
14 ((Pulmon* or vein or venous or lung) adj (Emboli* or thromb*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (192152)
15 (thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (597995)
16 (((deep or thromb* or stasis) adj2 (vein* or venous)) or (blood flow stasis or blood clot)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (182911)
17 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (752356)
18 8 and 17 (147813)

Prognosis filter:
19 follow-up.mp. (1606000)
20 prognos:.tw. (730265)
21 ep.fs. (986253)
22 19 or 20 or 21 (3063360)
23 18 and 22 (30227)

Clinical prediction guide filter:
24 validat:.mp. (630471)
25 index.tw. (873592)

26	model.tw. (2141395)
27	24 or 25 or 26 (3382557)
28	18 and 27 (15370)
29	23 or 28 (42534)
Records Retrieved: 42534	

Supplemental Table 2. Risk of bias assessments using PROBAST for risk assessment model studies

Author	Year	Participants	Predictors	Outcome	Analysis	Overall
Decousus et al.	2011	+	+	+	-	-
Grant et al.	2016	+	+	+	-	-
Mahan et al.	2014	+	+	+	-	-
Rosenberg et al.	2014	+	+	-	+	-
Rothberg et al.	2011	+	+	+	-	-
Spyropoulos et al.	2011	+	+	+	-	-
Zakai et al.	2004	+	+	-	-	-
Zakai et al.	2013	+	+	-	-	-
Zhou et al.	2018	+	+	-	+	-

Supplemental Table 3. Risk of bias assessments using Quips for prognostic factor studies

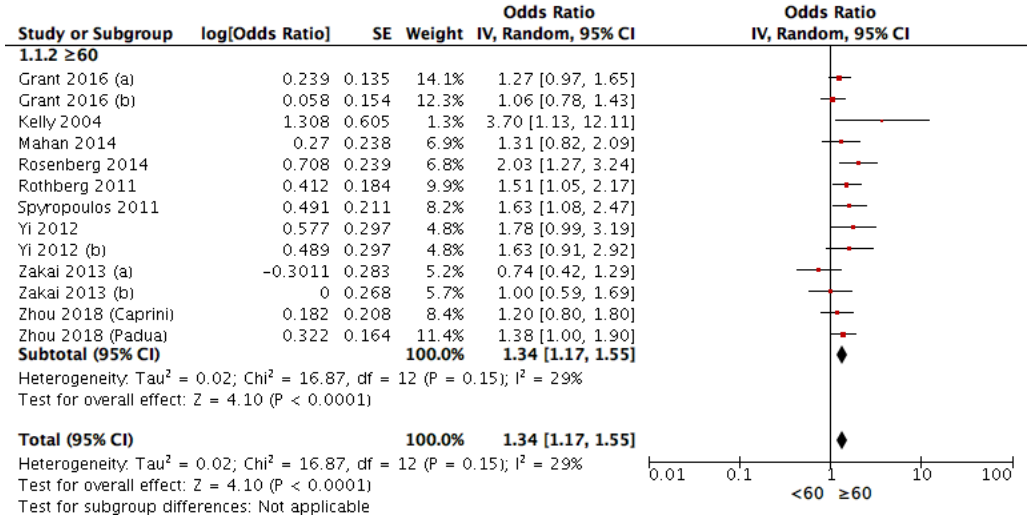
Author	Year	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Barclay et al.	2013	Yes	Not reported	Yes	Yes	Yes	No
Bembenek et al.	2011	Yes	29.6	Yes	Yes	Yes	Yes
Fan et al.	2011	Yes	26.8	Yes	Yes	Yes	No
Kelly et al.	2004	Yes	23.6	Yes	Yes	Yes	No
Mahan et al.	2013	Yes	32.6	Yes	No	Yes	No
Ota et al.	2009	Yes	0	Yes	Yes	Yes	No
Patell et al.	2017	Yes	3.8	Yes	No	Yes	No
Yi et al.	2012	Yes	4	Yes	Yes	Yes	No

Supplemental Table 4. Sensitivity analysis of studies that report an association between prognostic factors and symptomatic VTE only.

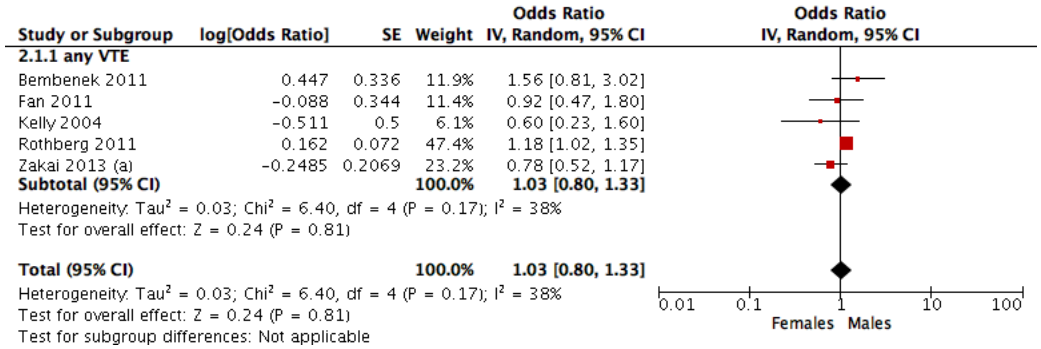
Prognostic factor	Analysis	# of effect estimates	Number of studies	Sample size	Pooled OR	95% CI	
Age	Primary analysis	13	9	130,349	1.34	1.17	1.55
	Sensitivity analysis	10	7	128,867	1.31	1.11	1.55
Sex	Primary analysis	5	5	48,262	1.03	0.80	1.33
	Sensitivity analysis	2	2	47,403	1.00	0.68	1.48
Immobility	Primary analysis	11	8	83,134	3.17	2.18	4.62
	Sensitivity analysis	8	6	81,652	2.69	1.64	4.40
Paresis	Primary analysis	4	4	16,214	2.97	1.20	7.36
	Sensitivity analysis	3	3	16,112	2.48	0.77	8.05
Previous VTE	Primary analysis	9	8	84,403	6.08	3.71	9.97
	Sensitivity analysis	8	7	83,945	6.51	3.81	11.12
Active malignancy	Primary analysis	9	9	128,853	2.65	1.79	3.91
	Sensitivity analysis	7	7	128,293	2.81	1.89	4.18
Critical illness	Primary analysis	7	7	65,777	1.65	1.39	1.95
	Sensitivity analysis	6	6	65,319	1.63	1.37	1.93
Infections	Primary analysis	9	5	66,898	1.48	1.16	1.89
	Sensitivity analysis	8	4	66,440	1.42	1.09	1.87
Acute heart failure	Primary analysis	2	2	64,006	0.82	0.42	1.60
	Sensitivity analysis	1	1	63,548	1.08	0.84	1.39
History of heart failure	Primary analysis	4	3	2,291	2.68	1.11	6.44
	Sensitivity analysis	3	2	1,992	2.96	1.03	8.49
Severe stroke	Primary analysis	5	4	66,227	1.79	0.77	4.18
	Sensitivity analysis	4	3	65,769	2.00	0.69	5.78
Respiratory failure	Primary analysis	6	4	66,710	1.04	0.69	1.58
	Sensitivity analysis	5	3	66,252	1.05	0.68	1.61
Coronary artery disease	Primary analysis	4	4	65,912	1.01	0.33	3.09
	Sensitivity analysis	2	2	65,352	2.02	0.32	12.64

Supplemental Figure 1. Forest plots showing the association between candidate prognostic factors and the outcome venous thromboembolism (Figure 1A-Figure 1AC)

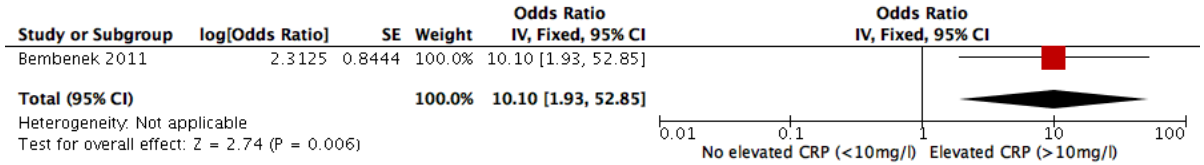
sFigure 1A. Forest plots showing the association between age and the outcome VTE



sFigure 1B. Forest plot showing the association between sex and the outcome VTE

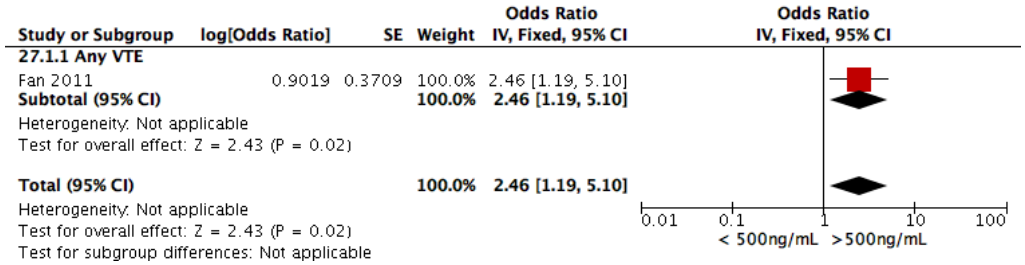


sFigure 1C. Forest plot showing the association between C-reactive protein and the outcome VTE

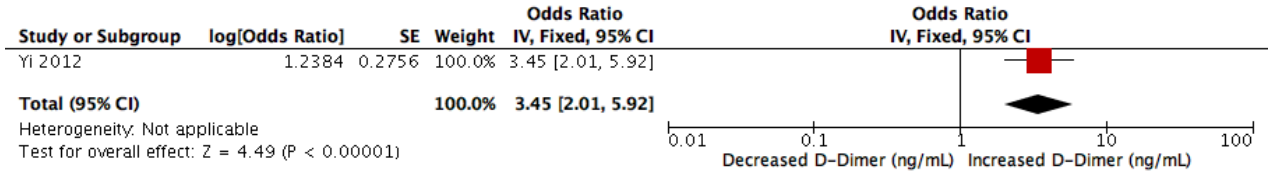


sFigure 1D. Forest plots showing the association between D-Dimer and the outcome VTE

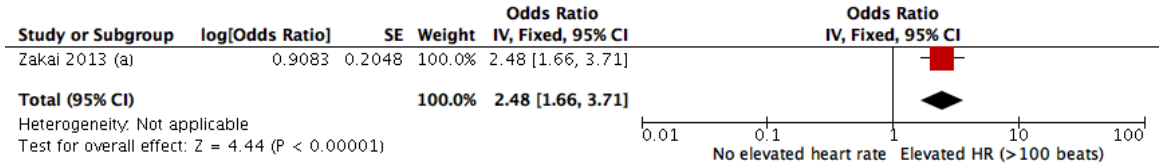
sFigure 1.1D. D-dimer (categorical)



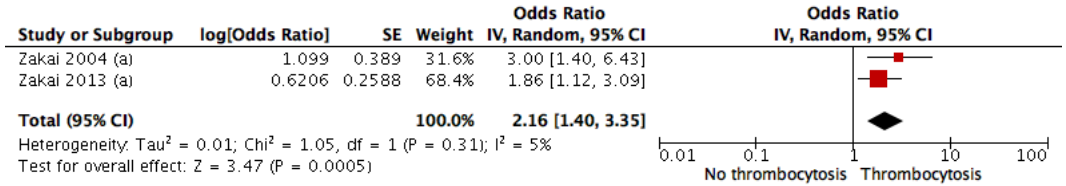
sFigure 1.2D. D-dimer (continuous)



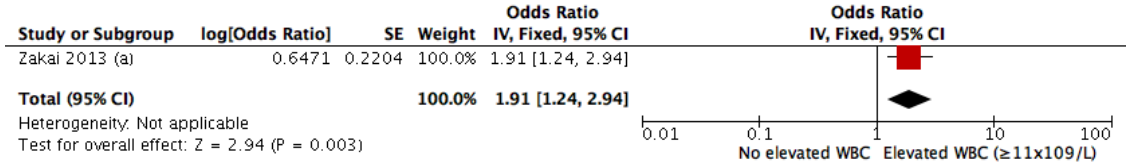
sFigure 1E. Forest plot showing the association between tachycardia and the outcome VTE



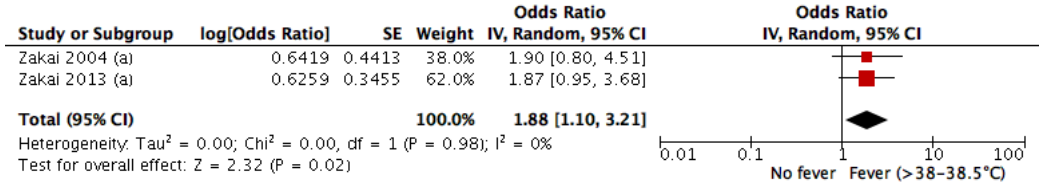
sFigure 1F. Forest plot showing the association between thrombocytosis and the outcome VTE



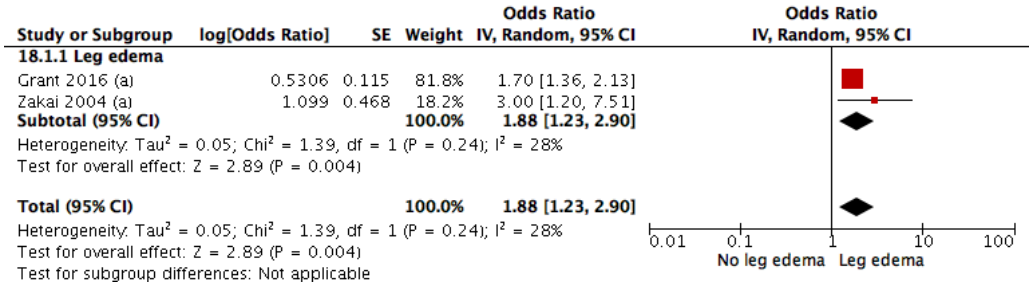
sFigure 1G. Forest plot showing the association between leukocytosis and the outcome VTE



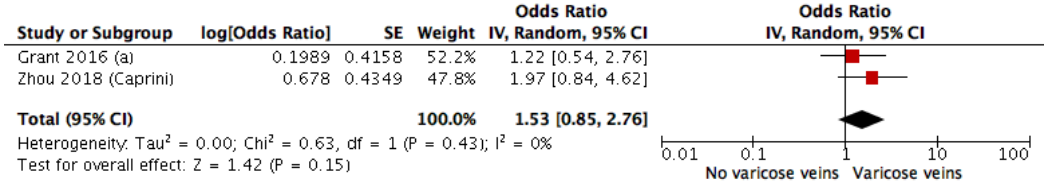
sFigure 1H. Forest plot showing the association between fever and the outcome VTE



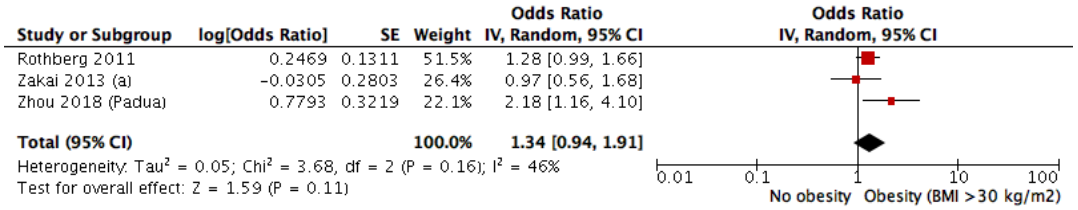
sFigure 1I. Forest plot showing the association between leg edema and the outcome VTE



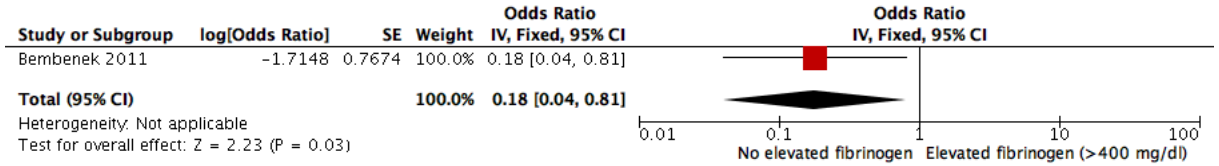
sFigure 1J. Forest plot showing the association between varicose veins and the outcome VTE



sFigure 1K. Forest plot showing the association between obesity and the outcome VTE

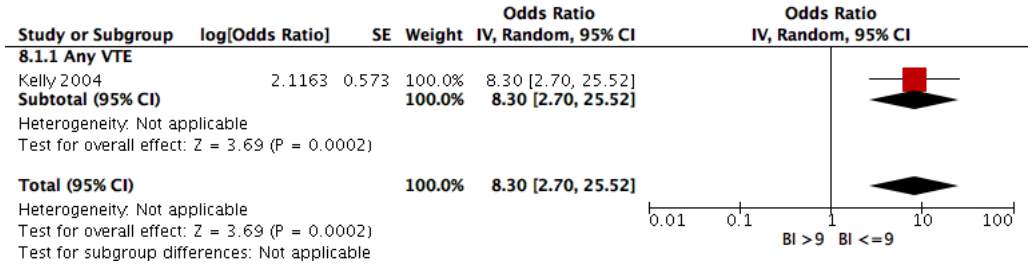


sFigure 1L. Forest plot showing the association between Fibrinogen levels and the outcome VTE

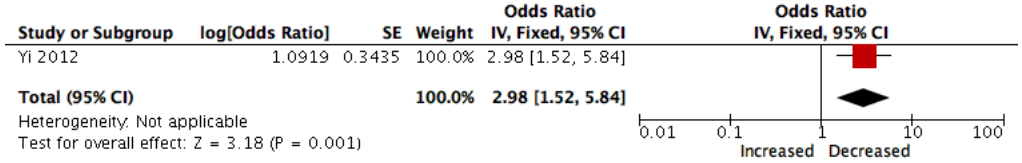


sFigure 1M. Forest plots showing the association between Barthel index score and the outcome VTE

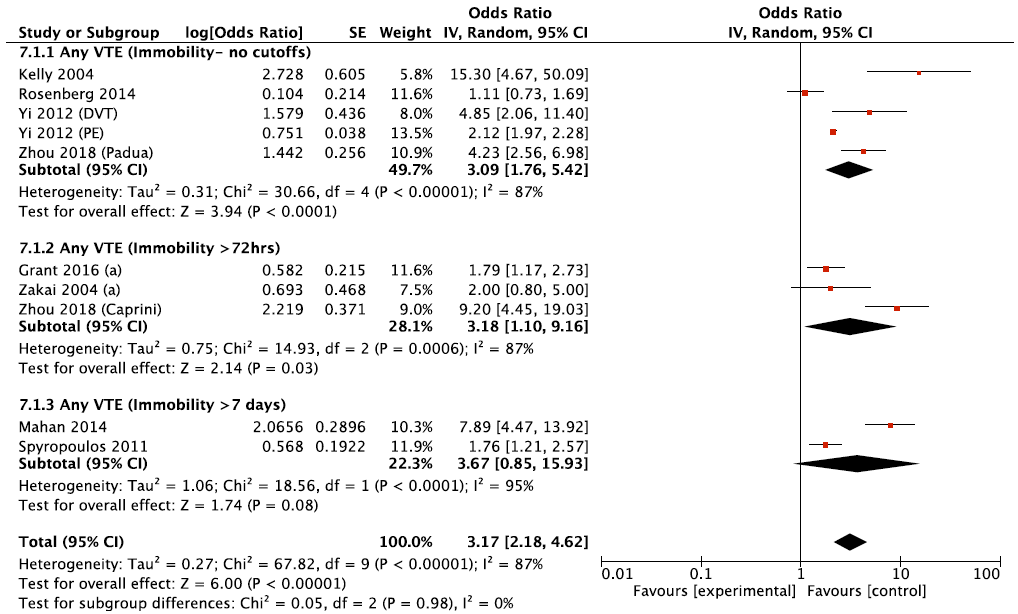
sFigure 1.1M.: Barthel index score (categorical)



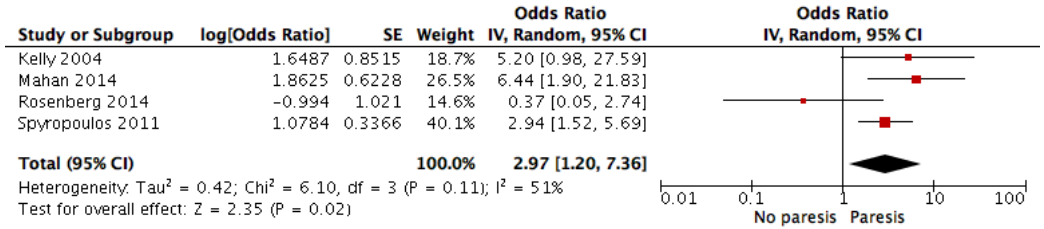
sFigure 1.2M. Barthel index score (continuous)



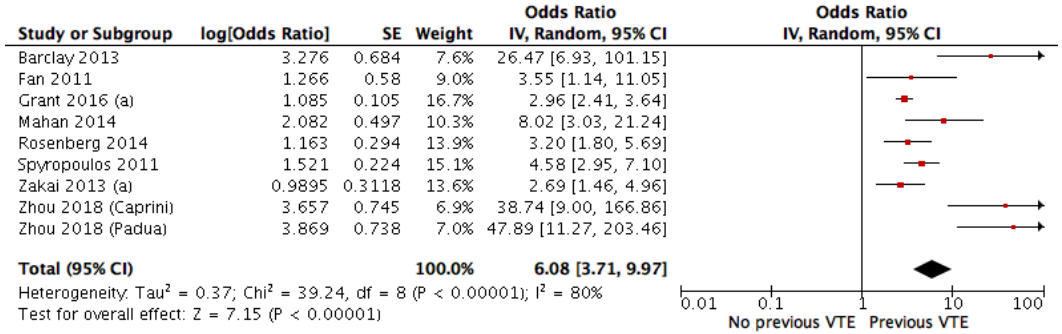
sFigure 1N. Forest plot showing the association between immobility and the outcome VTE



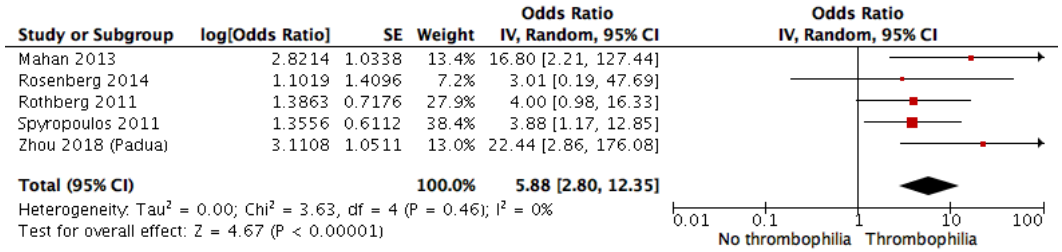
sFigure 1O. Forest plot showing the association between paresis and the outcome VTE



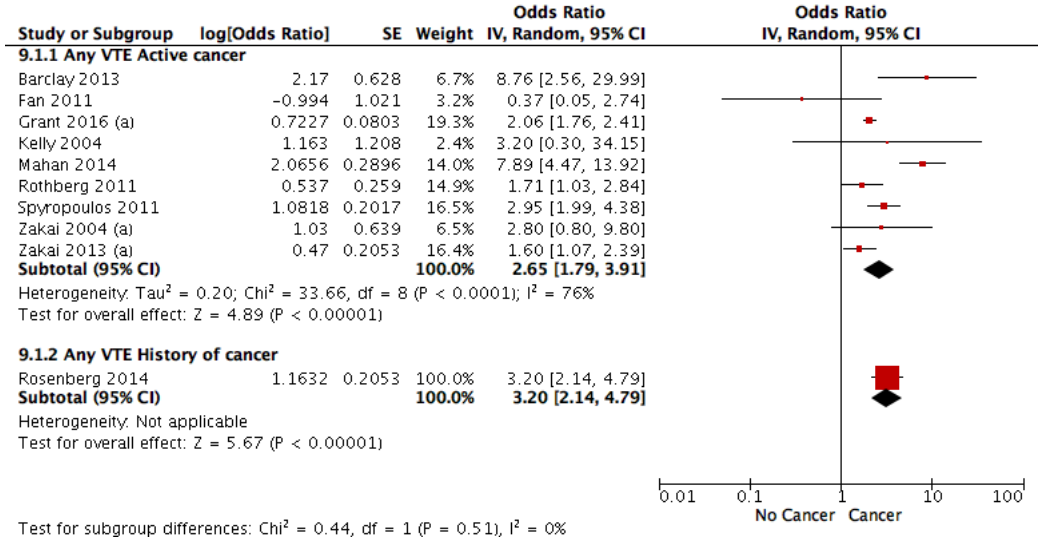
sFigure 1P. Forest plot showing the association between history of VTE and the outcome VTE



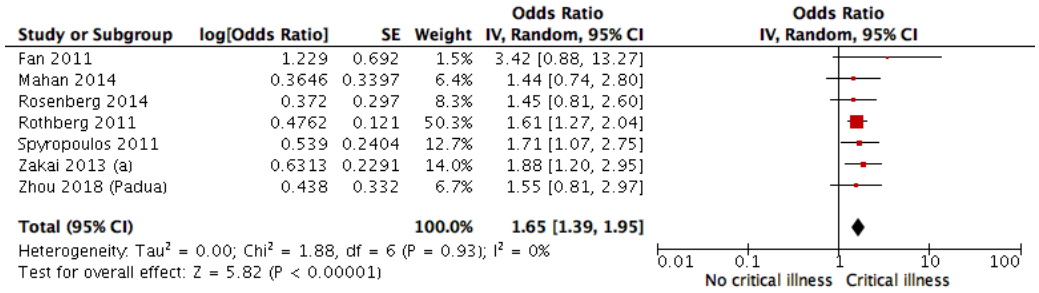
sFigure 1Q. Forest plot showing the association between thrombophilia and the outcome VTE



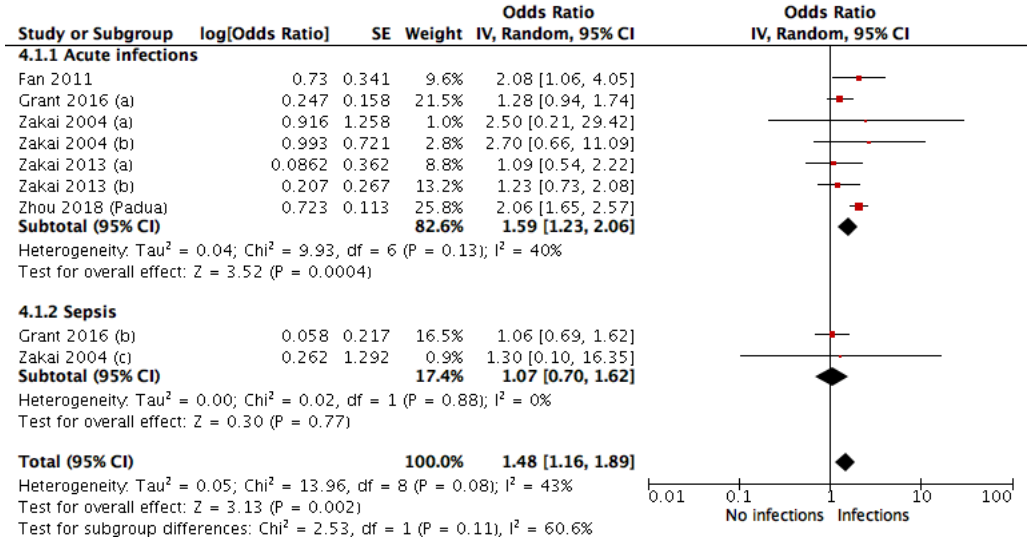
sFigure 1R. Forest plots showing the association between malignancy and the outcome VTE



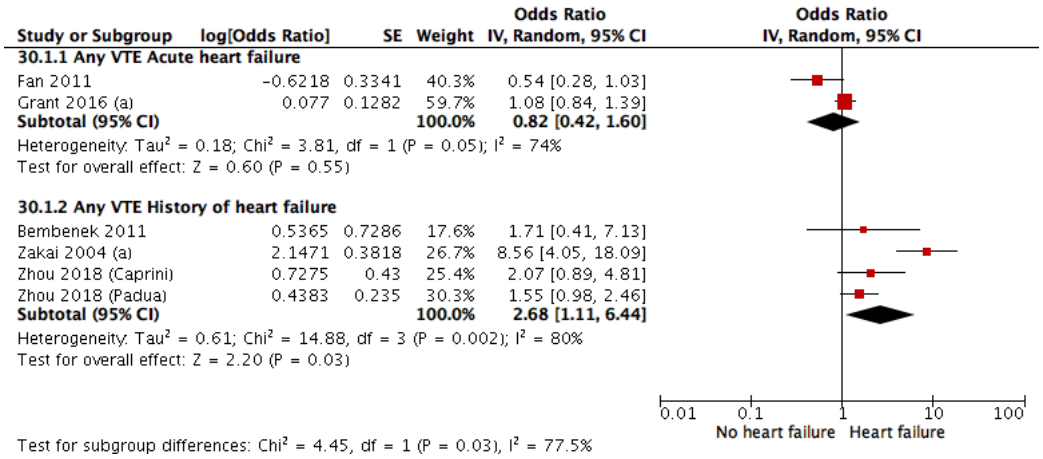
sFigure 1S. Forest plot showing the association between critical illness and the outcome VTE



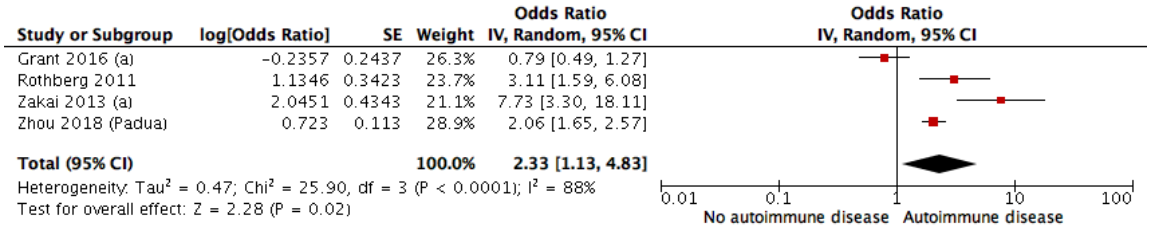
sFigure 1T. Forest plot showing the association between infections and the outcome VTE



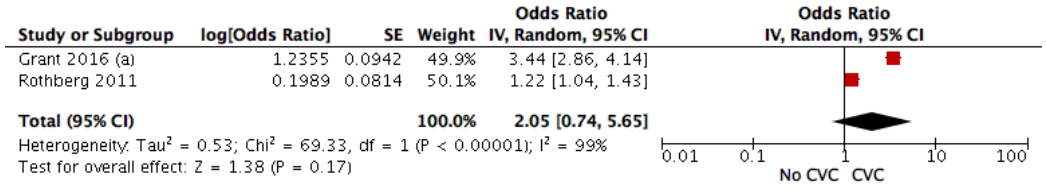
sFigure 1U. Forest plots showing the association between heart failure for the outcome VTE



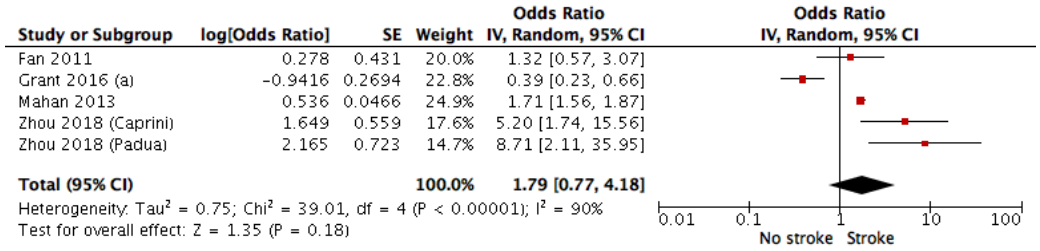
sFigure 1V. Forest plot showing the association between autoimmune disease and the outcome VTE



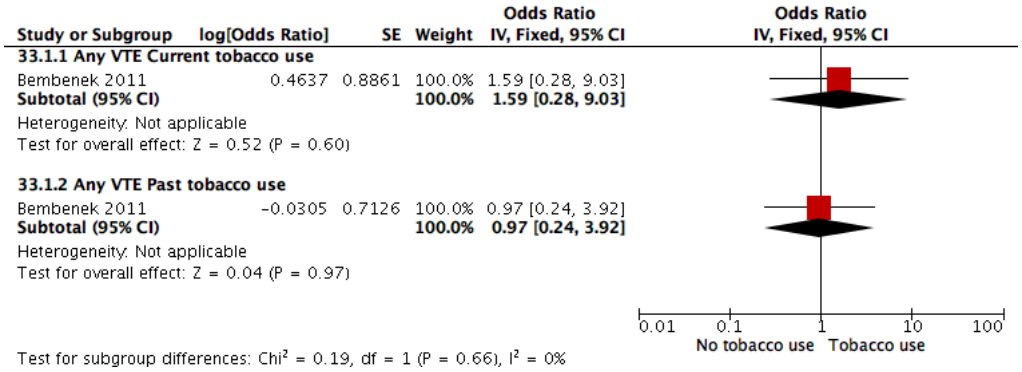
sFigure 1W. Forest plot showing the association between central venous catheters and the outcome VTE



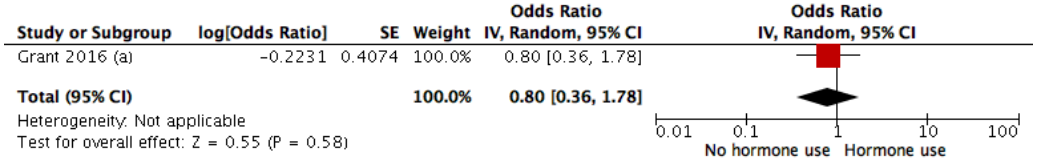
sFigure 1X. Forest plot showing the association between severe stroke and the outcome VTE



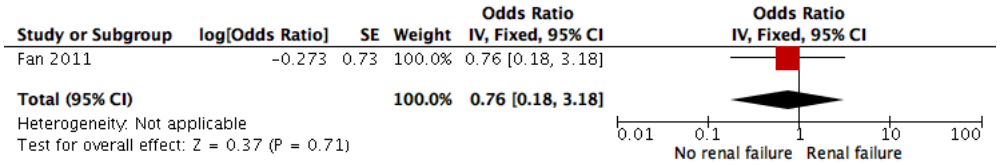
sFigure 1Y. Forest plots showing the association between tobacco use and the outcome VTE



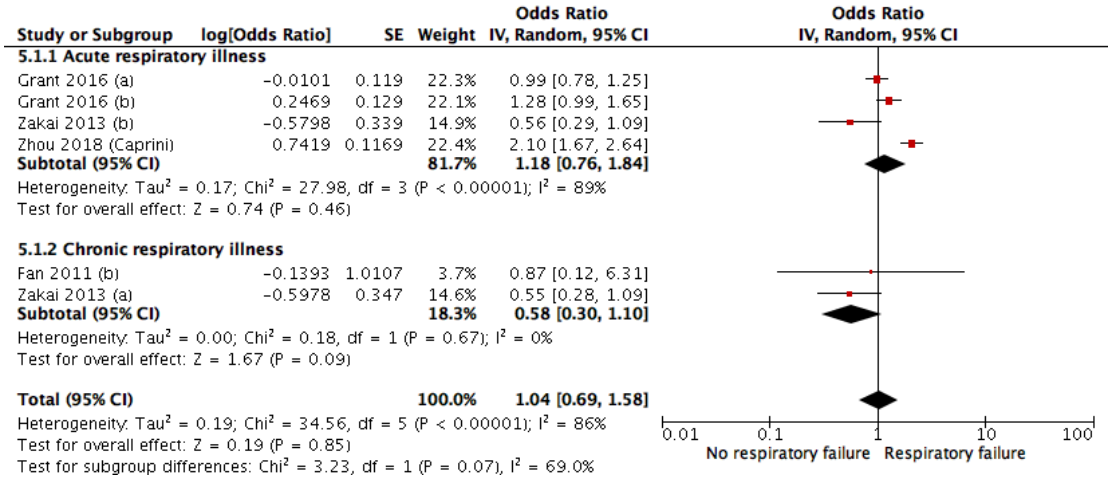
sFigure 1Z. Forest plot showing the association between hormone use and the outcome VTE



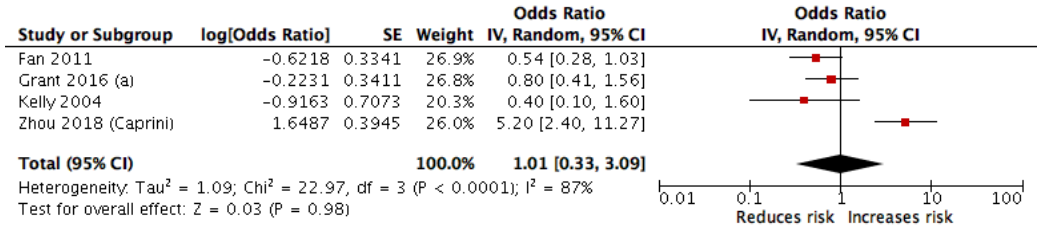
sFigure 1AA. Forest plot showing the association between renal failure and the outcome VTE



sFigure 1AB. Forest plot showing the association between respiratory failure and the outcome VTE

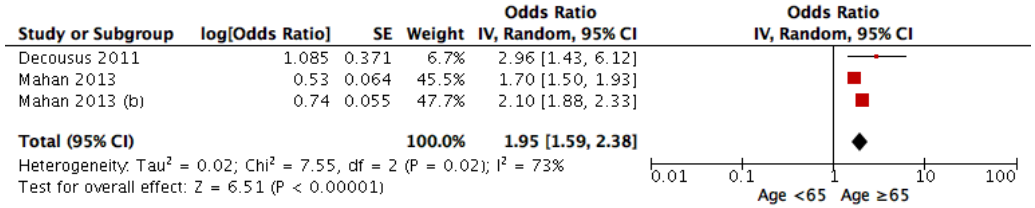


sFigure 1AC. Forest plot showing the association between coronary artery disease and the outcome VTE

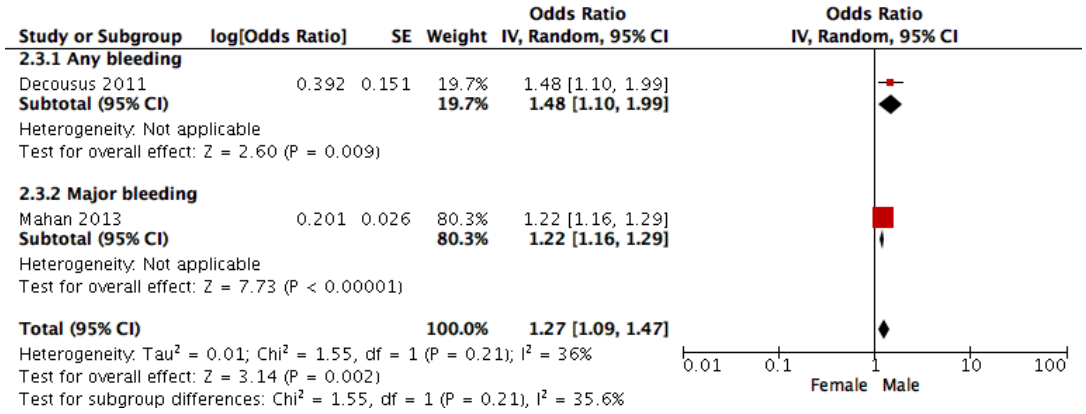


Supplemental Figure 2. Forest plots showing the association between candidate prognostic factors and the outcome bleeding (Figure 2A-Figure 2Q)

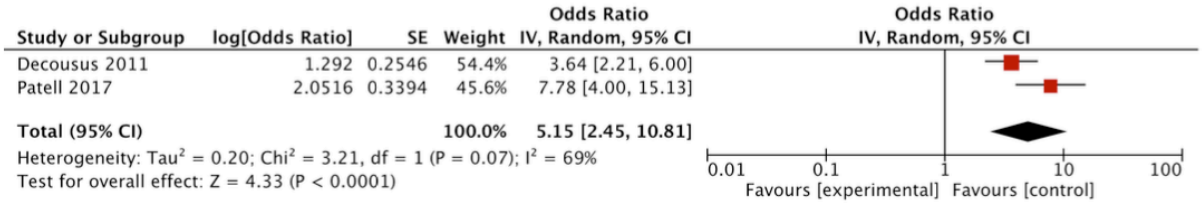
sFigure 2A. Forest plots showing the association between age and the outcome bleeding



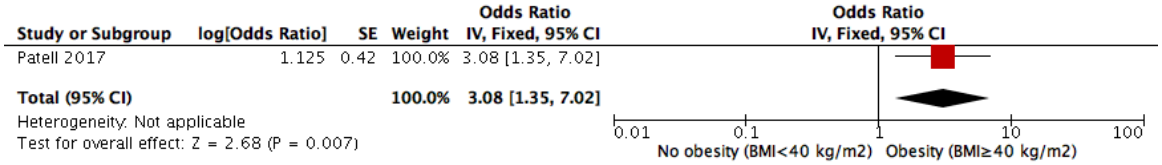
sFigure 2B. Forest plot showing the association between sex and the outcome bleeding



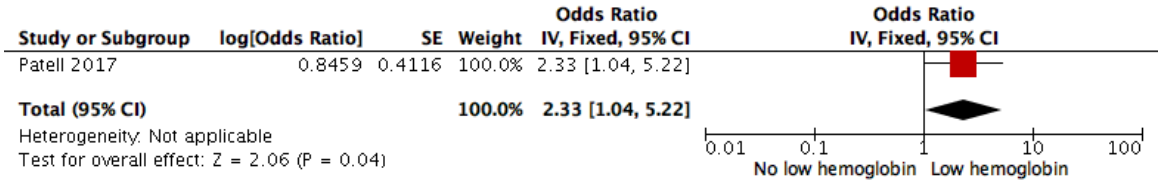
sFigure 2C. Forest plot showing the association between recent bleeding (presented as anemia as a reason for admission) and the outcome bleeding



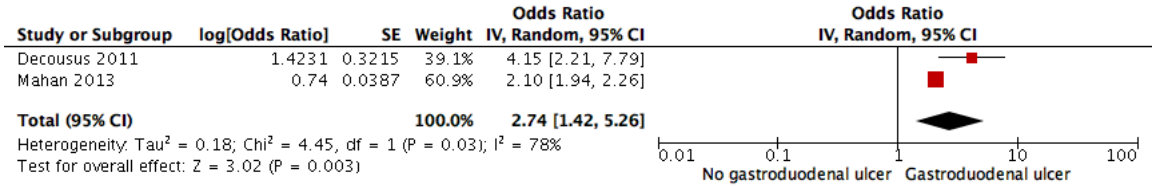
sFigure 2D. Forest plot showing the association between obesity and the outcome bleeding



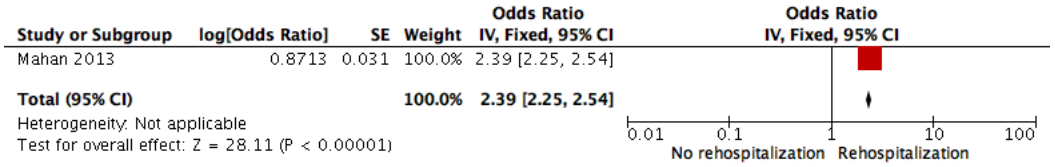
sFigure 2E. Forest plot of low hemoglobin for the outcome bleeding



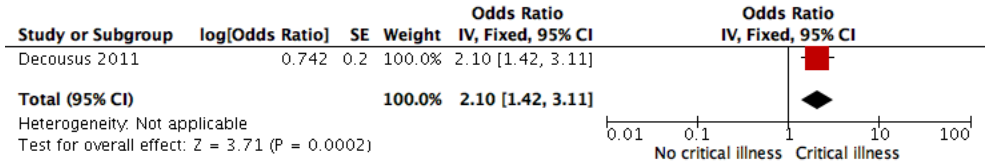
sFigure 2F. Forest plot showing the association between gastro-duodenal ulcers and the outcome bleeding



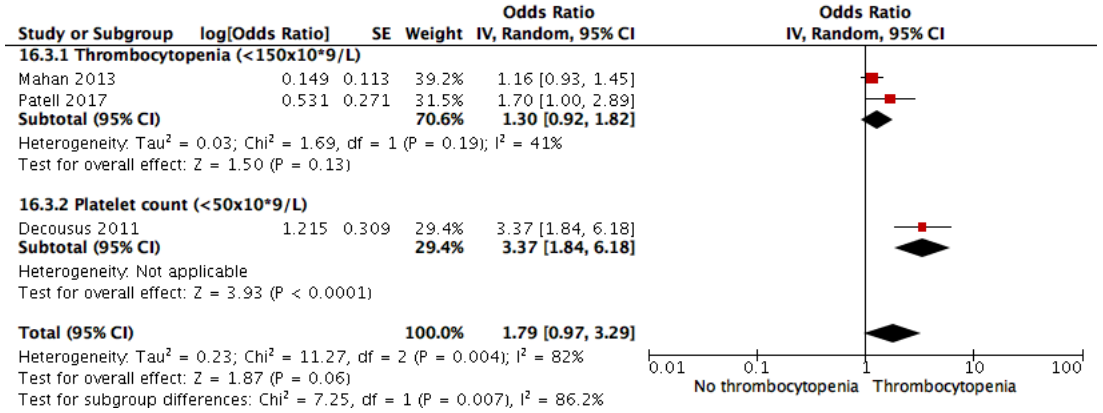
sFigure 2G. Forest plot showing the association between rehospitalisation and the outcome bleeding



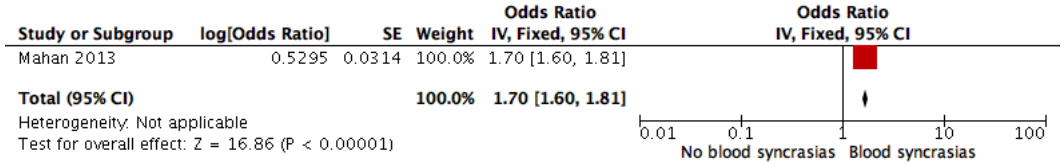
sFigure 2H. Forest plot showing the association between critical illness and the outcome bleeding



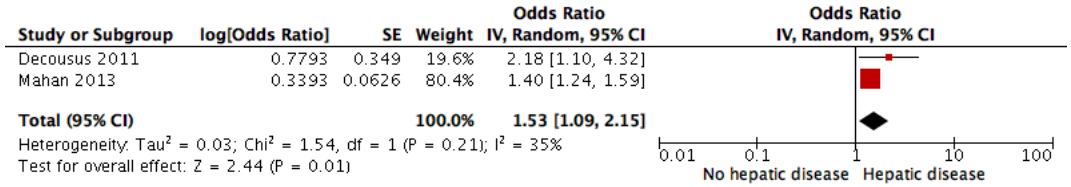
sFigure 2I. Forest plot showing the association between thrombocytopenia and the outcome bleeding



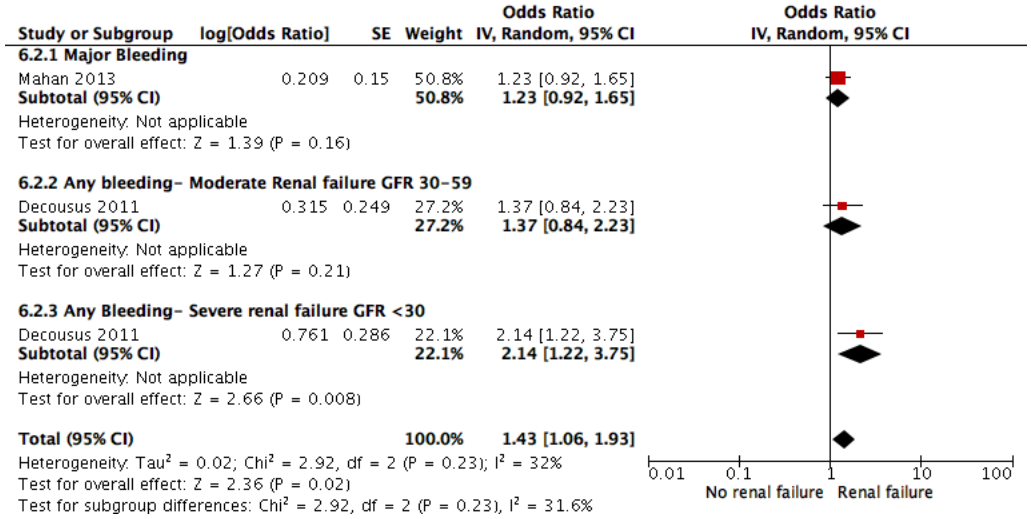
sFigure 2J. Forest plot showing the association between blood dyscrasia and the outcome bleeding



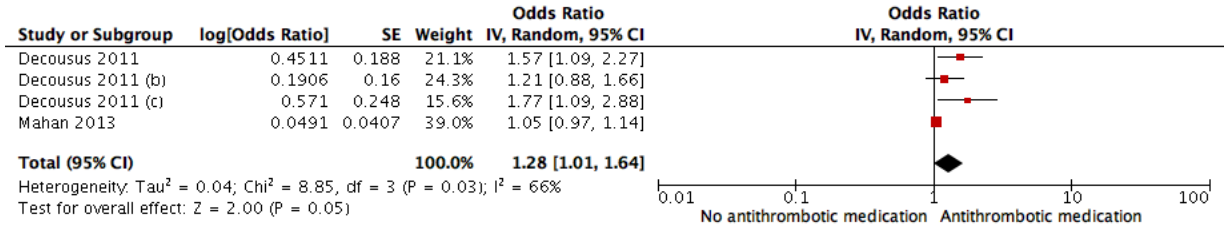
sFigure 2K. Forest plot showing the association between hepatic disease and the outcome bleeding



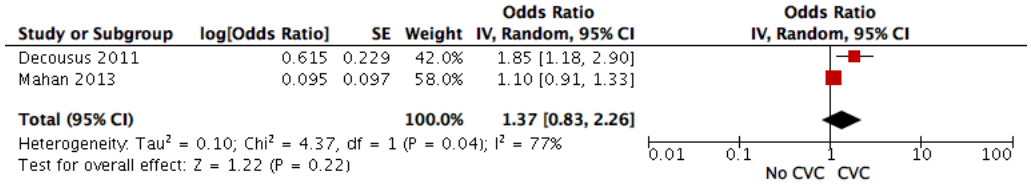
sFigure 2L. Forest plot showing the association between renal failure and the outcome bleeding



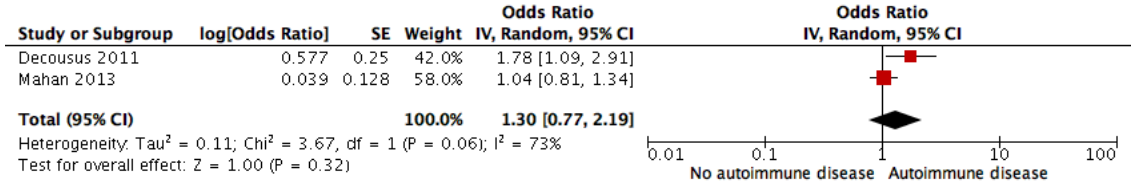
sFigure 2M. Forest plot showing the association between antithrombotic medication and the outcome bleeding



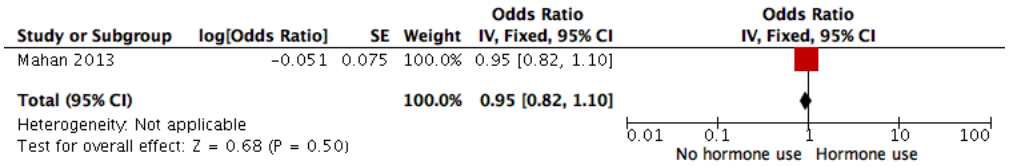
sFigure 2N. Forest plot showing the association between central venous catheters and the outcome bleeding



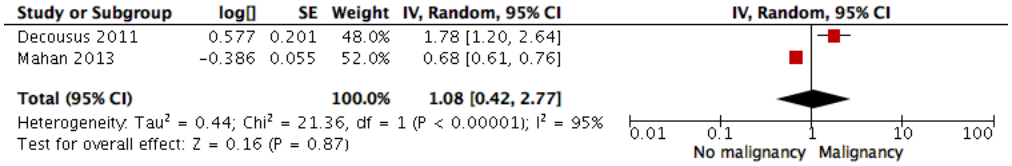
sFigure 2O. Forest plot showing the association between autoimmune disease and the outcome bleeding



sFigure 2P. Forest plot showing the association between hormone use and the outcome bleeding



sFigure 2Q. Forest plot showing the association between malignancy and the outcome bleeding



CHAPTER 4. RISK MODELS FOR VTE AND BLEEDING IN MEDICAL INPATIENTS:

SYSTEMATIC IDENTIFICATION AND EXPERT ASSESSMENT

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Risk models for VTE and bleeding in medical inpatients: Systematic identification and expert assessment

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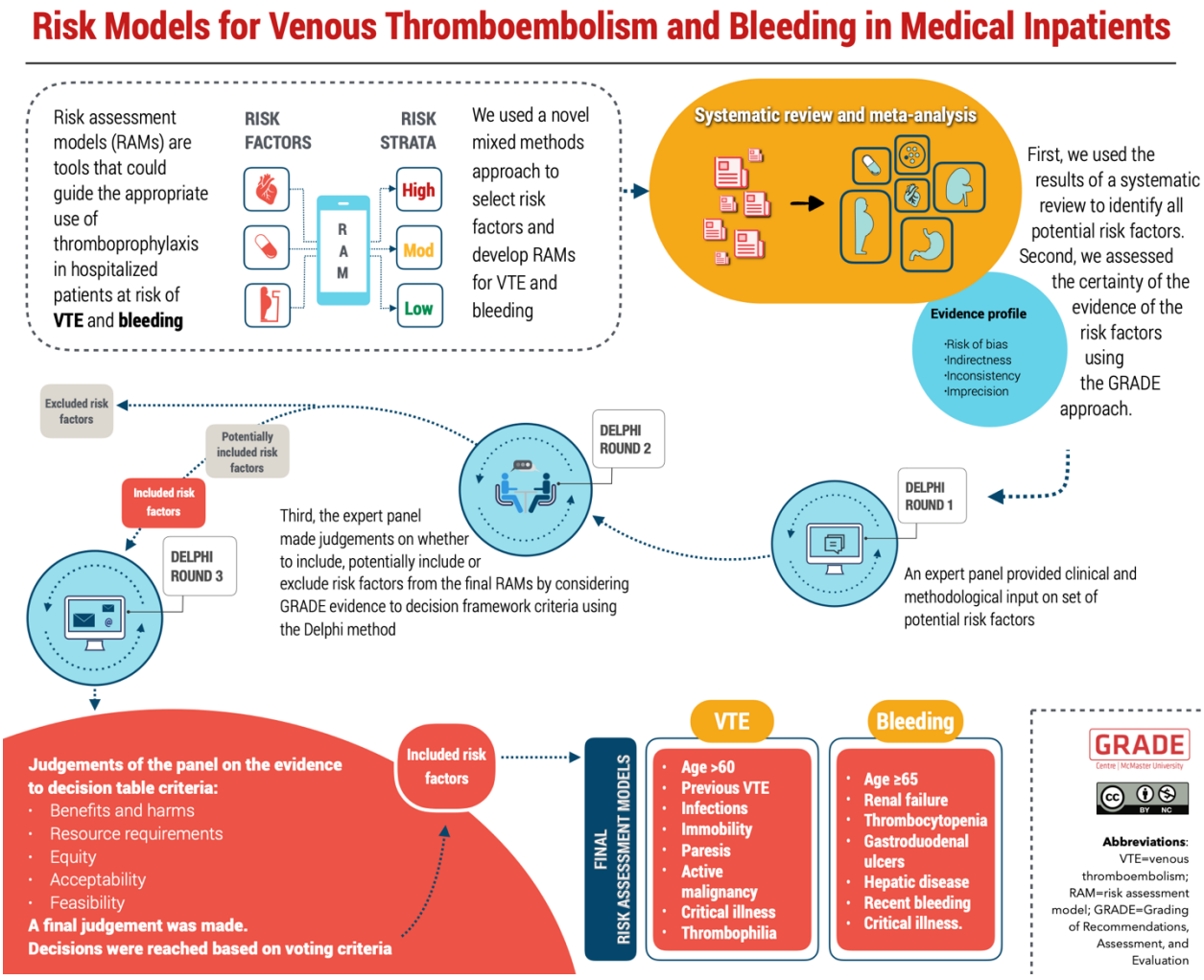
Key points

1. Using novel mixed-methods, we selected risk factors for venous thromboembolism and bleeding RAMs in medical inpatients
2. We also identified risk factors that require further research to confirm or refute their importance in RAMs

Visual abstract



Abstract

Risk assessment models (RAMs) for venous thromboembolism (VTE) and bleeding in hospitalized medical patients inform appropriate use of thromboprophylaxis. Our aim was to select risk factors for VTE and bleeding to be included in RAMs using a novel approach. First, we used the results of a systematic review of all candidate factors. Second, we assessed the certainty of the evidence for the identified factors using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Third, we selected factors to develop the RAMs using a structured approach building on clinical and methodological expertise. The expert panel made judgments on whether to include, potentially include or exclude risk factors using domains of the GRADE approach and the Delphi method. For our VTE RAM we included: age > 60, previous VTE, acute infections, immobility, acute paresis, active malignancy, critical illness and known thrombophilia. For our bleeding RAM we included: age $\geq$ 65, renal failure, thrombocytopenia, active gastroduodenal ulcers, hepatic disease, recent bleeding, and critical illness. We identified acute infection as a factor that was not considered in widely used RAMs. Also, we identified factors that require further research to confirm or refute their importance in a VTE RAM (e.g. D-Dimer). We excluded autoimmune disease which is included in the IMPROVE bleeding RAM. Our results also suggest that sex, malignancy and central venous catheters (factors in the IMPROVE Bleeding RAM) require further research. In conclusion, our study presents a novel

approach to systematically identify and assess risk factors to be included or further explored during RAM development.

Keywords: risk assessment model, prognosis, venous thromboembolism, bleeding, hospitalized medical patients, GRADE, Delphi, clinical expertise.

Introduction

Venous thromboembolism (VTE), comprising deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common cause of morbidity and mortality in hospitalized medical patients. The risk of VTE with hospitalization may increase more than eight-fold (25, 26). Patient and disease-specific risk factors and their interaction modulate the magnitude and duration of the VTE risk in hospitalized medical patients (25). Patients receive thromboprophylaxis to mitigate this risk, but inappropriate use of VTE prophylaxis in low-risk patients may not meaningfully reduce VTE rates and may cause bleeding (25). Knowing a patient's risk of VTE or bleeding will aid health care providers in selecting the appropriate prevention and management options to optimize patient care (1, 2). Risk assessment models (RAM) can help with stratification of an individual patients' risk of developing a VTE or bleeding event and the choice of preventive measures.

The American Society of Hematology (ASH) clinical practice guidelines on VTE prophylaxis for hospitalized and non-hospitalized medical patients described 15 existing RAMs and the authors called for more research to improve and validate them (4, 5, 33). Derived from various studies, most of the identified RAMs were not developed based on a systematic review. This means that while derived from large cohort studies, unmeasured potential risk factors in a specific cohort would have no possibility of being included in a RAM, while they might be captured as a candidate risk factor in a

systematic review. We identified only one systematic review conducted 11 years ago that assessed VTE as an outcome in medical patients, but it did not include a meta-analysis or weighted statistical analysis of the prognostic factors (51).

There are several additional reasons for improving or validating currently existing RAMs. First, RAMs of single studies often rely on statistical significance, and in this setting random variation or lack of power may or may not lead to a risk factor being statistically significant in a prediction model. Second, statistical methods should be complemented by clinical expertise to identify risk factors that are meaningful for health professionals. For example, if a RAM provides inaccurate or poorly calibrated estimates of VTE risk (i.e. it over or under predicts by ignoring clinical context), it may mislead healthcare professionals. Third, the lack of using standardized definitions for risk factors causes confusion across RAMs. For example, Ye et al. examined the various definitions of immobility used in previous studies (26) and observed inconsistencies which makes reproduction and validation of previous studies challenging (26). Fourth, RAMs should be able to accurately predict specific events and still be relatively easy to use. Fifth, there is no universal consensus on use of a specific RAM in hospitalized medical patients, in part because of the above mentioned reasons (68).

Therefore, we employed a novel approach to support the development of new RAMs and inform the update of widely used RAMs for VTE and bleeding in hospitalized acutely, critically and chronically ill medical patients. We first conducted a systematic review of

all relevant risk factors in hospitalized medical patients (16). In tandem, we used extensive clinical and methodological expertise to assess the certainty in the identified risk factors and select them using a structured approach that required clinical expertise.

Methods

Ethics

After the review of the project, the Hamilton Integrated Research Ethics Board (HIERB) waived the need for ethics approval for this study.

Study design

We conducted a study that combined systematic review methods and an assessment of the certainty of the evidence according to GRADE. This work then informed a structured Delphi-based expert judgment to include, potentially include or exclude risk factors for VTE and bleeding in hospitalized medical patients using the GRADE evidence to decision criteria (98). The process is described in Figure 1.

Participants

Expert panel and research team

The expert panel included clinicians and researchers with expertise in management of VTE and bleeding in hospitalized medical patients, and in the development, validation, and implementation of RAMs for clinical practice. Panel members participated in a face to face panel meeting, responded to surveys and questionnaires, and provided feedback on reports. They completed declarations of interest forms to ensure transparency on potentially existing conflicts with regards to existing RAMs and other factors.

The research team selected members of the expert panel using purposive sampling and the following criteria:

- Leading author on a journal article on VTE risk assessment in hospitalized medical patients,
- 2015 CDC healthcare associated-VTE Challenge Champion lead (99),
- Hospital VTE “champion”,
- ASH “Prevention of VTE Nonsurgical Patients” guideline author (5),
- International representation

The research team compiled the evidence for presentation, drafted the questions for the Delphi process, analysed the responses, and summarised the results.

Systematic review

Prior to this study, we conducted a systematic review to identify all potential risk factors for VTE and bleeding in hospitalized medical patients which we describe in detail elsewhere (16). In brief, we searched Medline and EMBASE from inception to May 2018. We considered prognostic factor and RAM studies that identified potential prognostic factors for the outcomes VTE and bleeding in hospitalized adult acutely, critically or chronically ill medical patients. We defined VTE as any symptomatic or asymptomatic DVT or PE within 90 days post discharge. Bleeding included major or non-major but clinically significant bleeding within 90 days post discharge (100, 101). Reviewers extracted data in duplicate and independently and assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (18). The results of the systematic review were used for this study (16).

Delphi process

Delphi Round 1

We asked the expert panel by email to provide input, e.g. identify gaps, on the list of risk factors that we identified through the systematic review. Expert panelists responded confidentially and independently in order not to influence other panel members.

Subsequent Delphi rounds aimed to build on this by requesting that the experts make clinical and methodological judgements based on the available evidence (18, 102).

Evidence to Decision Frameworks

For the second and third round of the Delphi process, we used the GRADEpro Guideline Development Tool (GDT) to facilitate the process (103). The tool includes standardized tables and frameworks:

1. Evidence Profiles. We used these tables during the third round of the Delphi process providing synthesized evidence for each risk factor based on a meta-analysis, and an assessment of the certainty of the evidence rated as high, moderate, low, or very low. We based these ratings on considerations of risk of bias, indirectness, inconsistency, and imprecision (18);
2. GRADE Evidence to Decision frameworks (EtDs). During the second and third round of the Delphi process, we used the following criteria from the EtDs: benefits and harms, resource requirements, equity, acceptability and feasibility, to facilitate the panel's decision-making process (15). These criteria allowed the expert panel to make judgements about the risk factors that were both evidence-based and clinically relevant. While this approach followed good practice in RAM development that suggests attaining high predictability while remaining relatively simple and

applicable in clinical settings, it is novel as it uses a structured approach based on EtD criteria (104, 105).

Delphi Round 2

We held a face to face panel meeting to discuss the systematic review findings and the approach to judge which risk factors should be included in the RAM for VTE and bleeding. We presented the results of the systematic review and the results of the first round of the Delphi process. The results included individual and pooled estimates of the associations and the corresponding confidence intervals for each identified risk factor using forest plots for each meta-analysis. After reviewing the results and discussing resource requirements, equity, feasibility and acceptability, the panel was asked to categorize the risk factors into three sets: 'included', 'potentially included', and 'excluded'. We defined the 'included' risk factors as those that should be included in a RAM. We defined the 'potentially included' factors as potential candidates for consideration in a RAM. The 'excluded' risk factors were those not to be considered for a RAM. Reasons for exclusion included potential interaction with other factors or no association with the outcome.

The research team and the expert panel noted inconsistencies in the definitions of the risk factors across studies and agreed that standardizing the definitions is critical for deciding which ones to include in a RAM, future research, data collection purposes, and most importantly clinical relevance. We standardized the definitions of the included and

potentially included risk factors by reviewing the definitions of the original study as detailed in Tables 6 and 7 of the supplemental material. We then obtained input from the panel to draft suggested definitions.

Delphi Round 3

We conducted a web-based anonymous survey through SurveyMonkey (106). We asked questions after presenting results of the previous round, the assessment of the certainty of the evidence, and a descriptive summary of findings for each risk factor from the systematic review. In this round, we asked the panel members to formally judge the effect estimate of the meta-analysis, the resource requirements, impact on equity, acceptability, and feasibility of each risk factor. Based on these criteria, the panel judged whether these risk factors should be 'included', 'potentially included', or 'excluded'.

We determined a priori that we would make final judgments based on simple majority votes. However, when votes were spread across all three categories and both the 'included' and 'excluded' category had more than one vote each, we determined that the risk factor should be 'potentially included'.

To harmonize the definitions of risk factors, we shared draft definitions with the expert panel based on the literature we identified. We asked them to review the information and provide feedback which we incorporated in final definitions of the risk factors (Table 8 in the supplemental material).

Final Risk Assessment Models

The risk of VTE or bleeding for each individual risk factor was presented as an odds ratio with the relative 95% confidence interval (derived from the meta-analysis). In order to develop the VTE and bleeding RAMs, we log transformed the odds ratios into Beta (β) coefficients and determined the linear predictor (Y) for VTE or bleeding (107). The final RAMs, presented as regression models are given as (107):

$$LP(Y) = \beta_0+\beta_1X_1+\beta_2X_{2\ldots}$$

Where LP is the linear predictor Y of the outcome VTE or bleeding that is derived from the logistic regression model presented above; β_0 is the intercept; β_1 is the Beta coefficient for the first risk factor and X_1 is the first risk factor and so on (107). To determine the contribution of each risk factor to the overall risk of VTE or bleeding, we summed the β coefficients, divided each by the total and multiplied by 100 (Tables 3 and 4). We did not evaluate non-linear logistic regression models.

We then presented a case scenario where we computed the patient-specific risk or predicted probability of VTE, and bleeding based on the formula:

$$P = \frac{Odds}{Odds + 1}$$

Where the odds is the exponent of the linear predictor (Y) ($Odds = e^{y}$) and Y is the linear predictor that was derived from the final RAM. If the risk factor in the RAM is present, X is given a value of 1 and if absent, a value of 0. In the case scenario, we applied a calculated β_0 corresponding to an VTE or bleeding risk of 0% because of the assumption that we would identify all risk factors. Absence of any risk factor would then approach a risk of 0%.

Results

Response rate and participant characteristics

We included nine physicians who are both clinical and methodological experts in the field (MC, MG, HJS, FAS, AS, MBS, SW, NAZ, LM), one of whom is a biostatistician (LM) (108, 109) (Table 1 in the supplemental material). For each of the three rounds of the Delphi process, we achieved a 100% response rate.

Systematic review findings

We identified 17 eligible studies, 14 of which reported on VTE and described 29 candidate prognostic factors (39, 42, 43, 45, 62, 86-89, 92-96) and 3 studies that reported on bleeding and described 17 candidate factors (31, 91, 110). Tables 2 and 3 in the supplemental material provide the evidence profiles for VTE and bleeding related

prognostic factors. A detailed description of the results of the systematic review and corresponding forest plots of the meta-analyses are published elsewhere (16).

VTE model risk factor selection

Delphi Round 1

We listed in Table 1 the 29 potential risk factors identified from the systematic review and the additional three factors suggested by the expert panel for a total of 32. The risk factors were all evaluated at the time of admission except for immobility, acute paresis and critical illness that were assessed both at admission and during the hospital stay.

Delphi Round 2

The panel judged nine of the 32 factors to be included: age, previous VTE, acute infections, immobility, acute paresis, malignancy, critical illness, D-Dimer level, and known thrombophilia. They potentially included the following 14 factors: sex, respiratory failure, severe stroke, autoimmune disease, obesity, thrombocytosis, central venous catheters (CVC) use, leg edema, fever, heart rate, leukocytosis, recent long bone fractures, recent travel and history of heart failure (acute heart failure was excluded). The expert panel excluded renal failure, hormone use, tobacco, and coronary artery disease (CAD) as the results showed little to no association with the outcome VTE. They excluded varicose veins, Low Barthel index score, elevated C-reactive protein (CRP), and fibrinogen levels, since they perceived these risk factors to be non-specific and not

routinely measured in patients admitted to the hospital. They also excluded recent surgery < 30 days prior to admission to focus on medical patients.

Delphi Round 3

Based on our voting criteria, the panel agreed to include the following eight risk factors for the VTE RAM: age > 60 (by consensus), previous VTE (by consensus), acute infections, immobility, acute paresis, active malignancy (by consensus) (past history of malignancy was excluded), critical illness and known history of thrombophilia. The final round of our approach eliminated sex, elevated heart rate and recent air travel from the list of potentially included risk factors (Table 3). The judgements for these factors are detailed in Table 4 in the supplemental material. The panel also agreed on definitions for these risk factors as described in Table 8 of the supplemental material.

Bleeding model risk factor selection

Delphi Round 1

A total of 17 risk factors were candidates based on the systematic review (Table 2). The expert panel agreed and did not suggest any additional factors. The risk factors were all evaluated at the time of admission except for antithrombotic medication use, and re-hospitalization that were assessed post index admission.

Delphi Round 2

During the face to face meeting, the panel judged eight of the 17 factors to be included in the RAM: age ≥ 65, critical illness, thrombocytopenia, active gastroduodenal ulcer in past three months, hepatic disease, recent bleeding, blood dyscrasias and antithrombotic medication use. They agreed that five of the 17 factors could potentially be included: sex, renal failure, malignancy, autoimmune disease and CVC use. The expert panel excluded hormone use, as the results showed little to no association with the outcome bleeding. They excluded obesity due to the low certainty of evidence for risk factor. They also excluded low hemoglobin and re-hospitalization due to very low certainty of evidence, and the lack of specificity with the outcome bleeding.

Delphi Round 3

The panel determined that the following risk factors should be included in the bleeding RAM: age ≥ 65, renal failure, thrombocytopenia (by consensus), active gastroduodenal ulcer in past three months, hepatic disease, recent bleeding, antithrombotic medication use and critical illness. However, we opted not to include antithrombotic medication use as a risk factor in the bleeding RAM since our aim was to develop a RAM that will assist health care professionals in identifying medical patients at admission that may be at increased risk of bleeding with anticoagulants to appropriately weigh benefits and harms before starting treatment. Sex, CVC use, blood dyscrasias and malignancy were rated as potentially included (Table 3) but autoimmune disease was excluded. The judgments for

these factors are detailed in Table 5 in the supplemental material. Table 8 in the supplemental material presents the agreed upon definitions for these risk factors.

Final risk assessment models

We developed the VTE and bleeding RAMs using the included risk factors as detailed in Tables 4 and 5, respectively. Based on these risk factors, their corresponding Beta (β) coefficients, and a baseline VTE or bleeding risk of 0%, the regression models for the linear predictors VTE and bleeding, respectively, are:

$$LP(VTE) = -5.80 + 0.29\ X_{Age>60} + 1.81\ X_{Previous\ VTE} + 0.39\ X_{Acute\ Infections} + 1.15\ X_{Immobility} + 1.09\ X_{Acute\ paresis} + 0.98\ X_{Active\ Malignancy} + 0.50\ X_{Critical\ illness} + 1.77\ X_{Known\ History\ of\ Thrombophilia}.$$

$$LP(Bleeding) = -5.60 + 0.67\ X_{Age\geq 65} + 0.36\ X_{Renal\ failure} + 0.58\ X_{Thrombocytopenia} + 1.01\ X_{Active\ Gastroduodenal\ ulcers} + 0.43\ X_{Hepatic\ disease} + 1.64\ X_{Recent\ bleeding} + 0.74\ X_{Critical\ illness}.$$

The risk factors with the largest contributions to the overall VTE risk (Table 3) are previous VTE (22.6%), known thrombophilia (22.2%), immobility (14.5%) and acute paresis (13.6%), while those with the largest contributions to the overall bleeding risk (Table 4) are recent bleeding (30.2%), active gastroduodenal ulcers in past three months (18.6%) and critical illness (13.7%).

Case scenario

The case scenario suggests how these RAMs can be used in clinical practice. Consider a young acutely ill medical patient ($X_{Age>60}$=0) who is admitted to the hospital for an acute infection ($X_{Acute\ Infection}$=1). The patient has no history of VTE ($X_{Previous\ VTE}$=0), is mobile ($X_{Immobility}$=0), has no acute paresis ($X_{paresis}$=0), no active malignancy ($X_{Active\ Malignancy}$=0), no critical illness ($X_{Critical\ Illness}$=0) and no known history of thrombophilia ($X_{Known\ History\ of\ Thrombophilia}$=0). Based on the VTE RAM, this patient has a linear predictor (y) = -5.41.

Applying the formula to calculate the Odds:

$$Odds = e^{y} = e^{-5.41} = 0.0045$$

Applying the formula for calculating the probability:

$$P = \frac{Odds}{Odds + 1} = \frac{0.0045}{0.0045 + 1} = 0.0045\ (or\ 0.45\%)$$

Therefore, the patient has a VTE probability of around 0.45%.

In terms of the bleeding risk profile, the patient ($X_{Age\geq 65}$=0) reported having known thrombocytopenia ($X_{Thrombocytopenia}$=1), an active gastroduodenal ulcer in the past three months ($X_{Active\ gastroduodenal\ ulcers}$=1), but none of the other risk factors included in the bleeding RAM; that is no recent bleeding episode ($X_{Recent\ bleeding}$=0), impaired renal function ($X_{Renal\ failure}$=0), hepatic disease ($X_{Hepatic\ disease}$=0), or any critical illness ($X_{Critical\ illness}$=0). Based on the developed bleeding RAM, this patient has a linear predictor (y)= -

4.01 which corresponds to a bleeding probability of around 1.8 % based on the above formulas.

One recommendation in the ASH guidelines on VTE prophylaxis in medical inpatients assessed the effect of any parenteral anticoagulation (unfractionated heparin, low molecular weight heparin or fondaparinux) compared to none (5). Based on the results of the meta-analyses, the relative risk was 0.58 for combined symptomatic PE and DVT and 1.48 for major bleeding, respectively (5). Based on the predicted probabilities in the case scenario and on the effects of parenteral anticoagulation on VTE and bleeding, if the above patient were prescribed thromboprophylaxis, the absolute risk of VTE would be reduced by around 0.2% while the absolute risk of bleeding would increase by around 0.9%. This would amount to an absolute risk for VTE of 0.26% and bleeding of 2.66%, respectively.

These risk estimates are useful for implementing the corresponding ASH recommendations regarding acutely or critically ill medical patients: mechanical VTE prophylaxis compared with a combination of pharmacological and mechanical or pharmacological VTE prophylaxis alone (5). Given the bleeding risk and if the patient places a relatively high value on avoiding bleeding complications, the harms would outweigh the benefits. Thus, interpreting the conditional recommendation “In acutely or critically ill medical patients, the ASH guideline panel suggests using pharmacological VTE prophylaxis over mechanical VTE prophylaxis (conditional recommendation, very

low certainty in the evidence of effects.)" (5) would suggest not using pharmacological thromboprophylaxis for this patient. Thus, the following ASH recommendation should be utilized for this patient "In acutely or critically ill medical patients who do not receive pharmacological VTE prophylaxis, the ASH guideline panel *suggests* using mechanical VTE prophylaxis over no VTE prophylaxis (conditional recommendation, moderate certainty in the evidence of effects)." (5)

Discussion

Summary of findings

We used a novel approach to systematically identify and assess risk factors to support the development of a RAM and inform the update of widely used RAMs for VTE and bleeding in hospitalized acutely, critically or chronically ill medical patients. First, we conducted a systematic review of all relevant risk factors in hospitalized medical patients (16). Second, we assessed the certainty of the evidence in identified risk factors. Third, we selected the factors to include in the RAMs, using an innovative structured approach based on GRADE that required extensive clinical and methodological expertise. The expert panel made judgments on whether to include, potentially include or exclude identified risk factors from the final RAMs using the Delphi method based on GRADE criteria. This novel approach allowed us to identify risk factors that should be included in

a RAM and factors that require further exploration. These findings aim to support the development or update of a RAM that can accurately predict specific events while remaining relatively simple and applicable to use in clinical settings. If a RAM provides inaccurate over- or underestimates of future event occurrences, this may lead to mismanagement of patient care and healthcare resources. On the other hand, if a model has high predictability power but is difficult to apply, time consuming, costly or less relevant, it will be not be commonly used. However, these RAMs should be externally validated and should be assessed in prospective impact studies.

Our eight factor VTE RAM was developed based on risk factors assessed at admission and during hospital stay and includes: age > 60, previous VTE, acute infections, immobility, acute paresis, active malignancy, critical illness, and known history of thrombophilia. Our seven-factor bleeding RAM was developed based on risk factors assessed only at admission and includes: age $\geq$ 65, renal failure, thrombocytopenia, active gastroduodenal ulcer in past three months, hepatic diseases, recent bleeding, and critical illness. The potentially included risk factors (Table 3) require further study to confirm or refute their importance for the respective RAMs.

Comparison with other risk assessment models

We developed RAMs for VTE and bleeding in hospitalized medical patients that were similar but not identical to some widely used RAMs in current practice such as IMPROVE

VTE RAM, IMPROVE Bleeding RAM, Intermountain RAM, MITH RAM and PADUA VTE RAM (31, 36, 45, 47, 62). Compared to the IMPROVE VTE RAM, acute infection was an additional important risk factor (45). Also, we identified 12 additional candidate risk factors, five of which were considered in other VTE RAMs including: CVC use in the Intermountain RAM (47), respiratory failure and heart failure in the PADUA and MITH VTE RAMs, severe stroke in the PADUA VTE RAM, and thrombocytosis and leukocytosis in the MITH RAM (36, 62). Compared to the PADUA model, we found that coronary artery disease does not predict VTE risk and obesity requires further research (36). As for risk of bleeding, our RAM suggests that autoimmune disease did not predict bleeding risk due to conflicting results in the included studies (31). Also, we did not include sex, malignancy and CVC use, that are included in the IMPROVE Bleeding RAM, as we judged that these were candidate risk factors that require further exploration (31).

Strengths

Our study is based on rigorous methods that is innovative for several reasons. First, the systematic review conducted by our group and the input from the expert panel in comprehensively identifying all potential risk factors, is a limitation of cohort studies. Second, assessing the certainty of the evidence based on a structured framework allowed for an expression of the confidence in the predictive ability of the factors. Third, the expert panel made judgements on the inclusion of risk factors into the RAMs using GRADE criteria by accounting for their resource requirements, impact on equity,

acceptability, and feasibility which are all relevant in clinical practice. Fourth, we are not aware of prior use of this approach to developing RAMs. Fifth, we also standardized the definitions of the included and potentially included risk factors to decrease variability in methods of measurement across settings. Standardized definitions will provide more clarity to health care professionals, including researchers, when evaluating and weighing patients' risks of VTE and bleeding and subsequent management options. Our work also strongly suggests the need to standardize definitions of risk factors if we are to make further progress in this area.

Limitations and challenges

Potential limitations of the systematic review findings are the inconsistency and variability across eligibility criteria in the included studies and variability in study design, study type, sample size, and definitions of the risk factors. Other limitations included the inconsistency in the diagnostic approaches employed across studies and contamination of the population with non-medical hospitalized patients for some of the risk factors. We were unable to conduct a meta-regression to adjust for study level characteristics as the number of studies was too small for this analysis. Also, we did not conduct an external validation which is an essential next step. However, validation is a continuous process and our approach should be viewed as a method to validate the content of current widely used RAMs. For example, our VTE RAM validated the findings in the IMPROVE

VTE RAM and also highlighted the need to include acute infection as an additional factor as well as a list of candidate factors that require further evaluation.

Implications for practice

The findings of this study can aid in RAM development or their updating. Our findings can also help health care professionals in evaluating the risk for VTE from index admission till discharge and the risk of bleeding on admission in hospitalized medical patients for optimal patient management. Ideally, this can be achieved by integrating the RAMs in clinical decision aids to assist with deriving individual-based recommendations from published population-based guideline recommendations for shared decision-making.

Implications for future research

Our developed RAMs should be tested in an external validation study using individual patient data sets. This will be essential prior to conducting an impact analysis that would allow them to be adopted in routine clinical practice. Also, the “potentially included” risk factors should be explored further in future research. We standardized the definitions of the risk factors to help researchers build more uniform datasets and registries. Decreasing variability will facilitate the reproduction and validation of studies across settings.

Reviewing the work done and based on discussions with the expert panel, we noted that a risk assessment for VTE and bleeding only on admission is insufficient and will not account for change in risk factors throughout hospitalization. For example, transferring a patient from a medical ward to the ICU or development of acute renal failure or acute infection may change their risk level. Therefore, developing a system for dynamic risk assessment of hospitalized medical patients from admission to discharge is important. The shortening hospital length of stays, the lack of routine post-discharge thromboprophylaxis, and the recent availability of thromboprophylactic agents that can be used for extended thromboprophylaxis in hospitalized medical patients makes testing our proposed VTE RAM for dynamic use especially important.

Conclusion

We employed a novel structured approach to select risk factors for VTE and bleeding in hospitalized medical patients that are evidence-based, clinically meaningful and relevant. Our findings aim to support the development of new RAMs and the update of widely used RAMs. also, our findings aim to inform external validation and prospective impact assessment studies to evaluate the performance of these RAMs in assessing VTE and bleeding risk for this population. These findings may assist decision makers in weighing the risk of VTE with that of bleeding to appropriately select VTE prevention strategies and optimize patient care for different patient risk groups.

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Authorship contributions

Conception and design: AJD, HJS

Data acquisition: AJD, SGK, FG, MR, HJS

Data analysis: AJD, LM, MR, HJS

Interpretation of results: AJD, SGK, FAS, ACS, LM, SCW, NAZ, MBS, MKG, MC, RC, IEI, FG, MR, AA, RZM, EAA, AI, HJS

Manuscript drafting: AJD, HJS

Critical revision of the manuscript and approval of the final version: AJD, SGK, FAS, ACS, LM, SCW, NAZ, MBS, MKG, MC, RC, IEI, FG, MR, AA, RZM, EAA, AI, HJS

Disclosure of Conflicts of Interest

Authors AJD, IEI, AI, EAA and HJS reported that they are members of the GRADE working group. HJS reported being co-chair of the American Society of Hematology (ASH) 2018 guidelines for prophylaxis for hospitalized and non-hospitalized medical patients and

grant funding from the CDC for this study. ACS reported receiving remuneration for consulting work for Bayer, Janssen, Portola and research support grants from Boehringer Ingelheim, Janssen, Centre for Medicare and Medicaid services. ACS also reported intellectual conflict as the lead in the group that derived and validated the IMPROVE VTE tool for venous thromboembolism (VTE) risk assessment in hospitalized medical patients. MBS reported receiving remuneration for consulting work for Bayer, Janssen, Pfizer and Portola and research support grants from Boehringer-Ingelheim, Janssen, Portola and Roche. MC reported being a former board director (2013-17) of the American Heart Association and chairing the American Society of Hematology (ASH) 2018 guidelines for management of VTE: prophylaxis for hospitalized and non-hospitalized medical patients. FAS and NAZ reported participating as panel members for the ASH 2018 guidelines for management of VTE: prophylaxis for hospitalized and non-hospitalized medical patients. NAZ also reported receiving honoraria in 2017 from ASH for the Highlights of ASH 2017 meeting (Dallas, New York, Latin America). SCW reports service as Co-Chair of the American College of Chest Physicians Guideline Panel on treatment for thrombotic disease. NAZ and MC reported intellectual conflicts as leads in the group that derived and validated the MITH RAM for VTE risk assessment in hospitalized medical patients. LM and MKG declared having no competing interests.

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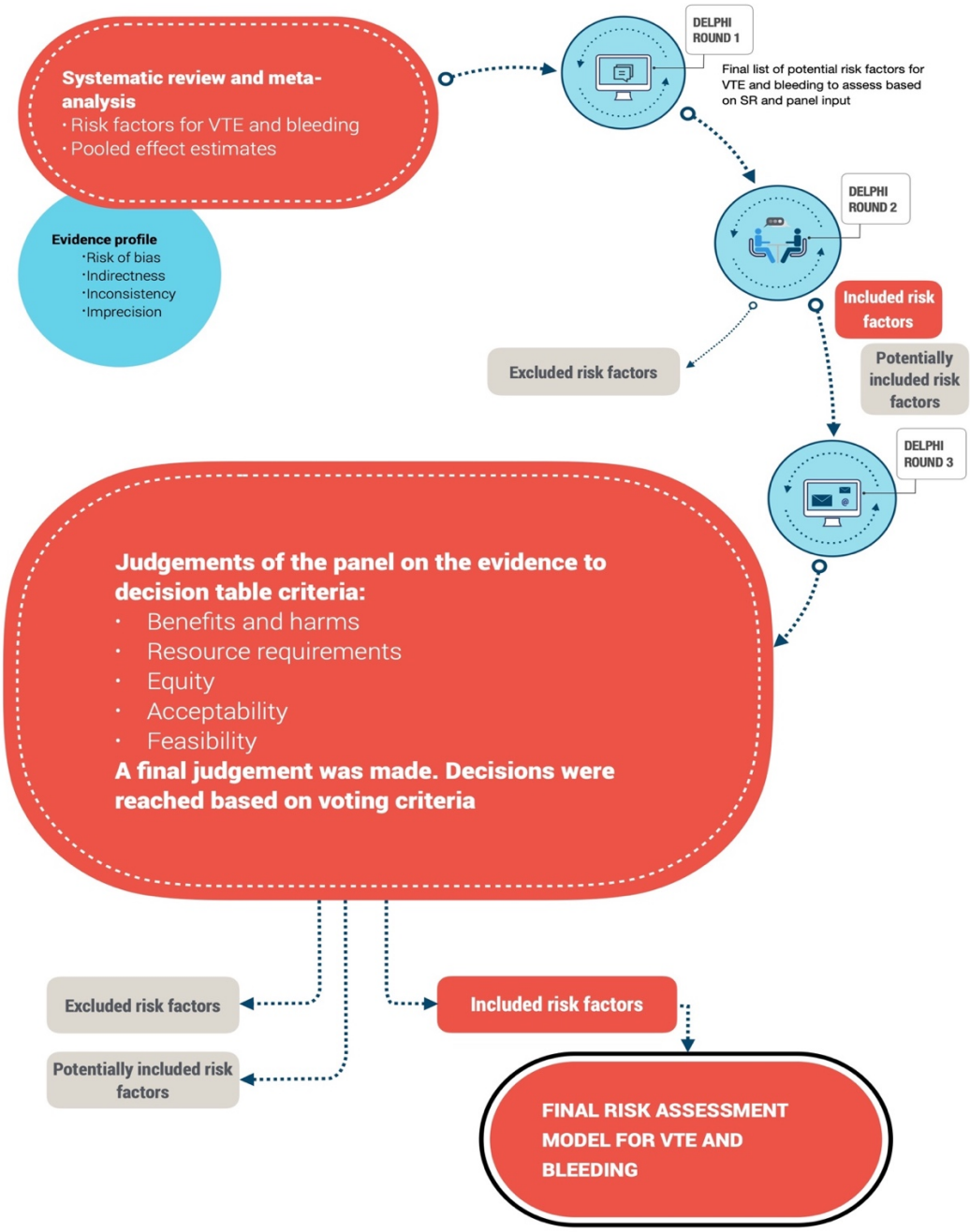
Figures

Figure 1. Flow chart of our approach to develop risk assessment models



Tables

Table 1. List of risk factors from empirical evidence and panel input for the outcome

VTE

Source	Risk Factors	
Included studies in the systematic review	1. Age > 60 2. Sex 3. Previous VTE 4. Acute infection 5. Respiratory failure 6. Renal failure 7. Immobility* 8. Acute paresis* 9. Severe stroke 10. Malignancy 11. Critical illness* 12. D-Dimer 13. Autoimmune disease 14. Obesity 15. Hormone use	16. Known history of thrombophilia 17. Thrombocytosis 18. Central venous catheter use 19. Varicose veins 20. Leg edema 21. Tobacco 22. Coronary artery disease 23. Heart failure 24. Fever 25. Elevated heart rate 26. Leukocytosis 27. Low Barthel index score 28. Elevated C-Reactive Protein 29. Fibrinogen levels
Panel input	1. Recent surgery < 30 days prior to admission 2. Recent long bone fractures 3. Recent air travel	

*Immobility, acute paresis and critical illness are risk factors that were assessed both at admission and during hospital stay

Table 2. List of risk factors from empirical evidence and panel input for the outcome bleeding

Source	Risk Factors	
Included studies in the systematic review	1. Age ≥ 65 2. Sex 3. Renal failure 4. Malignancy 5. Critical illness 6. Autoimmune disease 7. Obesity 8. Hormone use 9. Thrombocytopenia	10. Central venous catheter use 11. Active gastroduodenal ulcers in past three months 12. Hepatic disease 13. Antithrombotic medication use* 14. Re-hospitalization* 15. Blood dyscrasias 16. Recent bleeding 17. Low hemoglobin
Panel input	None	

*Antithrombotic medication use, and re-hospitalization are risk factors that were assessed post admission.

Table 3. Potentially included risk factors for VTE and bleeding

Outcome	Risk Factors
Risk of VTE	1. Respiratory failure 2. Severe stroke 3. Elevated D-dimer 4. Autoimmune disease 5. Obesity 6. Thrombocytosis 7. Central venous catheter use 8. Leg edema 9. History of heart failure 10. Fever 11. Leukocytosis 12. Recent long bone fracture
Risk of Bleeding	13. Sex 14. Central venous catheter use 15. Blood dyscrasias 16. Malignancy

Table 4. VTE risk assessment model

Included risk factors	OR (95% CI) from systematic review	Beta (β) coefficients (log OR)	SE	% contribution to overall VTE risk
Age > 60	1.34 (1.17-1.55)	0.29	0.07	3.6%
Previous VTE	6.08 (3.71-9.97)	1.81	0.25	22.7%
Acute infections	1.48 (1.16-1.89)	0.39	0.12	4.9%
Immobility	3.17 (2.18-4.62)	1.15	0.19	14.4%
Acute paresis	2.97 (1.20-7.36).	1.09	0.46	13.6%
Active malignancy	2.65 (1.79-3.91)	0.98	0.20	12.3%
Critical illness	1.65 (1.39-1.95)	0.50	0.09	6.3%
Known history of thrombophilia	5.88 (2.80-12.35)	1.77	0.38	22.2%
Total		7.98		

Table 5. Bleeding risk assessment model

Included risk factors	OR (95% CI) from systematic review	Beta (β) coefficients (log OR)	SE	% contribution to overall bleeding risk
Age ≥ 65	1.95 (1.59-2.38)	0.67	0.10	12.3%
Renal failure	1.43 (1.06-1.93)	0.36	0.15	6.6%
Thrombocytopenia	1.79 (0.97-3.29)	0.58	0.31	10.7%
Active gastroduodenal ulcers	2.74 (1.42-5.26)	1.01	0.34	18.6%
Hepatic disease	1.53 (1.09-2.15)	0.43	0.17	7.9%
Recent bleeding	5.15 (2.45-10.81)	1.64	0.38	30.2%
Critical illness	2.10 (1.42-3.11)	0.74	0.20	13.7%
Total		5.43		

Appendices

Supplemental Table 1. List of panel members and their affiliation and involvement

Name	Institution	Involvement
Holger J. Schünemann	McMaster University, Canada	Clinician, chair, principal investigator
Mary Cushman	University of Vermont, USA	Clinician and content expert
Neil A. Zakai	University of Vermont, USA	Clinician and content expert
Frederick A. Spencer	McMaster University, Canada	Clinician and content expert
Alex C. Spyropoulos	Northwell Health at Lenox Hill Hospital, USA	Clinician and content expert
Michael B. Streiff	John Hopkins, USA	Clinician and content expert
Michael K. Gould	Kaiser Permanente, USA	Clinician and content expert
Lawrence Mbuagbaw	McMaster University, Canada	Biostatistician (methodological expert)
Scott C. Woller	University of Utah School of Medicine, USA	Clinician and content expert

Supplemental Table 2. Evidence profile for VTE related prognostic factors

Question: Prognostic factors for medical patients

Outcome: VTE

Setting: Inpatient

Bibliography: see below

№ of studies	**Certainty assessment domains**						**Overall certainty in the evidence about this prognostic factor**	**Relative effect (95% CI)**
	Study design	**Risk of Bias**	**Indirect**	**Inconsistent**	**Imprecise**	**Publication bias**		
Age (>60 compared to <60) (39, 42, 43, 45, 62, 87, 89, 94, 96)								
9 [g]	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	Age as categorical: >60 years: OR 1.34 (95%CI 1.17-1.55)
Sex (male compared to female) (43, 62, 92-94)								
5	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	Male vs female: OR 1.03 (95%CI: 0.80-1.33)
C- Reactive protein (CRP) (CRP >10mg/l compared to CRP <10mg/l) (92)								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 10.10 (95%CI 1.93-52.85)
D-Dimer (>500ng/mL at baseline compared to <500ng/mL at baseline; and increase compared to no increase) (93, 96)								
2	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	Categorical: OR 2.46 (95%CI 1.19-5.10)

								Continuous: OR 3.45 (95%CI 2.01-5.92)
Heart rate (elevated >100 beats per minute compared to non-elevated <100 beats per minute) (62)								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 2.48 (95%CI 1.66-3.71)
Thrombocytosis (platelet count >350x10*9/L compared to platelet count <350x10*9/L) (62, 86)								
2	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 2.16 (95%CI 1.40-3.35)
Leukocytosis (WBC ≥11x109/L compared to WBC <11x109/L) (62)								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.91 (95%CI 1.24-2.94)
Fever (body temperature >38-38.5°C compared to body temperature <38-38.5°C) (62, 86)								
2	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.88 (95%CI 1.10-3.21)
Leg edema (presence compared to absence) (86, 89)								
2	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.88 (95%CI 1.23-2.90)
Varicose veins (presence compared to absence) (87, 89)								
2	Observational	Serious [a]	Not serious	Not serious	Serious [b]	Undetected	⊕⊕◯◯ LOW	OR 1.53 (95%CI 0.85-2.76)
Obesity (obesity with BMI >30 kg/m^2 compared to no obesity) (43, 62, 87)								
3	Observational	Serious [a]	Not serious	Not serious	Serious [b]	Undetected	⊕⊕◯◯ LOW	OR 1.34 (95%CI 0.94-1.91)
Fibrinogen levels (elevated levels >400 mg/dl) compared to no elevated levels) (92)								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 0.18 (95%CI 0.04-0.81)

Barthel Index (BI) score (BI ≤9 compared to BI >9) (94, 96)								
2	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 8.30 (95%CI 2.70-25.52)
Immobility: defined as confinement to bed for >72h or >7days or bedridden or non-ambulatory (yes compared to no) (42, 45, 62, 86, 87, 89, 94, 96)								
8	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 3.17 (95%CI 2.18-4.62)
Paresis (yes compared to no) (39, 42, 45, 94)								
4	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 2.97 (95%CI 1.20-7.36)
Previous VTE (yes compared to no) (39, 42, 45, 62, 87-89, 93)								
8	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 6.08 (95%CI 3.71-9.97).
Known history of thrombophilia (familial or acquired disorder of the hemostatic system) (yes compared to no) (39, 42, 43, 45, 87)								
5	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 5.88 (95%CI 2.80-12.35)
Malignancy (active malignancy (defined as the presence of cancer on admission or within the past year) compared to no active malignancy; and past history compared to no past history of malignancy) (39, 42, 43, 45, 62, 86, 88, 89, 93, 94)								
10	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	Active cancer: OR of 2.65 (95%CI 1.79-3.91) Past history of cancer: 3.20 (95%CI 2.14-4.79)
Critical illness: defined as intensive care unit (ICU) or coronary care unit (CCU) stay, or need for resuscitation (yes compared to no) (39, 42, 43, 45, 62, 87, 93)								
7	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.65 (95%CI 1.39-1.95)
Infections: including cellulitis, pneumonia and sepsis (yes compared to no) (86, 89)								

5	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	Any infection: OR 1.48 (95%CI 1.16-1.89) a) Acute infection: OR 1.59 (95%CI 1.23-2.06 b) Sepsis: OR 1.07 (95%CI 0.70-1.62)
Heart failure (HF) (acute HF compared to no acute HF; history of HF compared to no history of HF) (86, 87, 89, 92, 93)								
5	Observational	Serious	Not serious	Not serious	Serious [b]	Undetected	⊕⊕◯◯ LOW	Acute heart failure: OR 0.82 (95%CI 0.42-1.60) History of heart failure: OR 2.68 (95%CI 1.11-6.44)
Autoimmune disease: including rheumatological diseases and inflammatory diseases (yes compared to no) (43, 62, 87, 89)								
4	Observational	Serious [a]	Not serious	Serious	Not serious	Undetected	⊕⊕◯◯ LOW	OR 2.33 (95%CI 1.13-4.83)
Central venous catheters (CVC) (presence compared to absence) (43, 89)								
2	Observational	Serious	Not serious	Serious [d]	Not serious	Undetected	⊕⊕◯◯ LOW	OR 2.05 (95%CI 0.74-5.65)
Severe stroke: defined as acute ischemic stroke (yes compared to no) (87, 89, 90, 93)								
4	Observational	Serious [a]	Not serious	Not serious	Serious [b]	Undetected	⊕⊕◯◯ LOW	Acute ischemic stroke: OR 1.79 (95%CI 0.77-4.18) When stroke was assessed in terms of the NIH Stroke Scale (NIHSS), we found consistent results [f].
Tobacco (current use compared to no current use; previous use compared to no previous use) (92)								

1	Observational	Serious	Not serious	Not serious	Serious [b]	Undetected	⊕⊕◯◯ LOW	Current tobacco use: OR 1.59 (95%CI 0.28-9.03) Previous tobacco use: OR 0.97 (0.24-3.92)
Hormone use: defined as estrogen intake (yes compared to no) (89)								
1	Observational	Serious	Not serious	Not serious	Serious [b]	Undetected	⊕⊕◯◯ LOW	OR 0.80 (95%CI 0.36-1.78).
Renal failure [w] (yes compared to no) (93)								
1	Observational	Serious [c]	Not serious	Not serious	Very Serious [b, e]	Undetected	⊕◯◯◯ VERY LOW	OR 0.76 (95%CI 0.18-3.18)
Respiratory failure (yes compared to no) (62, 87, 89, 93)								
4	Observational	Serious [a]	Not serious	Not serious	Serious [b]	Undetected	⊕⊕◯◯ LOW	Any respiratory failure: OR 1.04 (95% 0.69-1.58). a) acute respiratory failure: OR 1.18 (95%CI 0.76-1.84) b) chronic respiratory failure: OR 0.58 (95% 0.30-1.10).
Coronary artery disease (CAD) (yes compared to no) (87, 89, 93, 94)								
4	Observational	Serious [a]	Not serious	Serious [d]	Not serious	Undetected	⊕⊕◯◯ LOW	OR 1.01 (95%CI 0.33-3.09)

Explanations

a. Certainty in evidence was downgraded for risk of bias given a follow-up time of more than three months in the included studies that may cause an overestimation of the magnitude of the association (Zhou 2018: 6 months after discharge and Yi 2012: 12 months after discharge)
b. Certainty in evidence was downgraded for imprecision given the confidence interval suggests that there may be no association.
c. Certainty in evidence was downgraded for risk of bias given that a results of each prognostic factor in the multivariate analysis were not reported and therefore we had to rely on the unadjusted measures of association. Also, the multivariate analysis only included factors statistically significant in the univariate analysis.
d. Certainty in evidence was downgraded for inconsistency but not imprecision given the inconsistency is the likely cause for the imprecision.
e. Certainty in evidence was downgraded for imprecision given the small number of events (n=32)

f. Bembenek 2012 assessed the severity of a stroke experienced by an individual by using the NIH Stroke Scale (NIHSS), a diagnostic tool, results showed consistent results with the meta-analysis that severe stroke may result in an increase in risk of any DVT (OR 2.11; 95%CI: 0.50-8.90) for NIHSS >7 compared with a NIHSS score <7. Also, severe stroke may result in an increase in risk of any DVT (OR 1.34; 95%CI: 0.25-7.18) for NIHSS > 14 compared with a NIHSS < 14 (92). When NIHSS was assessed continuously, results showed that severe stroke may result in an increase in risk of any DVT (OR 1.21; 95%CI: 0.86-1.70) for each additional 4 points on the NIHSS scale.

g. Fan et al., with 458 patients older than 60 years of which 45 patients had any VTE, presented age as a continuous variable and showed no association between age and any VTE with an OR of 1.03 (95%CI 0.98-1.08). Another study by Bembenek et al., with 299 patients of which 9 had any DVT, 7 of which were distal, presented age per 10 year increase and showed a decrease in risk per 10 year increase in age with any DVT with an OR of 0.64 (95%CI 0.33-1.24).

Supplemental Table 3. Evidence profile for the Bleeding related prognostic factors

Question: Prognostic factors for medical patients

Outcome: Bleeding

Setting: Inpatient

Bibliography: see below

№ of studies	Certainty assessment domains						Overall certainty in the evidence about this prognostic factor	Relative effect (95% CI)
	Study design	Risk of Bias	Indirect	Inconsistent	Imprecise	Publication bias		
Age (≥65 compared to <65) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	Age ≥ 65: OR: 1.95 (95CI% 1.59-2.38)
Sex (male compared to female) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.27 (95%CI 1.09-1.47).
Anemia as a reason for admission (presence compared to absence) (91)								
1	Observational	Serious [c]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 7.78 (95%CI 4.00-15.13)
Morbid obesity (BMI ≥40 kg/m2 compared to BMI < <40 kg/m2) (91)								
1	Observational	Serious [c]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 3.08 (95%CI 1.35-7.02)

Low hemoglobin: defined as <13 gm/dl for males and <11.5 gm/dl for females (yes compared to no) (91)								
1	Observational	Serious [c]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 2.33 (95%CI 1.04-5.22)
Gastroduodenal ulcers (yes compared to no) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 2.74 (95%CI 1.42-5.26)
Rehospitalisation (yes compared to no) (90)								
1	Observational	Serious [b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 2.39 (95% 2.25-2.54)
Critical illness (yes compared to no) (31)								
1	Observational	Serious [a]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 2.10 (95%CI 1.42-3.11).
Thrombocytopenia (yes compared to no) (31, 90, 91)								
3	Observational	Serious [a,b,c]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	All: OR 1.79 (95%CI 0.97-3.29) a) <50 x109 /L: OR 3.37 (95%CI 1.84-6.18) b) <150 x109 /L :OR 1.30 (95%CI 0.92-1.82)
Blood dyscrasias defined as the presence of any bleeding disorders on admission (presence compared to absence) (90)								
1	Observational	Serious [b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.70 (95%CI 1.60-1.81)
Hepatic disease (yes compared to no) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.53 (95%CI 1.09-2.15)
Renal failure (yes compared to no) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	Total: OR 1.43 (95%CI 1.06-1.93) Any renal failure (RF): OR 1.23 (95%CI 0.92-1.65).

								Moderate RF (GFR<30): OR 1.37(95%CI 0.84-2.23) Severe RF (GFR<30): OR 2.14 (95%CI 1.22-3.75)
Antithrombotic medication (yes compared to no) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 1.28 (95%CI 1.01-1.64)
Central venous catheters (yes compared to no) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	1.37 (95%CI 0.83-2.26)
Autoimmune disease (yes compared to no) (31)								
2	Observational	Serious [a]	Not serious	Not serious	Serious [d]	Undetected	⊕⊕◯◯ LOW	OR 1.30 (95%CI 0.77-2.19)
Hormone use: defined as estrogen intake (yes compared to no) (90)								
1	Observational	Serious [b]	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ MODERATE	OR 0.95 (95%CI 0.82-1.10)
Malignancy (yes compared to no) (31, 90)								
2	Observational	Serious [a,b]	Not serious	Not serious	Serious [d]	Undetected	⊕⊕◯◯ LOW	OR 1.08 (95%CI 0.42-2.77).

Explanations

a. Certainty in evidence was downgraded for risk of bias given patients were enrolled both prospectively and retrospectively in the Decousus et al. study. The retrospective enrollment of patients may have introduced classification bias.

b. Certainty in evidence was downgraded for risk of bias given the authors evaluated bleeding risk in medical patients after hospitalisation, that may overestimate the magnitude of the association. This is possibly due to patients being discharged on thromboprophylaxis without proper risk stratification for bleeding placing unmonitored patients at a higher risk of having a bleeding event.

c. Certainty in evidence was downgraded for risk of bias given the population is specific to hospitalized cancer patients that are at a higher risk of VTE and may be given thromboprophylaxis placing them at a higher risk of having a bleeding event. This in turn may overestimate the magnitude of the association.

d. Certainty in evidence was downgraded for imprecision given the confidence interval suggests that there may be no association

Supplemental Table 4. Delphi process round 3 survey results for VTE

Risk Factors (Judgement in Round 2 of Delphi process)	Resources required: How large are the resource requirements (costs)?	Equitable: Would the factor have an impact on health equity?	Acceptable: Is the risk factor acceptable to key stakeholders?	Feasible: Is the risk factor feasible to assess?	Final judgement by participants	Major Vote
Age (Included)	Trivial (7); Small (1)	Yes (4); No (4); Probably yes (1)	Yes (7); Probably no (1)	Yes (8)	Included (consensus: 8/8)	Included list
Sex (Potentially included)	Trivial (7); Small (1)	No (3); Probably yes (3); Yes (2)	Yes (7); Probably no (1)	Yes (8)	Excluded (6); Included (2)	Excluded
Previous VTE (Included)	Trivial (3); Small (4); Moderate (1)	Yes (3); No (3); Probably no (2)	Yes (8)	Yes (5); Probably yes (3)	Included (consensus: 8/8)	Included list
Infections (Included)	Trivial (2); Small (2); Moderate (4)	No (4); Probably no (2); Probably yes (1); Yes (1)	Yes (4); Probably yes (4)	Yes (4); Probably yes (3); Probably no (1)	Included (6); Potentially included (2)	Included list
Acute respiratory failure (Potentially included)	Trivial (4); Small (3); Moderate (1)	No (5); Probably no (1); Probably yes (1); Yes (1)	Yes (7); Probably yes (1)	Yes (4); Probably yes (4)	Included (3); Excluded (3); Potentially included (2)	Potentially included list
Immobility (Included)	Moderate (3); Trivial (3); High (1); Small (1)	No (4); Probably no (2); Probably yes (1); Yes (1)	Yes (5); Probably yes (3)	Probably yes (5); Yes (2); Probably no (1)	Included (7); Potentially included (1)	Included list
Paresis (Included)	Moderate (4); Trivial (3); Small (1)	No (4); Probably no (2); Probably yes (2)	Yes (5); Probably yes (1); Probably no (2)	Yes (3); Probably no (2); Probably yes (3)	Included (6); Potentially included (2)	Included list
Severe stroke (Potentially included)	Moderate (4); High (1); Trivial (2);	No (3); Probably no (2); Probably yes (2); Yes (1)	Yes (4); Probably no (2); Probably yes (2)	Probably yes (2); Yes (3); Probably no	Potentially included (5); Excluded (1);	Potentially included list

	Small (1)			(2); No (1)	Included (2)	
Active Malignancy (Included)	Small (4); Moderate (2); Trivial (2)	No (4); Probably no (2); Probably yes (1); Yes (1)	Yes (6); Probably yes (2)	Yes (6); Probably yes (2)	Included (Consensus: 8/8)	Included list
Critical illness (Included)	Trivial (3); Moderate (3); High (1); Small (1)	No (5); Probably no (2); Probably yes (1)	Yes (4); Probably yes (3); Probably no (1)	Yes (3); Probably no (2); Probably yes (3)	Included (6); Potentially included (2)	Included list
D-Dimer (Included)	High (4); Trivial (2); Small (1); Moderate (1)	No (4); Probably no (1); Probably yes (2); Yes (1)	Probably no (4); Yes (2); No (1); Probably yes (1)	Probably yes (4); Yes (2); No (2)	Potentially included (4); Excluded (3); Included (1)	Potentially included list
Autoimmune disease (Potentially included)	High (2); Small (2); Trivial (2); Moderate (2)	No (4); Probably no (3); Probably yes (1)	Yes (3); Probably no (2); Probably yes (3)	Probably yes (4); Yes (3); Probably no (1)	Potentially included (6); Excluded (1); Included (1)	Potentially included list
Obesity (Potentially included)	Trivial (5); Small (2); Moderate (1)	No (5); Yes (2); Probably no (1)	Yes (5); Probably yes (3)	Yes (6); Probably yes (2)	Potentially included (4); Excluded (1); Included (3)	Potentially included list
Thrombophilia (Included)	High (3); Moderate (3); Small (1); Trivial (1)	No (4); Probably yes (2); Yes (2)	Yes (4); Probably no (2); Probably yes (2)	No (3); Probably yes (2); Yes (2); Probably no (1)	Included (6); Potentially included (1); Excluded (1)	Included list
Thrombocytosis (Potentially included)	Small (4); Trivial (4)	No (4); Probably no (1); Probably yes (1); Yes (2)	Probably yes (4); Yes (3); Probably no (1)	Yes (6); Probably yes (2)	Potentially included (4); Excluded (1); Included (3)	Potentially included list
Central venous catheter (Potentially included)	Moderate (3); Trivial (2); Small (2); High (1)	No (4); Probably no (3); Yes (1)	Yes (6); Probably yes (2)	Yes (5); Probably yes (2); Probably no (1)	Potentially included (5); Included (3)	Potentially included list
Leg edema (Potentially included)	High (3); Trivial (3); Small (2)	No (5); Probably no (3)	Probably yes (3); Probably no (2); No (1); Yes (2)	Probably no (3); No (2); Probably yes (1); yes (2)	Excluded (4); Potentially included (2); Included (2)	Potentially included list
History of heart failure (Potentially included)	Small (5); Trivial (2); Moderate (1)	No (4); Probably no (3); Probably yes (1)	Probably yes (4); Yes (4)	Yes (5); Probably yes (3)	Included (4); Potentially included (4)	Suggestion: Potentially included list

Fever (Potentially included)	Trivial (6); Small (2)	No (4); Probably no (1); Probably yes (1); Yes (2)	Probably yes (3); Probably no (2); Yes (3)	Yes (6); Probably yes (2)	Excluded (3); Potentially included (2); Included (3)	Potentially included list
Heart rate (Potentially included)	Trivial (6); Small (2)	No (4); Probably no (2); Yes (2)	Probably no (3); Probably yes (2); Yes (3)	Yes (7); Probably yes (1)	Excluded (5); Included (3)	Excluded
WBC (Potentially included)	Small (5); Trivial (3)	No (4); Probably no (2); Yes (2)	Probably yes (4); Yes (3); Probably no (1)	Yes (6); Probably yes (1); No (1)	Potentially included (5); Excluded (1); Included (2)	Potentially included list
Recent long bone fracture (Potentially included)	Trivial (3); Small (3); Moderate (2)	No (4); Probably no (2); Probably yes (2)	Probably yes (4); Yes (3); Probably no (1)	Yes (4); Probably yes (3); No (1)	Potentially included (5); Excluded (1); Included (2)	Potentially included list
Recent air travel (Added for revision)	High (3); Trivial (3); Moderate (1); Small (1)	No (4); Probably no (2); Probably yes (2)	Probably no (3); Yes (3); No (1); Probably yes (1)	Yes (3); Probably yes (2); Probably no (2); No (1)	Excluded (5); Potentially included (3)	Excluded

Supplemental Table 5. Delphi process round 3 survey results for bleeding

Risk Factors (Judgement in Round 2 of Delphi process)	Resources required: How large are the resource requirements (costs)?	Equitable: Would the factor have an impact on health equity?	Acceptable: Is the risk factor acceptable to key stakeholders?	Feasible: Is the risk factor feasible to assess?	Final judgement by participants	Major Vote
Age (Included)	Trivial (7); Small (1)	No (3); Yes (3); Probably yes (2)	Yes (7); Probably yes (1)	Yes (7); Probably yes (1)	Included (7); Potentially included (1);	Included list
Sex (Potentially included)	Trivial (7); Small (1)	No (4); Yes (2); Probably yes (2)	Yes (7); No (1)	Yes (8)	Excluded (4); Potentially included (2); Included (2)	Potentially included
Renal failure (Potentially included)	Small (6); Trivial (2)	Probably yes (2); No (4); Probably no (2)	Yes (5); Probably yes (3)	Yes (6); Probably yes (2)	Included (6); Potentially included (2);	Included list
Autoimmune disease (Potentially included)	Moderate (3); Small (2); Trivial (2); High (1)	Probably yes (2); No (4); Probably no (2)	Yes (3); Probably no (2); Probably yes (3)	Probably yes (4); Probably no (2); Yes (2)	Excluded (5); Potentially included (3)	Excluded
Thrombocytopenia (Included)	Small (4); Trivial (4)	No (4); Probably no (2); Probably yes (1); Yes (1)	Yes (6); Probably yes (2)	Yes (8)	Included (Consensus: 8/8)	Included list
Central venous catheter (Potentially included)	Trivial (2); Small (4); Moderate (1); High (1)	No (4); Probably no (3); Yes (1)	Yes (4); Probably no (2); Probably yes (2)	Yes (4); Probably yes (3); Probably no (1)	Potentially included (3); Excluded (4); Included (1)	Potentially included
Gastroduodenal ulcer (Included)	Trivial (2); Small (2); Moderate (2); High	No (4); Probably yes (2); Probably no (2)	Yes (4); Probably no (2); Probably yes (2)	Probably no (3); Yes (3); Probably yes (2)	Included (7); Potentially included	Included list

	(2)				(1);	
Hepatic disease (Included)	Small (5); Moderate (1); Trivial (2)	No (4); Probably no (2); Probably yes (1); Yes (1)	Yes (5); Probably yes (3)	Yes (5); Probably yes (2); Probably no (1)	Included (7); Potentially included (1);	Included list
Recent bleeding (Included)	Moderate (4); Trivial (2); Small (2)	No (4); Probably no (2); Probably yes (1); Yes (1)	Yes (5); Probably yes (2); Probably no (1)	Yes (4); Probably yes (3); Probably no (1)	Included (7); Potentially included (1);	Included list
Blood dyscrasias (Included)	Small (3); Trivial (2); Moderate (1); High (2)	No (4); Probably no (2); Probably yes (1); Yes (1)	Yes (5); Probably yes (3)	Yes (4); Probably yes (4)	Included (5); Excluded (2); Potentially included (1)	Potentially included list
Anti-thrombotic medication (Included)	Trivial (4); Small (4)	No (4); Probably no (2); Probably yes (1); Yes (1)	Yes (5); Probably yes (2); Probably no (1)	Yes (6); Probably yes (2)	Included (7); Excluded (1)	Included list (We then excluded it from our RAM as the objective of our RAM is to assist health care professionals in making a decision on whether to provide prophylaxis to the patient in question)
Malignancy (Included)	Small (5); Trivial (3)	No (4); Probably no (2); Probably yes (1); Yes (1)	Yes (4); Probably yes (4)	Yes (7); Probably yes (1)	Included (4); Excluded (2); Potentially included (2)	Potentially included list
Critical illness (Included)	Trivial (3); Small (2); Moderate (2); High (1)	No (4); Probably no (2); Probably yes (2)	Yes (4); Probably yes (3); Probably no (1)	Yes (5); Probably yes (3)	Included (6); Potentially included (2)	Included list

Supplemental Table 6. Definitions of each prognostic factor from the included studies for VTE and suggested definitions

Barclay 2013	**Bembenek 2011**	**Fan 2011**	**Grant 2016**	**Kelly 2004**	**Mahan 2014**	**Ota 2009**	**Rosenberg 2014**	**Rothberg 2011**	**Spyropoulos 2011**	**Yi 2012**	**Zakai 2004**	**Zakai 2013**	**Zhou 2018**
Age (years)													
	10-year increments	Continuous	≥75; 61-74; 41-60; <60	>70; ≤70	>60; ≤60y		>60; ≤ 60	>65; 50-64; <49	>60; ≤60	>70		≥ 60 (ref <60) ≥ 70 (ref <70)	≥ 75 vs. <70y Caprini ≥ 70 vs. <70y Padua
Previous VTE													
Prior history of VTE		Prior history of VTE	Prior history of VTE		Prior history of VTE		Prior history of VTE		Prior history of VTE			Prior history of VTE	Prior history of VTE
Infections													
		Infectious Disease	Sepsis (<1month) Severe lung disease (including pneumonia)								Cellulitis, pneumonia, and sepsis at admission	Pneumonia- Any Infection	Acute infectious or rheumatoid disease
Immobility													

			Patient confined to bed >72 hrs and another reduced mobility	non-ambulatory			immobility >72 hrs		Immobilized > 7days	Bed-ridden	immobility >72 hrs		Patient confined to bed >72 hrs and another reduced mobility
Paresis													
				Leg paresis	Current lower limb paralysis		Lower limb paralysis; adopted from IMPROVE		Current lower limb paralysis				
Malignancy													
Active malignancy (not explained further) (active)		Prevalence of patients with cancer (active)	Admission or treatment of cancer (active)	Not stated clearly but by context assumed active	Present at or during current admission (active)		Prior Cancer from ICD codes	Chemotherapy (active)	present at or during current admission (active)		Active cancer within the past year	Active cancer within the past year	
Critical illness													
		Respiratory failure: Acute: Reason			ICU/CCU stay		ICU/CCU stay	Mechanical ventilation	ICU/CCU stay			Respiratory dysfu	Heart or respiratory

		s for enrollment were heart failure, respiratory failure, acute ischemic stroke or acute infectious disease										nction	failure (Padua)
D-Dimer													
		Elevated Baseline D-Dimer level defined as >500 ng/ml								Elevated Baseline D-Dimer level evaluated at the time of hospitalization			

										(was measured as a continuous outcome)			
Thrombophilia													
					Known thrombophilia		Known thrombophilia; adopted by IMPROVE	Inherited thrombophilia	Current thrombophilia				Already known thrombophilia (adopted by Padua score)
Sex													
similar across- male vs female or female vs male													
Respiratory													
		COPD chronic	COPD or abnormal pulmonary function acute and Severe lung disease, including pneumoni									COPD medical history (chronic) and COPD on admis	COPD (Not clear if acute or chronic)

			a (<1month)									sion (acute)	
History of heart failure													
	Congestive heart failure (3 months)					NYHA functional class							Heart failure (6 months): Caprini Heart or respiratory failure (6 months: Padua
Severe stroke													
	Stroke severity: NIHSS >14 pts; >7 pts; each additional 4 pts	Acute ischemic stroke	Stroke (not explained)										Stroke< 1 month (Caprini) And Acute MI or ischemic

													stroke (Padua)
Autoimmune diseases													
												Inflammatory disease	Acute infectious or Rheumatoid disease (adopted by Padua score
Obesity													
								Obesity (not defined)				BMI> 29.9 kg/m*2	BMI≥30 kg/m*2
Thrombocytosis													
											Platelet count >350x 10*9/L	Platelet count >350x 10*9/L	
Edema													
			Swollen legs (current)								leg edema on admission		

Heart rate													
												Tachycardia on admission ≥100 BPM	
Fever													
											Admission temp >38C	Temperature > 38.5 °C (found not eligible for multivariate analysis)	
WBC													
												WBC ≥ 11x10 9/L	
Catheters													
			CVC present on admission					CVC					

Long bone fracture													
			Hip, pelvis, or leg fracture(<1 month)									Long bone fracture in past 3 months	Hip, pelvis, or leg fracture(<1month)

Supplemental Table 7. Definitions of each prognostic factor from the included studies for bleeding and suggested definitions

Decousus 2011	**Mahan 2013**	**Patell 2017**
Age		
40-84 vs. <40; ≥ 85 vs. <40	55-64 vs. 40-54 65-74 vs. 40-54 ≥75 vs. 40-54	
Sex		
similar across- male vs female or female vs male		
Renal failure		
Moderate renal failure GFR 30-59 (ref: ≥60 mL/min/m2) and Severe renal failure GFR <30 (ref: ≥60 mL/min/m2	Insufficient renal function	
Malignancy		
Present at or during admission(active)	Newly diagnosed cancer at admission (active)	
Autoimmune diseases		
Rheumatic Disease	Rheumatoid Arthritis captured at index admission	
Thrombocytopenia		
Platelet count <50x10*9/L	Thrombocytopenia (level not reported)	Low Platelets <150 x10*9/L
Gastroduodenal ulcers		
Active gastro-duodenal ulcer	Active gastro-duodenal ulcer	
Hepatic disease		

Hepatic failure (defined as international normalized ratio > 1.5)	Liver disease from ICD codes	
Antithrombotic and Antiplatelet medication		
Any pharmacological prophylaxis, low molecular weight heparin, unfractionated heparin, and aspirin	Post-discharge antithrombotic medication	
Blood dyscrasias		
	No definition given	
Recent bleeding		
Bleeding in 3 months before admission		

Supplemental Table 8: Results of panel input and final definitions

Prognostic factor: Age (Short list)

Suggested definition: Age (10-year increase)

Panel member 1	**2 options:** Use age as a continuous variable, should that be something that could be modeled. That could then be easily applied in a computerized algorithm that would run in an EMR. If we look at the studies while heterogeneity exists, age 60 years seems to be a commonly elected cut point (Grant 2016, Mahan 2014, Rosenberg 2014, Spyropoulos 2011, Zakai 2013) that would be easily applicable for which some evidence exists. Likewise, as a cut point it would be inherently easier to implement than based upon a score for additional years. Likewise, the forest plot when calculated for ≥ 65 is most strong. **Regarding age and bleeding:** from a pragmatic perspective, if we elect age ≥ 65 as the cut point for VTE risk, then we could use the same for bleeding risk. I guess that by doing so it contributes to both scores which may be confounding but at least there would be consistency. (With ≥40 being the other option)
Panel member 2	I would use >60 or < 60 years (definition used most commonly)
Panel member 3	Age > 75 years. RCT data is quite consistent with this cut off
Panel member 4	Due to confounding, there is likely a non-linear relationship (many studies exclude younger individuals). Would not use as continuous variable
Panel member 5	Agree with creating a categorical variable for age; would use 10-year increments. The comment in the margin of the survey that risk is higher for >60 compared with >70 does not seem correct. Both >60 and >70 have been shown to have higher risk than younger patients. I have never seen direct comparison of >60 versus >70 (nor do I see how it could be done because they are not mutually exclusive categories

Summary of panel comments	One panelist suggested either maintaining the variable as continuous for the purpose of modelling but suggested for pragmatic purposes to consider dichotomizing it as ≥and <65 years when discussing VTE as an outcome and considering the same cut-off or ≥ and < 40 as another alternative when considering bleeding as an outcome. Another panelist suggested ≥ and < 60 while a third suggested 75 as the cut off. Another panelist gave a different perspective and suggested a using 10-year increments. His justification was based on the fact that both ">60 and >70 have been shown to have higher risk than younger patients." But no direct comparison between the two age groups, >60 and >70, have been done because they are not mutually exclusive categories. The research team suggests based on the comments that categorising age in 10-year categories would be a wise way to approach this prognostic factor in aim of accounting for the non-linear relationship with VTE and all the while not oversimplifying the potential increase in risk in the older age groups.
Final suggested definition	**Age:** categorised variable using 10-year increments.

Prognostic factor: Previous VTE (Short list)

Suggested definition: Any past medical history of VTE

Note by Research team: Is distinction of provoked versus unprovoked necessary?

Panel member 1	While I concur with the above, I suggest that inadequate evidence exists to implement this distinction. Because the studies included in our review considered any prior VTE, I recommend against the distinction. This also facilitates capture upon history (or EMR interrogation) and obviates complexity associated with "minimally provoked" such as long-haul travel, etc.
Panel member 2	If possible would be important
Panel member 3	Any previous VTE. Does not matter in hospitalized setting if provoked or not
Panel member 4	I think the literature supports the belief that patients with a history of unprovoked VTE are at greater risk for subsequent events than those with provoked events particularly surgically provoked events
Panel member 5	None

Summary of panel comments	One panel member mentioned that the literature supports the distinction of provoked versus unprovoked VTE, with history of unprovoked VTE having a greater risk of VTE. One panel member agreed that it might be important. Two other panelists recommended against the distinction, with one panel member highlighting that the lack of distinction will facilitate the capture of previous VTE in patient's history and eliminates potential complexities associated with minimally provoked VTE.
Final suggested definition	**Previous VTE:** Any past medical history of VTE

Prognostic factor: Infections (Short list)

Suggested definition: Infectious disease including pneumonia, cellulitis, and sepsis.

Note by Research team: What other infections would be equivalent in severity?

Panel member 1	Infection is hard because of heterogeneity in the definition. I suggest that the evidence does not suggest "sepsis" (Forrest plot) and that this level of illness contributing to thrombosis risk is likewise captured elsewhere. While we did not discuss it per se, the one commonality that exists for "infection" is the administration of antibiotics (and perhaps preferentially IV antibiotics). This might be able to serve as a surrogate for infection although it would be less specific than, for example + blood cultures. IV antibiotics would be easily identified, suggest clinically severe disease, and could be queried on a daily basis. Alas, from a "deliverables" perspective it may not pass muster given that it was not explicitly studied. Maybe something to keep in mind for future research. I do concur with the difficulty of a good definition and likely cannot otherwise offer anything better than cellulitis, pneumonia, and sepsis from the review.
Panel member 2	(abscess/infected fluid collection anywhere, meningitis)
Panel member 3	None

Panel member 4	What would happen if you were not sure at admission? I would think that meningitis, pyelonephritis, osteomyelitis and cholangitis would also be considered severe infections. However, given the available data I think we should lump all infections serious enough to warrant hospital admission together for model simplicity and end user.
Panel member 5	None
Summary of panel comments	One panel member acknowledged the heterogeneity in the definition. He mentioned that the evidence does not support sepsis and contributing factors for VTE in this level of illness is likely captured elsewhere. IV antibiotics was suggested as a surrogate for serious infection that should be investigated in future research. Another panel member suggested adding abscess and infected fluid collections, and meningitis. The last panel member who contributed offered lumping all severe infections warranting hospital admission together for model simplicity.
Final suggested definition	**Infections**: Severe infectious disease requiring hospital admission (e.g.: pneumonia, cellulitis, abscess, meningitis, sepsis…)

Prognostic factor: Immobility (Short list)

Suggested definition: Order for bed rest or Immobile at admission

Panel member 1	I appreciate the comments above and the challenges. No matter how you slice it, immobility is a biggie for any VTE, DVT or PE. Likewise, while defined in varying ways (immobility >72h, bedrest order, "bedridden") the risk persisted. I suggest that asking the physician to assess for "immobility" may be a place to spend capital. Otherwise I continue to favor the old "order for bedrest" given how it has worked at our place, and that it is easy to capture electronically.
Panel member 2	Answer to comment by panel member 4: True but they are still not getting up.
Panel member 3	Agree with order for bedrest. First 24 hours of immobility contains the greatest weight of immobility as an independent (though weak) RF
Panel member 4	Many hospitals do not use this - ICU patients are 'up at tolerated'. Bedrest etc. is reserved for people who may be hurt by getting up.

Panel member 5	This can be (and has been) defined in a thousand ways—for implementation in Epic-based EHRs, we use something called the CLOF and PLOF scores (current and prior level of function), both scaled from 1-5 with 1-3 indicating non-ambulatory.
Summary of panel comments	A panel member recognized the challenges with the definition but highlighted the persisting risk no matter how immobility is defined. He favors the order of bed rest as it is easy to capture and has worked. Another member mentioned that the first 24 hours of immobility has the greatest weight as an independent risk factor. One panel member mentioned that in some hospitals this will not work, and ICU patients might have an "up as tolerated" order. A panel member commented on this and mentioned that these ICU patients are still not getting up. Another panel member suggested using the CLOF and PLOF scores to indicate level of ambulation of patients which are integrated in EPIC- based EHRs. Order of bed rest was agreed upon and easy to operationalize, we will leave definition as is.
Final suggested definition	**Immobility:** Order of bed rest or immobile at admission.

Prognostic factor: Paresis (short list)

Suggested definition: Current lower limb paralysis on admission

Panel member 1	Historically applying the axis of time has been challenging in this setting. I suggest that paresis might be more easily identified using ICD codes which may be operational. You will note that the adjusted. ORs for paresis and immobility are nearly identical for the outcome of thrombosis. Because paresis is likely an important condition to capture on admission (CMS pre-existing diagnosis to identify risk for skin ulcers associated with admission) I wonder if we would consider lumping these into "immobility/paresis" then it could be defined as of course paresis identified by ICD admit dx code off a problem list OR order for bedrest (or whichever metric that is used).
Panel member 2	I would define this as unable to weight-bear. Paralysis or paresis in medical record would be adequate. I think we should include a time element to this risk factor. The risk of DVT associated with limb paralysis is primarily in the first 6 months so I would say "acute lower limb paralysis (within 6 months).
Panel member 3	None

Panel member 4	How weak does this mean?
Panel member 5	None
Summary of panel comments	A panel member mentioned that paresis could be easily identified using ICD codes. He also suggested to lump paresis and Immobility together. Another panel member suggested to define paresis as "unable to weight bear" and acknowledged that paralysis or paresis in medical record would be adequate. It was also mentioned that a time element should be included in the risk factor, since DVT risk is primarily associated with paresis in the first 6 months. We defined acute as within 6 months to avoid chronic patients and added it to the definition.
Final suggested definition	**Paresis:** Acute (within 6 months) lower limb paralysis or paresis

Prognostic factor: Malignancy (short list)

Suggested definition: Active cancer within 12 months suggested by receiving therapy for cancer or demonstrable disease

Panel member 1	I suggest that in addition to "receiving therapy" which would be heterogeneous (surgery, different chemo regimens, XRT, etc.) and arguably tough to find, plus "demonstrable disease" which might require interrogation of pathology reports (or involve the MD at the time of admit) that for the definition of active cancer we also include an encounter ICD code associated with cancer diagnosis in the last 12 months. Most encounters in the absence of active cancer would likely not bill on this code.
Panel member 2	In response to research team comment: No. Would add or receiving palliation. I would shorten this to 3 months. I think a definition of malignancy that includes patients who have received therapy or had evidence of cancer in the last 12 months is too liberal. Using this definition, one would end up designating patients who had completed therapy for Hodgkin's disease and were cured in the cancer group. In Walker's study of VTE in breast cancer patients from the UK event rates

	returned to the population baseline within 3 months of completing chemotherapy. Therefore, I would use a definition of evidence of measurable disease at present or therapy for cancer within the last 3 months
Panel member 3	Data would suggest any cancer within 5 years confers similar risk to active cancer in hospitalized setting
Panel member 4	None
Panel member 5	Exclude non-melanoma skin cancers?
Summary of panel comments	A panel member mentioned that we include ICD code associated with cancer in the last 12 months be added to the suggested definition. Another member suggested to shorten the 12 months to 3 months, after pointing out Walker's study which showed VTE rate in breast cancer patients return to baseline after 3 months of completing chemotherapy. Another panel member mentioned that data shows similar risk of VTE with active cancer and cancer within 5 years. Another panel member questioned the inclusion of non-melanoma skin cancers in the definition. We included ICD code to the definition to increase capture rate.
Final suggested definition	**Malignancy**: Active cancer within 12 months, suggested by receiving therapy or palliation for cancer, demonstrable disease, or ICD code related to cancer within the last 12 months

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Prognostic factor: Critical illness (short list)

Suggested definition: Admission or transfer to ICU/CCU or mechanical ventilation or respiratory/heart failure requiring intensive/critical care

Panel member 1	I agree with the above. Yet if we look at the Forrest plots for VTE then the easily identifiable combination of ICU admission and/or mechanical ventilation (both documented and readily found electronically) would capture virtually all of the folks included in the studies that we selected.
Panel member 2	Response to red: Nothing to be done about it. I agree with this statement. Perhaps use of mechanical ventilation or drugs for hemodynamic support (e.g., vasopressors) would be more specific for the critically ill patient population

Panel member 3	Agree. We cannot define everything for everyone. Any ICU admission should suffice
Panel member 4	This is variable by hospital. A community's hospital ICU might be someone with mild pneumonia and a tertiary care medical center may require intubation.
Panel member 5	None
Summary of panel comments	A panel member agreed with the suggested definition and mentioned that looking at our data a combination of ICU and/or mechanical ventilation would include virtually all patients included in the studies we selected. Another panel member mentioned that community hospitals may admit less severe cases into the ICU. Two panel members agreed with this and one suggested that the use of mechanical ventilation or hemodynamic support medications might be more specific for critically ill patients, while the other panel member mentioned that we cannot define everything for everyone, and ICU admission should suffice.
Final suggested definition	**Critical illness:** Admission or transfer to ICU/CCU, mechanical ventilation, or respiratory/heart failure requiring intensive/critical care

Prognostic factor: D-Dimer (short list)

Suggested definition: Elevated D-Dimer level at admission (cut-off >500 ng/ml)

Panel member 1	I concur that inadequate evidence exists at present to leave this on the list for inpatients.
Panel member 2	Agree with red
Panel member 3	Maybe a cost burden, but RCT data now are consistent that this is likely the most important independent RF in this patients < 75 years. Any risk model without elevated DD would be useless in terms of discrimination
Panel member 4	Not routinely assessed - would be a huge cost burden.

Panel member 5	None
Summary of panel comments	A panel member suggested that this prognostic factor should not be considered routinely for inpatients and would be a huge cost burden to consider, therefore should be taken of the list and not be used in the model. Two other panelists agreed that it would be a cost burden, and one panelist mentioned insufficient evidence at the moment. However one panel member mentioned that RCT data show that it is an important independent RF for VTE.
Final suggested definition	**D-Dimer:** Elevated D-Dimer level at admission (cut-off >500 ng/ml)

Prognostic factor: Thrombophilia (short list)

Suggested definition: Known thrombophilia

Panel member 1	Easy to interrogate the EMR for this. I suggest that it may likely stay in and contribute if present.
Panel member 2	Yes, but that is captured with VTE variable. Usually will show up on history if present. Any KNOWN thrombophilia. Weight of this independent RF different from history of VTE Although thrombophilia is not routinely measured in hospitalized patients, its presence has been associated with a significant increased risk of VTE. I do not think the studies that noted an association between thrombophilia measured it in patients. In addition, those studies did not differentiate between patients who had thrombophilia identified as part of family screening versus a personal history of VTE. I think we should include it. May want to consider define it as presence of Factor V Leiden, factor II mutation and protein C or S or AT deficiency or APS which some studies specified in their definition.
Panel member 3	None
Panel member 4	Not routinely assessed - difference between those assessed due to family history versus personal history.
Panel member 5	None

Summary of panel comments	The panel members mentioned that thrombophilia is not routinely assessed, however thrombophilia is a significant independent risk factor for VTE, and its presence could be captured in patients' history. One panelist mentioned expanding the definition and mentioning the individual diseases that constitute thrombophilia.
Final suggested definition	**Thrombophilia:** Any known history of hereditary or acquired thrombophilia including Factor V Leiden, prothrombin gene mutation, protein C deficiency, protein S deficiency, antithrombin deficiency, and antiphospholipid antibody syndrome.

Prognostic factor: Sex (long list)

Suggested definition: Male versus female

Panel member 1	None
Panel member 2	None
Panel member 3	None
Panel member 4	None
Panel member 5	None
Summary of panel comments	No comments were made. Suggested definition stays as is.
Final suggested definition	**Sex:** Male versus female

Prognostic factor: Respiratory (long list)

Suggested definition: Acute COPD exacerbation on admission

Panel member 1	None
Panel member 2	None
Panel member 3	Not really, based on admission codes
Panel member 4	Difficult to determine many times.
Panel member 5	Need to be clear as to whether these refer to acute admission diagnoses or chronic comorbid conditions
Summary of panel comments	Panel members mentioned concern due to difficulty in diagnosing acute COPD exacerbation. Another panel member highlighted the importance in differentiating between acute admission COPD diagnosis and comorbid condition.
Final suggested definition	**Respiratory:** Acute COPD exacerbation on admission

Prognostic factor: Renal failure (long list)

Suggested definition: Renal failure at GFR<60 mL/min/m^2

Note by Research team: Will it require age adjustment?

Panel member 1	Regarding renal failure as a bleeding risk factor: I suggest GFR ≤ 30. I believe that the 60 cut point would be achieved often among inpatients and that this could disproportionately affect Hospitalist willingness to apply chemoprophylaxis. Also we see 30 is more predictive.
Panel member 2	No. But consider three levels (<60, 30-60, <30)

Panel member 3	Completely agree
Panel member 4	None
Panel member 5	None
Summary of panel comments	One panelist suggested lowering the cut-off point to <30. Another two panel members suggest defining renal failure at three different rates. Therefore, we adjusted the suggested definition to accommodate for that.
Final suggested definition	**Renal failure:** Renal failure at GFR<30, 30-60 and <60 mL/min/m^2

Prognostic factor: History of heart failure (long list)

Suggested definition: Past medical history of congestive heart failure

Panel member 1	None
Panel member 2	Consider within last 6-12 months
Panel member 3	Within 12 months
Panel member 4	None
Panel member 5	None
Summary of panel comments	The two panel members suggest defining a time in terms of history of heart failure, one suggested 6-12 months, another within 12 months. We have revised the suggested definition to state within 12 months as this incorporates both and is more inclusive.

Final suggested definition	**History of heart failure:** Past medical history of congestive heart failure within 12 months prior to admission.

Prognostic factor: Severe stroke (long list)

Suggested definition: Acute stroke within 1 month causing disability (excluding TIA)

Panel member 1	None
Panel member 2	Seems reasonable. Stroke with immobility might show greater discrimination.
Panel member 3	None
Panel member 4	None
Panel member 5	None
Summary of panel comments	One panelist commented that the suggested definition appears reasonable. No other relevant comments were made therefore we will keep the suggested definition as is.
Final suggested definition	**Severe Stroke:** Acute stroke within 1 month causing disability (excluding TIA)

Prognostic factor: Autoimmune disease (long list)

Suggested definition: All autoimmune diseases including rheumatoid arthritis and inflammatory bowel disease

Panel member 1	None
Panel member 2	None
Panel member 3	None
Panel member 4	None
Panel member 5	None
Summary of panel comments	No input from the panelist, we will leave the definition as is.
Final suggested definition	**Autoimmune disease:** All autoimmune diseases including rheumatoid arthritis and inflammatory bowel disease

Prognostic factor: Obesity (long list)

Suggested definition: BMI≥30 kg/m^2 on admission

Panel member 1	None
Panel member 2	None
Panel member 3	Or history of morbid obesity
Panel member 4	None

Panel member 5	None
Summary of panel comments	One panelist commented on adding to the suggested definition, a history of morbid obesity. No time frame to the history was discussed by the panelists, so we will not add it to the suggested definitions. Cut-off of 30 was not objected by any panel member so we will leave definition as is.
Final suggested definition	**Obesity:** BMI≥30 kg/m^2 on admission

Prognostic factor: Thrombocytosis (long list)

Suggested definition: Platelet count >350x10^9/L

Panel member 1	None
Panel member 2	Too bad studies did not use >500
Panel member 3	OK with this cut off, though data from one study very limited
Panel member 4	None
Panel member 5	None
Summary of panel comments	Two panelist commented on the cut-off limit, and the limited number of studies. However, no objections to the suggested cut-off at the moment, maybe an area of future research. We will leave definition as is.
Final suggested definition	**Thrombocytosis:** Platelet count >350x10^9/L

Prognostic factor: Leg edema (long list)

Suggested definition: Current Lower limb edema or swollen legs, excluding varicose veins

Panel member 1	None
Panel member 2	I think this will be difficult to define operationalize.
Panel member 3	Difficult if not impossible to operationalize
Panel member 4	Any versus a certain threshold?
Panel member 5	Need to be careful about direction of causality. Were the studies able to establish which came first?
Summary of panel comments	Most of the panel members showed concern on how to operationalize this, and one panel member voicing concern on causality (which came first). We will leave the definition as is, since no panel member suggested removal from model despite concerns.
Final suggested definition	**Leg edema:** Current lower limb edema or swollen leg, excluding varicose veins.

Prognostic factor: Heart rate (long list)

Suggested definition: Tachycardia on admission ≥100 BPM

Panel member 1	None

Panel member 2	None
Panel member 3	Again, variable in one study...not convinced at all of HR as independent predictor
Panel member 4	Could consider in future studies as a continuous variable?
Panel member 5	None
Summary of panel comments	One panelist voiced concerns due to lack of sufficient evidence to consider heart rate as an independent predictor, another panelist suggested using a continuous variable. We will leave the definition as is for now and await final decision about inclusion in the model.
Final suggested definition	**Tachycardia:** Tachycardia on admission ≥100 BPM

Prognostic factor: Fever (long list)

Suggested definition: Admission temp >38 C

Panel member 1	None
Panel member 2	None
Panel member 3	Same as infection
Panel member 4	None

Panel member 5	None
Summary of panel comments	One panel member considered this duplicating capture from infections. We will keep the current definition as is for now and await final decision about inclusion in the model.
Final suggested definition	**Fever:** Admission temperature >38°C

Prognostic factor: WBC (long list)

Suggested definition: Admission white cell count ≥11 x 10^9 cells per L

Panel member 1	None
Panel member 2	None
Panel member 3	Again, one study, very doubtful of WBC as independent predictor
Panel member 4	None
Panel member 5	None
Summary of panel comments	The panel member that commented was doubtful of defining WBC as a potential prognostic factor. We will leave the suggested definition as is for now.
Final suggested definition	**WBC:** Admission white cell count ≥11 x 10^9 cells per L

Prognostic factor: Catheters (long list)

Suggested definition: Presence of central venous catheter

Panel member 1	None
Panel member 2	Need for VTE prophy should be continuously assessed
Panel member 3	Again, this would be helpful to distinguish of admission mode vs discharge model
Panel member 4	Difference between present on admission versus placed after admission.
Panel member 5	None
Summary of panel comments	Two of the three panelists suggested it would be important to distinguish between the presence of a central venous catheter at admission or discharge. Another noted the need for continuous assessment throughout the stay. If a catheter is placed during hospital stay, need for prophylaxis needs to be reassessed. We suggest adding to the definition above "the presence of CVC at admission" for the admission model.
Final suggested definition	**Catheters:** Presence of a central venous catheter at admission

Prognostic factor: Recent pelvic and long bone fracture (long list)

Suggested definition: Hip, pelvis, or long bone fracture in the past 3 months

Panel member 1	None

Panel member 2	Yes, last 3 months
Panel member 3	None
Panel member 4	None
Panel member 5	None
Summary of panel comments	One panelist stated that the definition suggested was appropriate therefore no changes will be made to the suggested definition.
Final suggested definition	**Recent pelvic and long bone fracture:** Hip, pelvis, or long bone fracture in the past 3 months

Prognostic factor: Thrombocytopenia (short list)

Suggested definition: Platelet count <150x10^9/L at admission

Panel member 1	Would suggest <50K. I agree with the comment exact cut off not established however, IMPROVE study provides the best data for the association of thrombocytopenia and bleeding and it identified a cut off of 50K which seems more reasonable that 150K. The 150K cut off was identified by Patell in a cancer patient population which have inherently higher risks of bleeding than patients without cancer, so I do not think their data should be used to identify a definition of thrombocytopenia in medically ill patients
Panel member 2	None
Panel member 3	None

Panel member 4	Easy to assess, but exact cut-off not established.
Panel member 5	None
Summary of panel comments	One panel member suggested changing the cut-off of platelet to <50K as Patel et al. 2017 used a cutoff of $150x10^9$/L in their cancer patient population that have inherently higher risks of bleeding than patients without cancer. Another panel member mentioned that exact cut-off is not yet established.
Final suggested definition	**Thrombocytopenia:** Platelet count < $50x10^9$/L at admission

Prognostic factor: Hepatic disease (short list)

Suggested definition: Liver disease with elevated INR>1.5

Panel member 1	I suggest off the list. Perhaps this represents a RF that, if present, could be incorporated into an algorithmic score. I suggest that inadequate evidence exists (2 studies AOR 1.53) that would be supportive of making INR ordering include the on the MD at the time of admission. I think that the other interesting opportunity for future research would be to look at comparatively other metrics of liver disease (e.g. LFTs > 3x ULN) as they would be likewise easily calculated numerically per routine.
Panel member 2	And there are other reasons for INR elevation beside liver disease. I disagree. I think INRs are very commonly assessed on admission. An inexpensive and commonly ordered test. Which is a reasonable measure of hepatic dysfunction particularly as a risk factor for bleeding. IMPROVE used this as a measure of hepatic disease and it was associated with bleeding.
Panel member 3	True but INRs routinely done, easy to do, feasible, and easy to incorporate an opt out approach if other causes found
Panel member 4	INR not routinely done on admission.

Panel member 5	None
Summary of panel comments	One panel member suggested removing it from the model due to insufficient evidence to routinely order INR, mentioning that it is an opportunity for future research looking while also looking at other metrics of liver disease. Another panel member mentioned that INR is commonly assessed on admission and that it is an inexpensive test, while there are other reasons other than hepatic disease for INR elevation. It was also mentioned that IMPROVE has used this as a measure for hepatic disease and was associated with bleeding. Another panel member mentioned that it is true that other causes for INR exist, but INR is easy to do, feasible, and easy to incorporate an opt-out approach if other causes found.
Final suggested definition	**Hepatic disease:** Liver disease with elevated INR>1.5

Prognostic factor: Gastroduodenal ulcer (short list)

Suggested definition: Active gastroduodenal ulcer

Panel member 1	This was from the IMPROVE registry data therefore active ulcer would have been identified upon admission or during hospitalization. These data would not be readily available until scope made sometime after admission. Perhaps analogous to the chart review by IMPROVE would be an ICD code for ulcer within a period of time (? 3 mo.)? I believe that consensus would exist that a PUD ulcer would heal with modern treatment after about 3 months.
Panel member 2	Perhaps ulcer demonstrated by endoscopy in last 1-3 months. I agree we should define this term. I think we could use data from studies looking at GI bleeding from ulcers in patients on AC to define this term better. Majeed et al recommended to resume AC after 3-6 weeks so we could use this to guide appropriate time period. 6 weeks?
Panel member 3	Agree any GU within 3 months
Panel member 4	I do not know what the definition of active is? Currently bleeding, within x time of diagnosis?
Panel member 5	None

Summary of panel comments	All panel members agreed that a time frame should be added to define gastroduodenal ulcer. Diagnosis of Gastroduodenal ulcer by GED within the last 6 weeks or 3 months.
Final suggested definition	**Gastroduodenal ulcer:** Diagnosis of active gastroduodenal ulcer by GED within the last 3 months

Prognostic factor: Recent bleeding (short list)

Suggested definition: Bleeding in 3 months before admission

Panel member 1	With this being 1 study (Decousus from IMPROVE data) we may wish to exclude. From an operationalization perspective it would be easy for EMR interrogation to find any code demonstrative of major bleeding within 3 months.
Panel member 2	any type of major or clinically relevant bleeding (could use ISTH def.) I think we should use major or clinically relevant non-major bleeding as our definition. Decousus used this definition in the IMPROVE study.
Panel member 3	Agree. Though will be difficult to operationalize ISTH definitions
Panel member 4	What type of bleeding?
Panel member 5	None
Summary of panel comments	A panel member wondered if this should be excluded from the model, however he did mention that it would be easy to operationalize using EMR. Another panel member suggested using any type of major or clinically relevant bleeding maybe by using ISTH definitions, but another member was concerned that ISTF would be difficult to operationalize.
Final suggested definition	**Recent Bleeding:** Any major or clinically relevant non-major bleeding within 3 months of admission

Prognostic factor: Bleeding disorders (no studies identified)

Suggested definition: Bleeding disorders on admission

Panel member 1	Agreed
Panel member 2	Although I agree this is poorly defined I think it makes sense from the standpoint of clinically expediency to use a single category for all inherited or acquired bleeding disorders. Could provide a few examples (e.g., hemophilia, Bernard Soulier syndrome, etc.) Decousus used congenital or acquired bleeding disorder in their study
Panel member 3	None
Panel member 4	Would exclude these patients -they are high risk for bleeding and too heterogenous to lump into one category.
Panel member 5	None
Summary of panel comments	One panel member suggested lumping all bleeding disorders together, however two other panelist agreed to remove from model.
Final suggested definition	**Bleeding disorders**: Any bleeding disorder on admission

Prognostic factor: Antithrombotic and antiplatelet medication (short list)

Suggested definition: Any anticoagulant medication started including low molecular weight heparin, unfractionated heparin, and warfarin versus aspirin.

Panel member 1	None
Panel member 2	None
Panel member 3	I would not include aspirin as a contraindication to pharmacologic prophylaxis
Panel member 4	None
Panel member 5	None
Summary of panel comments	One panelist suggested removing aspirin form the definition.
Final suggested definition	**Antithrombotic medication:** Any anticoagulant medication started, including low molecular weight heparin, unfractionated heparin, and oral anticoagulants.

CHAPTER 5. DISCUSSION

Discussion

Summary of findings

This dissertation describes three main studies evaluating the current status and development of RAMs for VTE and bleeding in hospitalized medical patients. Our findings highlight the need to integrate a RAM in health care systems to better standardize the approach to estimating patients' risks of outcomes and selecting appropriate prevention strategies accordingly. In Chapter 2 we identified and described previously developed VTE RAMs, some of which are widely used in clinical practice (6). However, we recognized numerous shortcomings that may limit the interpretation and clinical utility of the developed VTE RAMs for hospitalized medical patients. The limitations of the existing RAMs led us to conceptualize a novel mixed methods approach that we present in Chapter 4 (19). The first step of this approach was conducting a systematic review of prognostic factors for VTE and bleeding in hospitalized medical patients that is described in Chapter 3 (16). The systematic review ensured the consideration of all candidate prognostic factors for VTE and bleeding in hospitalized medical patients, as some factors may not be measured and reported in certain datasets (16). After identifying the candidate prognostic factors and reporting pooled estimates of effect, we used the GRADE EtD framework to assess the certainty of the evidence of those factors to evaluate the certainty in their predictive ability (16). Using the EtD criteria the expert panel then judged whether prognostic factors should be

included, potentially included or excluded from the VTE and bleeding RAMs (19). These judgements were made in a Delphi process based on the evidence derived in the systematic review and the GRADE criteria (19). Although our work was specific to selecting VTE and bleeding prognostic factors in hospitalized medical patients for the development or update of RAMs, this approach may be used for any outcome or disease state.

Strengths and limitations

This work presents a novel approach that has not been previously used to select prognostic factors for the development or update of RAMs. The strength of this work is in the rigorous, comprehensive and structured methods used.

A strength of the overview of reviews presented in Chapter 2 was in the applicability of our findings in informing guideline developers. Also, the findings may aid health care practitioners and health systems in standardizing their methods for risk assessment to optimize prevention strategies (6). The systematic review, described in Chapter 3, presents many strengths. One of the strengths was the process of comprehensively identifying all candidate prognostic factors with input from an expert panel, which overcomes limitations of cohort studies. This was noted in our findings, where we identified a list of candidate factors that were omitted from many models, likely because of data limitations (16). Another strength was dealing with potential correlation among the factors identified. We were able to address this concern by collapsing the factors

that appeared to be highly correlated. For example, some studies reported rheumatoid arthritis as a candidate prognostic factor for VTE and bleeding while other studies reported inflammatory bowel disease as a factor for either outcome. We considered these two conditions to be correlated with one another and collapsed them into a single prognostic factor which we defined as autoimmune diseases. Also, conducting a systematic review enabled us to pool the results from multiple types of prognostic studies, that individually have a more selected population and a smaller sample size, therefore providing more genuine and generalizable findings (3). In our systematic review we also addressed the concern of the effect of prophylaxis on the risk of a VTE or bleeding event in untreated patients. We did so by only including studies that had less than 10% of the population on thromboprophylaxis or had adjusted for the use of thromboprophylaxis during their statistical analysis. After identifying studies for inclusion, we conducted meta-analyses of our findings when applicable and evaluated the pooled effect estimates of each of the factors. This was done by evaluating the magnitude of effect and the confidence interval rather than relying solely on statistical significance to select factors using the p-value. Assessing the certainty of the evidence based on a structured framework is another strength of our work as it allowed for an expression of the confidence in the predictive ability of the identified factors (18). The novel approach used in Chapter 4, allowed the expert panel to select prognostic factors for the VTE and bleeding RAMs that are evidence based and clinically relevant by using GRADE criteria that accounts for benefits and harms, resource requirements, impact on

equity, acceptability and feasibility (19). We addressed issues of correlation at this stage as well by removing candidate prognostic factors that appeared highly correlated with other factors. For example, when assessing the factors CRP and infection, the panel judged infection to be included in the final VTE model while CRP was excluded. This decision was based on CRP being highly sensitive and requiring high costs. Also, CRP may be considered in the assessment of patients presenting to the hospital with an infection. By relying on statistical and clinical significance in developing RAMs, we provided face and content validity to the models developed. Standardizing the definitions of the prognostic factors may provide more clarity to health care professionals and help decrease the variability in the methods of measurement across settings.

Common limitations resulted from the studies included in the evidence syntheses. One of the systematic reviews included in our overview of reviews restricted their search to one database and both restricted their searches to specific languages which may have led to missing relevant studies (6). Also, in the systematic review we were unable to conduct a meta-regression to adjust for study level characteristics as the number of studies was too small for this analysis (19). Limitations relevant to the individual studies included inconsistency and variability in eligibility criteria and variability in study design, sample size, and definitions and methods of measurement of the prognostic factors (6, 16). Another limitation was the issue of dichotomization of prognostic factors that is often done arbitrarily and through data dredging a cut point value to create two

categories of participants. Through dichotomization, the power to detect genuine prognostic factors is reduced and the predictive performance of prognostic models deteriorates. We were unable to address this limitation as we were pooling data at a study level rather than at an individual level. This can potentially be addressed when validating the RAMs using individual patient data by maintain the factors as continuous variables whenever possible. Furthermore, despite our efforts to address correlation between prognostic factors in multiple ways, we were not able to fully control for all potential correlations as individual studies did not always present fully adjusted results or did not provide the necessary data to do so.

Implications for practice

The RAMs may support health care practitioners in estimating an individual patient's risk of a VTE or bleeding event based on their individual characteristics (1). RAMs can also be used in health care institutions as part of a shared decision making-process using clinical decision aids to decide on the optimal patient- specific management strategy based on population level recommendations.

Implications for future research

Existing RAMs that are currently used in clinical practice may need to be updated as they may not have considered or included all relevant factors. The next steps for our developed RAMs should include testing them in an external validation study using

individual patient datasets in order to evaluate their predictive performance by assessing the calibration, discrimination and their overall fit. After an external validation effort, conducting a prospective impact study prior to adopting them in routine clinical practice is essential. This would ideally be done by conducting a randomized controlled trial using the RAMs we developed in one arm and usual care in the other and assessing clinical outcomes, patient important outcomes, process measures and cost. Another area of research is further exploring the candidate prognostic factors that the expert panel judged as relevant but were not included due to insufficient evidence (19). The variability across studies highlighted the need to create more uniform datasets and registries to facilitate the reproduction, and validation of studies and the comparability of findings across settings.

Further testing of the novel approach that we conceptualized is necessary in fields other than in the ones tested (VTE and bleeding in hospitalized medical patients) to validate our approach. This can involve both prospective as well as retrospective approaches of already developed RAMs. Developing guidance for the future use of this approach may also be helpful.

Conclusion

In this dissertation, we proposed and tested a novel approach to select prognostic factors for the development or updating of RAMs based on evidence from a systematic review and expert input through a structured approach using GRADE criteria. Our

findings emphasize the need to supplement known modelling strategies with different approaches, such as our conceptualized novel approach, to ensure the selection of prognostic factors that are evidence-based, clinically meaningful and relevant. Also, these findings may assist decision makers in evaluating the risk of an individual having an outcome, in this case weighing the risk of VTE to that of bleeding, to individualize population-based recommendations and optimize patient care.

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