Oral Anticoagulation Persistence in Atrial Fibrillation

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Evaluating Oral Anticoagulation Persistence in Patients with Atrial Fibrillation

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Table of Contents

LAY ABSTRACT (149 words)

Oral anticoagulants (OAC) are approved for stroke prevention in atrial fibrillation (AF) patients, however discontinuation rates are high and associated with poor patient outcomes. Prior to the last decade, medications to reduce blood clotting by reducing vitamin K action [vitamin K antagonists (VKA)] were primarily used. However, up to 50% of patients discontinue VKA within one year. The introduction of non-VKA (NOAC) anticoagulants that do not require continuous monitoring or dose adjustments, show some promise of improvement in persistence.

This thesis examines and reports on long-term persistence over 2 years to the first NOAC available, dabigatran. Reasons, clinical predictors, and periods of risk for discontinuation as well as outcomes following discontinuation are prospectively examined. A systematic review of educational interventions examines existing evidence for improving outcomes with structured education. Finally, important considerations for interpreting OAC persistence research as well as recommendations for future research in this area are discussed.

ABSTRACT (300 words)

Long-term persistence with oral anticoagulants (OAC) in atrial fibrillation (AF) is associated with improved outcomes. However, 1-year discontinuation of vitamin K antagonists (VKA) is as high as 50%. Persistence to non-VKA oral anticoagulants (NOAC) show some signal of improvement but the estimates are variable.

This thesis includes a prospective evaluation of newly diagnosed AF patients in 44 countries using physician reported start and stop dates of anticoagulation. One-year persistence to dabigatran was 75.6% and 69.2% at 2 years. Approximately half of discontinuers switched to another OAC, increasing estimates of general overall 2-year OAC persistence to 84.1%. Probability of discontinuation was highest in the first 6 month period (83.7%, 95% confidence interval [CI] 82.7-84.8%) and lower in successive periods. Patients persistent with dabigatran at 1 year had >90% probability of remaining persistent at 2 years. Patients with symptomatic AF, and prior bleeding had higher discontinuation, those with prior stroke, lower discontinuation. Standardized stroke incidence rates post-discontinuation were (95% CI) 1.76 (0.89 to 2.76) in non-switchers, and 1.02 (0.43 to 1.76) in those who switched, consistent with the expected benefit of remaining on treatment.

Supplemental patient education may be one mechanism to improve persistence to treatment and improve patient outcomes. A systematic review of the impact of education on outcomes in 9 randomized clinical trials showed low to very low certainty of evidence for benefit of education over usual care. Sufficiently powered trials or different approaches are required to further assess the impact of education on patient outcomes.

Finally, important considerations for interpreting available research in OAC persistence, including differences in study methodology, setting, and timing are examined, and patient factors associated with higher or lower persistence reported. A framework for assessing persistence studies is presented to assist researchers and clinicians in evaluating current research and to support planning of future studies.

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LIST OF ABBREVIATIONS

DR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
ARR	Absolute Risk Reduction
CHA_2DS_2-VASc	Atrial Fibrillation Risk Score with acronym: C-Congestive heart failure (or Left ventricular systolic dysfunction), H-Hypertension: blood pressure consistently above 140/90 mmHg, A-Age≥75 years, D-Diabetes Mellitus, S-Prior Stroke or TIA or thromboembolism, V-Vascular disease, A-Age 65–74 years, Sc- Sex category
CI	Confidence Interval
DOAC	Direct Oral Anticoagulant
DVT	Deep Vein Thrombosis
GLORIA-AF	**G**lobal Registry on **L**ong-Term **O**ral Anti-thrombotic T**R**eatment **I**n P**A**tients with **A**trial **F**ibrillation
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS-BLED	Bleeding risk assessment (acronym): H-Hypertension, A-Abnormal renal and liver function, S-Stroke, B-Bleeding, L-Labile INR, E-Elderly, D-Drugs or alcohol
HR	Hazard Ratio
INR	International Normalized Ratio
NOAC	Non-VKA Oral Anticoagulant
OAC	Oral Anticoagulation

PDC	Proportion of Days Covered
PE	Pulmonary Embolism
PPI	Proton Pump Inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Clinical Trial
RoB	Risk of Bias
RR	Risk Ratio
SAE	Serious Adverse Event
SR	Systematic Review
TEE	Thromboembolic Event
TTR	Time in Therapeutic Range
USA	United States of America
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

DECLARATION OF ACADEMIC CONTRIBUTION

For all chapters included in this thesis, I confirm that under the supervision and guidance of Professor Robby Nieuwlaat and my PhD supervisory committee members Professors Alfonso Iorio and Lawrence Mbuagbaw, I was the primary contributor for the conception, design and writing of included chapters. I am the first author for the 4 included papers in this sandwich thesis, published (chapters 2-4) and submitted for publication (chapter 5).

For the studies represented in chapter 2 and 3, the Steering Committee Members and co-authors jointly designed the study but the persistence hypotheses to be evaluated were conceived by me. The analyses for these 2 chapters were conducted by a trial statistician with discussion and guidance from myself and other co-authors. Programming support was provided by contracted programmers. I wrote the first and subsequent drafts of the final published manuscripts.

The systematic review presented in chapter 4 was part of an invited review from the American Society of Hematology. Under the supervision and guidance of Professor Robby Nieuwlaat, I screened and extracted data, conducted the analyses, wrote the first draft of the manuscript, incorporated author and reviewer revisions and approved the manuscript. Members of the guideline panel and co-authors provided substantial feedback and approval for the final published version.

Chapter 5 is a review of methodological aspects of persistence literature and this paper was conceived in discussion with and guidance from the members of my PhD supervisory committee. Professors Alfonso Iorio, Lawrence Mbuagbaw and Robby Nieuwlaat

provided substantial input for the content, and reviewed and approved the final submitted manuscript. I wrote the first, intermediate and final drafts as well as designing figures and tables for the manuscript.

Further details of my contributions as well as those of other co-authors are included as a preface to chapters 2, 3, 4 and 5.

THESIS OBJECTIVES AND OUTLINE

Thesis Objectives and Outline

The general objective of this thesis is to investigate persistence to non-vitamin K anticoagulants, to better understand predictors of and reasons for non-persistence. This thesis is comprised of 6 chapters that examine methods and inform knowledge gaps in the area of oral anticoagulation persistence in patients with atrial fibrillation (AF).

Methodological Issues Addressed in this Thesis

The methods and study designs vary for the investigations included in this thesis, with different associated challenges. Chapters 2 and 3 examine persistence outcomes in a global observational registry conducted in the second of 3 distinct phases of the registry. In addition to assessing probability of dabigatran persistence using a Kaplan-Meier time-to-event analysis, these chapters also evaluate predictors of and reasons for non-persistence. Additional investigation of periods of risk for non-persistence and outcomes following non-persistence are explored in chapter 3.

In chapter 3, two Cox-regression approaches were employed. The first was a multivariable Cox-regression analysis to identify overall predictors of dabigatran discontinuation including region, patient and sociodemographic characteristics, producing hazard ratios with 95% confidence intervals for the factors explored. The second Cox-regression model included interactions between covariates and time indicator functions

for each time interval (0 to 3, 3 to 6, 6 to 12, and ≥12 months) as certain characteristics may have differential predictive importance over time.

Chapter 4 is a systematic review and meta-analysis of the pooled treatment effects of supplemental patient education on thromboembolic and mortality outcomes in patients on oral anticoagulants as examined in randomized clinical trials.

Chapter 5 is a review of methodological characteristics of the literature in oral anticoagulation persistence. The heterogeneity of study and patient characteristics, precluded meta-analysis of results but illustrating these differences across studies provides important context for evaluating and designing investigations in oral anticoagulation persistence.

CHAPTER 1: Introduction

1.1 Background – Atrial Fibrillation and Anticoagulation

Atrial fibrillation (AF) is an increasingly prevalent arrhythmia associated with growing disease burden and increased morbidity and mortality[1]. Clinical expert focus on the management of this disease has resulted in important updates to clinical guidelines, yet AF remains one of the most significant causes of stroke, heart failure and overall mortality globally[2]. AF patients have a fivefold higher risk for stroke compared with the general population, and one in five strokes is attributable to AF[3]. For patients with at least one additional stroke risk factor, the appropriate use of oral anticoagulation (OAC) with vitamin K antagonists (VKA) has been well established to reduce ischemic strokes by about two thirds and prolong life[4]. Anticoagulation in these patients is considered a lifetime requirement, as stroke risk increases with age and additional comorbidities associated with aging further contribute to increasing risk.

Prior to 2010 when anticoagulants were limited to VKA, variable-dosing requirements produced an additional layer of complexity for measuring patient adherence. Since 2010, important therapeutic advances have been made with the availability of non-vitamin K anticoagulants (NOAC) including the direct thrombin inhibitor, dabigatran and Factor Xa inhibitors (rivaroxaban, apixaban and edoxaban), with standard once or twice daily dosing, which are increasingly adopted in clinical practice[5]. The overall efficacy of these medications is established to be comparable to or better than that of VKAs [6-10] and their relative ease of use and lack of required monitoring provide important advantages for

anticoagulation management. While the net clinical benefit and comparable ease of use with NOACs is established, overall reports of medication persistence remain highly variable and prospective studies evaluating persistence to NOACs are limited[11].

1.2 Definitions of Medication Adherence and Persistence

Medication adherence refers to the constellation of drug taking behaviours, which is broadly divided into 3 components: initiation, implementation and discontinuation[12]. Initiation commences with the first dose, implementation includes intake of accurate doses, with correct timing and frequency as prescribed by a health care practitioner.

Although failure to initiate treatment is recognized as a serious treatment gap, the root causes for these gaps are likely different from causes of poor adherence once medication is started. Following initiation, discontinuation is the worst of the outcomes on the adherence spectrum[13], and the focus of this thesis is on this aspect of medication adherence, with rationale for focusing on persistence as an outcome further outlined. Goals and measurement characteristics for adherence components are outlined in Table 1.

For medications with standard dosing regimens, characterized by high rates of absolute discontinuation, persistence rates (or time to discontinuation) are important to establish before more complex measurements of adherence such as accurate dosing, and intake frequency are explored. If baseline measurements of anticoagulation persistence are low, measures of anticoagulation implementation will be less informative.

Furthermore, patients who fail to continue taking any dose are presumably worse off than patients who take some proportion of prescribed doses less than 100% (although the

argument may not necessarily hold for patients who take *more* than the prescribed doses[14]). Patients who stop taking their OAC altogether are a high risk group of patients for harmful outcomes[13] and may be most likely to benefit from interventions to improve persistence. The main OAC adherence risk is therefore, likely related to discontinuation.

1.3 Anticoagulation for Stroke Prophylaxis

The importance of anticoagulation persistence for AF patients at risk for stroke is undisputed and the expected link between discontinuation of OAC and negative outcomes such as stroke and mortality has been established[13,15]. However, in some cases, less than 50% of patients are reported to remain on anticoagulation over a 12-month period[16] and there is high variability in estimates across and within anticoagulant types including NOACs[11].

While there is a growing body of evidence to suggest that persistence with NOACs may be superior to that of VKA[11], some investigations conversely report that persistence is superior with warfarin compared to a NOAC and this may be due to the more frequent monitoring required with VKA and higher persistence resulting by virtue of closer follow-up[17]. Therefore, despite their established net therapeutic benefit, a clear understanding of the expected rates of anticoagulation persistence with NOACs is lacking.

The majority of primary studies evaluating anticoagulation persistence in AF are retrospective in nature, with varying definitions of persistence, periods of follow-up, and estimates of persistence[11]. Reviews of anticoagulation persistence and adherence similarly

show high heterogeneity in methods and outcomes, precluding synthesis of results by meta-analysis[18].

Persistence can be measured by various methods. For example, by examining frequency and timing of prescription refills[19,20], by abstraction from patient records[21], by patient or physician report[22,23], or by more direct quantitated measures of medication intake such as wearable sensors[24]. The relative difficulty, cost and practical utility of measurement as well as the value of precision in measurement are important considerations when selecting measures of persistence. One practical measurement with higher precision relative to prescription refill information is the use of initiation and discontinuation dates obtained through patient interview or by chart abstraction. The period of persistence is calculated from the interval in days between intake of the first to the last doses (as defined by a period by which medication is not subsequently resumed, e.g. 30 days).

1.4 Overview of Chapters Included in Thesis

Chapter 1 provides an introduction and overview of the topic of anticoagulation persistence for improving patient important outcomes in AF. In addition, the rationale and objectives for conducting the studies included in the thesis are detailed.

Chapters 2 and 3 of this thesis include original data generated from prospective investigations of persistence in a large global registry. Newly diagnosed AF patients, enrolled in clinical practice settings were followed up over 2 years to describe treatment patterns and outcomes. Information to describe reasons for discontinuation, were also reported by investigators participating in the registry from 44 countries (For participating

countries - see chapter 2 Figure 1: Distribution of Patients Initiated on Dabigatran) and over 900 clinical practice settings. The design of the global registry is described in an earlier publication but in brief includes 3 phases, assessing anticoagulation patterns: (i) prior to the availability of NOACs, (ii) following availability of NOACs; and (iii) once baseline characteristics between patients prescribed warfarin and NOACs were assessed to be comparable. The second phase was included to mitigate the concern of potential channeling bias, which could result if patients were selectively prescribed medications based on clinical characteristics[25].

Chapter 2: Persistence with Dabigatran Therapy at 2 Years in Patients with Atrial Fibrillation

Chapter 2 is a published report of a prospective evaluation of 2-year persistence in over 2900 patients newly initiating dabigatran in routine clinical practice[22]. In addition to reporting long-term persistence rates, this study explores predictors of, and reasons for discontinuation as well as regional differences in persistence.

Chapter 3: Dabigatran Persistence and Outcomes Following Discontinuation in Atrial Fibrillation Patients from the GLORIA-AF Registry

Chapter 3 is a published report of a study that further evaluates persistence to dabigatran in a larger sample of over 4900 patients (including the first 2900 patients) from the same global registry[23]. The study describes when and which patients are at highest risk for discontinuation, explores reasons for discontinuation and reports on outcomes following discontinuation. Understanding periods of greatest risk for anticoagulation discontinuation can inform optimal periods when interventions may be most effective to

implement. Establishing which patient subgroups are at risk for discontinuation can further improve the potential benefits of interventions by specifically targeting patient subgroups most likely to discontinue.

Finally, establishing outcomes following discontinuation is critical as efforts to enhance medication persistence are predicated on the implicit premise that persistence to efficacious medications will improve outcomes. Without demonstrating this important link, costs to patients and the health care system for employing interventions to improve persistence may not be reasonably justified.

Chapter 4: A Systematic Review and Meta-Analysis of Supplemental Education in Patients Treated with Oral Anticoagulation

Data for chapter 4 were obtained through a systematic search for randomized controlled trials (RCT) of patients treated with OACs for any indication, if they had at minimum, one intervention of supplemental educational and at least one control group comprised of no supplemental education (usual care). This systematic review and meta-analysis evaluated the impact of supplemental patient education on patient important outcomes including thromboembolic events and mortality.

Patients are active participants in health care decisions. Thus, improving patient disease and medication knowledge may improve outcomes by improving adherence through increased understanding of medication benefits and consequences for discontinuation. Patient education could also promote recognition of early signs or symptoms of adverse events associated with anticoagulation, most notably outcomes related to bleeding. In addition, education could work to ameliorate other cardiovascular risk factors such as

smoking, hypertension, diabetes and hypercholesterolemia[27-29] thereby improving outcomes.

Ultimately, interventions shown to improve medication adherence alone are insufficient (particularly if accompanied by high costs to the health care system or patient burden), if they cannot be tied to improvements in patient important outcomes. In addition to thromboembolic, bleeding and mortality outcomes, this review evaluated the impact of supplemental education on time in therapeutic range, and measures of patient knowledge.

Chapter 5: Methodological Considerations for Investigating Oral Anticoagulant Persistence in Atrial Fibrillation

Research in the area of anticoagulation persistence is growing, however there are varying estimates of persistence even for the same anticoagulant medications[11], which may be attributable to differences in methodological characteristics of the studies. To date, systematic reviews and meta-analysis with aims to elucidate rates of oral anticoagulant medication adherence or persistence in clinical practice are lacking, although there is a protocol published to indicate this is in progress[31].

In randomized clinical trials, methods to assess interventions to enhance adherence vary widely with differences in measurement of outcomes, patient enrolment and quality of studies. These differences have been posited to account for the failure of some studies to demonstrate that interventions improve adherence[32]. A comprehensive systematic review of randomized clinical trials to evaluate interventions to improve medication adherence

across broad disease conditions similarly reported heterogeneity in adherence measures, interventions and clinical outcomes, which precluded meta-analysis[33].

The objective of the fifth chapter is to highlight important considerations for interpreting research and designing studies in the area of OAC persistence and interventions to improve adherence or persistence. Variability in study methodology, settings and patient factors that may produce varying estimates of persistence are outlined. Discussion of these methodological differences in design and measurement in persistence studies permits researchers to apply a more consistent and structured assessment of strengths and limitations of research in this area.

To help guide researchers to design robust studies in OAC persistence, a framework for assessing and designing studies is proposed, considering various facets of study design including: (1) patient selection, (2) reliability and validity of selected measures, (3) definitions of persistence, (4) clinical utility of measures for development of interventions, (5) outcome and follow-up measures, and; (6) analysis. A scoring system is proposed to facilitate assessment of study characteristics to guide researchers in design of future studies. This is a framework which has not yet been validated. Validation for use in OAC persistence research could increase the utility of this tool and potentially support a methodological review of OAC persistence studies.

Chapter 6: Conclusions and Future Directions

Chapter 6 summarizes learnings, and highlights strengths, limitations and implications of the methods used in the included studies. In addition, areas for future research are outlined and conclusions summarize the overall implications of the research.

The key findings from the thesis are summarized, including description of:

(i) Prospectively established long term persistence rates with a NOAC;

(ii) The period when patients are most likely to discontinue a NOAC;

(iii) Reasons why patients discontinue a NOAC;

(iv) Patient subgroups that may be at highest risk to discontinue;

(v) Comparative outcomes of patients who discontinue without switching to an alternative oral anticoagulant, to those who switch;

(vi) The impact of supplemental patient education to improve patient outcomes;

(vii) Methodological differences in studies that may produce varying persistence estimates, and;

(viii) A framework for evaluating and designing studies in oral anticoagulation persistence.

This final chapter also discusses relative strengths, weaknesses of the current body of research as well as opportunities for future research.

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Table 1: Measures of Adherence and Persistence

Adherence Definition Components[12]	**Definitions**[12]*	**Common Measurements**[12]	**Questions answered by Measurement**	**Potential Applications**
Initiation	Defined as patient intake of the first dose of a prescribed medication	(i) First observed intake (ii) First reported intake (iiii) First documented intake (iv) First bottle opening (v) First prescription filled	Proportion of patients: (i) Receiving prescription for medication (ii) Taking prescribed medication	(i) Examine adherence to prescribing guideline (ii) Drug initiation barriers (iii) Valid measure for acute illness
Implementation (Used interchangeably with adherence in literature)	Extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose	(i) Proportion of prescribed drug taken (ii) Proportion of days with correct # doses (iii) Proportion of doses taken as scheduled (iv) Distribution of inter-dose intervals (v) Number of drug holidays (vi) Longest interval between two doses (vii) Serum blood levels of drug	(i) Patient dosing errors (ii) General adherence to drug regimen (iii) Association of drug intake with adverse events and outcomes	(i) Estimate drug levels with safety/efficacy outcomes (ie. over- or under-dosing) (ii) Explore drug interactions (iii) Valid for complex dosing regimens and drugs with narrow therapeutic window
Discontinuation	Defined as stop of prescribed medication irrespective of reason	(i) Last reported dose taken (ii) Last documented intake (iii) Last bottle opening (iv) Last prescription filled	(i) Drug efficacy (ii) Disease outcomes	(i) Validate drug efficacy (ii) Evaluate consequences of drug discontinuation
Persistence	Period of time between initiation and discontinuation	Period between: (i) First and last observed intake (ii) First and last reported intake (ii) First and last documented intake (iiii) First and last bottle opening (iv) First and last prescription filled	In addition to above for discontinuation: (i) How long patients remain on medication	In addition to above for discontinuation: (i) Examine chronic disease drug maintenance (ii) Appropriate for drug with simple dosing regimens

The general definition of adherence refers to "The process by which patients take their medications as prescribed, composed of initiation, implementation and discontinuation"[12]. The term can also be used to reflect a particular aspect of adherence described as implementation which is the focus for this illustration.

CHAPTER 2: Persistence with Dabigatran Therapy at 2 Years in Patients with Atrial Fibrillation

PREFACE TO CHAPTER 2

The manuscript entitled, “Persistence with Dabigatran Therapy at 2 Years in Patients with Atrial Fibrillation” was submitted to the Journal of the American College of Cardiology on 21 May 2017, submitted with revisions on 14 July 2017 and accepted for publication on 25 July 2017. The final manuscript was published 26 September, 2017. This dissertation includes the final revised submitted version (published online https://doi.org/10.1016/j.jacc.2017.07.793).

Contributions of Authors

Miney Paquette wrote the first draft of the manuscript, addressed critical revisions, and incorporated all author and reviewer comments into the final accepted version of the manuscript. She also contributed to the design and conduct of the study, analysis plan, interpretation of the data, and writing of results.

Lionel Riou França, Christine Teutsch, Shihai Lu, and Kristina Zint contributed to the design and conduct of the study, interpretation of the data, and writing of results. Shihai Lu conducted the analysis. Professor Chris Diener, Dr. Sergio Dubner, Professor Changsheng Ma, Dr. Kenneth Rothman, Dr. Jonathan Halperin, Dr. Menno Huisman, and Professor Gregory Y.H. Lip contributed to the design of the study, interpretation of the data, and writing of the manuscript. Dr. Robby Nieuwlaat contributed to the interpretation of the data and writing of the manuscript.

All authors reviewed and approved the final version of the accepted manuscript.

Persistence with Dabigatran Therapy at 2 Years in Patients with Atrial Fibrillation

Brief title: Therapy Persistence with Dabigatran over 2 years

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Abstract

BACKGROUND Guidelines recommend long-term oral anticoagulation for stroke prevention in patients with atrial fibrillation (AF). Treatment discontinuation rates in vitamin K antagonist (VKA)–treated patients are high and may be lower with non-VKA oral anticoagulants (NOACs).

OBJECTIVES To describe and explore predictors of dabigatran etexilate (dabigatran) persistence in patients with newly diagnosed AF over 2 years of follow-up.

METHODS Consecutive patients newly diagnosed with AF and ≥1 stroke risk factor were followed for 2 years. Dabigatran non-persistence was defined as discontinuation of dabigatran >30 days. Multivariable Cox regression model included region, and patient clinical and sociodemographic characteristics to explore predictors of non-persistence.

RESULTS 2,932 eligible patients took ≥1 dabigatran dose; mean age was 70.3 ± 10.2 years; 55.3% were male. The 2-year probability of dabigatran persistence was 69.2%. Approximately 7% switched to a Factor Xa inhibitor and 6% to a VKA. Approximately one third of dabigatran discontinuations were primarily due to serious or non-serious adverse events. Patients from North America had the greatest discontinuation risk, and Latin America the lowest risk. Minimally symptomatic/asymptomatic AF and permanent AF were associated with a lower risk for dabigatran non-persistence. Prior proton pump inhibitor (PPI) use was associated with higher risk for dabigatran non-persistence.

CONCLUSIONS Probability of treatment persistence with dabigatran after 2 years was approximately 70%. Approximately half of the patients who stopped dabigatran switched to another oral anticoagulant. Patients from North America, and those with paroxysmal/persistent or symptomatic AF, may be at higher risk for discontinuing dabigatran.

KEY WORDS atrial fibrillation, stroke prevention, dabigatran, persistence

Condensed Abstract:

This investigation describes persistence with dabigatran etexilate over 2-year follow-up and explores predictors of persistence in consecutively enrolled, newly diagnosed atrial fibrillation (AF) patients at risk for stroke. In 2,932 eligible patients, the 2-year probability of dabigatran persistence was close to 70%. Approximately one third of dabigatran discontinuations were primarily due to adverse events and patients from North America had the greatest discontinuation risk. Surrogate markers of AF severity such as permanent and asymptomatic AF were associated with lower risk of treatment discontinuation, suggesting that patients without these characteristics may be an important group to target to increase treatment persistence.

ABBREVIATIONS AND ACRONYMS

AE = adverse event

AF = atrial fibrillation

CI = confidence interval

GLORIA-AF = **G**lobal Registry on **L**ong-Term **O**ral Anti-thrombotic T**R**eatment **I**n P**A**tients with **A**trial **F**ibrillation

HR = hazard ratio

NOAC = non-VKA oral anticoagulant

OAC = oral anticoagulant

SAE = serious adverse event

VKA = vitamin K antagonist

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia. It is well documented as an independent factor for ischemic stroke (1), and is associated with considerable mortality and morbidity (2-4). Current guidelines recommend long-term oral anticoagulation for stroke prevention in patients with AF who are at risk for stroke (5). Until 2010, when dabigatran etexilate (dabigatran), the first non-vitamin K oral anticoagulant (NOAC) became available, vitamin K antagonists (VKAs) were the standard anticoagulation therapy for patients with AF. Although VKAs are effective in preventing strokes, treatment discontinuation rates are pronounced, with only 39% to 60% remaining on VKA treatment after 1 year (6-8).

Several factors contribute to suboptimal treatment adherence with VKAs. These include narrow therapeutic windows requiring frequent laboratory monitoring, a variable dose response relationship, and interactions with food and medications for comorbid conditions. These problems are diminished with NOACs, which have been endorsed as a class 1A recommendation in the most recent European Society of Cardiology guidelines for the management of AF (5).

Medication adherence is defined as the accurate intake of medications based on the dose, frequency, and schedule prescribed (9). A closely related concept, and the main target of this investigation, is medication persistence, defined as “the duration of time from the initiation to discontinuation of therapy” (10). The evidence evaluating the persistence of VKA and NOAC therapies shows highly variable reports of both

persistence and medication adherence, with generally better rates of adherence and persistence with NOACs versus VKAs (11).

Adherence and particularly persistence are expected to be affected by various factors including the incidence of adverse events (AEs). Nonetheless, the reasons for treatment non-persistence (used interchangeably with treatment discontinuation) in patients taking oral anticoagulant (OACs) for stroke prevention have not been extensively described, especially from large prospective patient cohorts. Therefore, we sought to describe and assess reasons for non-persistence with treatment, including those related to AEs.

This global, prospective cohort study aims to describe dabigatran non-persistence, with or without subsequent treatment with another OAC, in patients receiving dabigatran and enrolled in the **G**lobal Registry on **L**ong-Term **O**ral Anti-thrombotic T**R**eatment **I**n P**A**tients with **A**trial **F**ibrillation (GLORIA-AF registry program), between 2011 and 2014.

METHODS

The GLORIA-AF registry program enrolled consecutive adult patients with AF seen in routine clinical practice in 44 countries in 5 regions. Sources used to identify a broad range of potential sites and physicians, included professional directories, referrals from selected investigators and national co-ordinators, and sites who had previously worked with the study sponsor that funded the registry. Sites were selected only on the basis of confirmation that they diagnose and follow AF patients and prior research experience was not a prerequisite. Patients were managed according to routine standard practice and were not required to be prescribed any specific OAC or any OAC at all.

Once dabigatran was approved for the indication of stroke prevention in a respective country, countries were immediately approached to start Phase II. The time to initiate the study in the countries varied and was dependent on site identification, regulatory review timelines and ethical committee reviews at participating sites. Additional details on the design of the GLORIA-AF program have been previously published (12). Baseline characteristics of all eligible patients enrolled in program phase II have been described previously (13). In phase II of this study, only dabigatran patients were followed-up. Patients were recruited from various outpatient settings including university and community hospitals and specialist and general practice offices. Patients with newly diagnosed documented AF within 3 months of baseline visit and at least 1 risk factor for stroke by CHA_2DS_2-VASc criteria (14) were eligible for inclusion into the registry program. Patients with prior VKA therapy for >60 days, AF due to generally reversible causes, and patients with mechanical heart valves were excluded.

Patients who had important protocol violations (e.g., lack of appropriate informed consent, or participation in a clinical trial or international registry), or data insufficiently cleaned (i.e., >2 open manual queries) were excluded from the analysis. For this analysis, only patients taking at least 1 dose of dabigatran and who had follow-up data were included.

Standard electronic case report forms were used to record baseline characteristics including stroke and bleeding risk factors that constitute the CHA_2DS_2-VASc (14) and HAS-BLED scores (15), respectively, as well as AF type (paroxysmal, persistent, permanent), AF-related symptoms based on the European Heart Rhythm Association

classification of symptomatic, minimally symptomatic or asymptomatic (16), antithrombotic treatment, medical history, concomitant medications, and reimbursement status of prescribed OAC. Start and stop dates of antithrombotic therapies and concomitant medications were recorded by the treating physician based on information included in the patient source data records.

THERAPY PERSISTENCE. Index therapy was the treatment prescribed for long-term anticoagulation following AF diagnosis and recorded at the baseline visit. At the follow-up intervals (approximately 3, 6, 12, and 24 months after baseline), changes to medical conditions, antithrombotic treatment changes, and all serious AEs (SAEs), interventions, and adverse drug reactions (ADRs) including major and life-threatening bleeding events were recorded. The primary and mutually exclusive reasons for discontinuing index dabigatran treatment were also captured. Physicians could choose 1 reason from a pre-specified list including bleeding events, alcohol intake, dementia, AEs, dyspepsia, hypersensitivity, drug interactions, cost, or "other" if the former options did not apply.

Therapy non-persistence was defined in 2 ways to characterize the probability of discontinuing the index dabigatran therapy:

1) **Dabigatran non-persistence:** Patients who stop index dabigatran treatment (for >30 days) during the follow-up period *or* switch to another OAC within 30 days.
2) **Dabigatran non-persistence without switch:** Subgroup of patients from 1) who stop index dabigatran treatment (for >30 days) *and* do not start another OAC within 30 days of dabigatran discontinuation.

STATISTICAL ANALYSIS. All data were analyzed using SAS version 9.4 [SAS Institute, Cary, North Carolina (USA)]. Baseline data were summarized descriptively overall, by region and for factors related to treatment non-persistence. Continuous variables were reported as means and standard deviations, and categorical variables were reported as absolute frequencies and percentages. In addition, reasons for discontinuation of dabigatran treatment at 2 years were summarized descriptively.

Probabilities of dabigatran persistence were evaluated using a Kaplan-Meier time-to-event analysis. Dose changes (e.g., lowering dose from 150 mg twice daily to 110 mg twice daily) were not considered as switched treatment, as dose adjustments represent part of the antithrombotic therapy management process.

Variables included in the Cox regression models to evaluate risk factors associated with dabigatran discontinuation included region, reimbursement status of medication, and patient clinical and socio-demographic characteristics. Patients were followed until study withdrawal, death, end of study, or occurrence of dabigatran non-persistence, whichever came first.

To evaluate whether reclassification of patients who switched treatments after a longer period after dabigatran discontinuation (i.e., >30 days) would change the results, an additional sensitivity analysis was conducted, reclassifying the 28 patients who switched to another OAC *after* the 30-day period following dabigatran discontinuation.

RESULTS

A total of 3,002 patients were enrolled; 65 of these patients were not eligible (2.2%) including 45 who did not meet inclusion/exclusion criteria and 20 who did not meet data

cleaning requirements. The main reason for not meeting inclusion criteria was due to absence of new AF diagnosis (35 patients). The remainder (10 patients) had AF with reversible cause, had more than 60 days of warfarin or had exclusionary valve disease. There were 5 patients (0.5%) who were prescribed dabigatran but were not treated, providing a total of 2,932 patients for the analysis who were eligible, prescribed dabigatran, and took at least 1 dose. Most patients were enrolled in Europe (51.2%), followed by North America (27.9%), these being the regions where NOACs were first approved. In regions with later NOAC approvals, fewer dabigatran patients were enrolled: Asia (12.4%), Latin America (6.6%), and Africa/Middle East (1.8%) (**Figure 1**).

PATIENT CHARACTERISTICS. The mean age was 70.3 ± 10.2 years, and 1,620 patients were male (55.3%). Approximately half had paroxysmal AF (n = 1,481, 50.5%), 1,063 (36.3%) had persistent AF, and a minority had permanent AF at the time of enrollment (n = 388, 13.2%). Approximately one-quarter of the patient group had symptomatic AF (26.5%), 46.5% reported having minimally symptomatic AF, and 27.0% reported asymptomatic AF.

About one-third (36.7%) of patients were ≥75 years old and most were considered at high risk for stroke (CHA_2DS_2-VASc score was ≥2 in 88.2% of patients). The majority of patients were considered at low risk for bleeding (HAS-BLED score <3, 83.5%) and only 5.0% had a prior bleed. The majority of patients had a history of hypertension (78.9%), and 20.2% had coronary artery disease. The baseline characteristics of patients by region and other risk factors for discontinuation are shown in **Table 1 and 2**.

OVERALL TREATMENT PERSISTENCE. The probability of dabigatran treatment persistence was 76.6% at 1 year and 69.2% at 2 years, and the probability of remaining on dabigatran *or* discontinuing dabigatran and starting another OAC within 30 days was 87.7% at 1 year and 84.1% at 2 years (**Figure 2**).

At the end of follow-up, a total of 828 patients had discontinued dabigatran. Of the total 2,932 dabigatran patients, 1,859 remained on dabigatran (63.4%) until the study termination, 438 (14.9%) discontinued treatment without switching to another OAC, and 390 switched to another OAC (13.3%). Baseline characteristics of the patients who remained on dabigatran, discontinued with switching to another OAC or discontinued without switching are shown in **Supplementary Table 1**. There were 214 patients (7.3%) who switched to a Factor Xa inhibitor and 176 patients (6.0%) who switched to a VKA; 128 patients were lost to follow-up (4.4%), and 117 died before the end of follow-up (4.0%).

REASONS FOR DABIGATRAN NON-PERSISTENCE AT 2 YEARS. Primary reasons for discontinuing dabigatran treatment are presented in **Table 3**. Among patients discontinuing dabigatran (n = 828, 28.2%), 66 (8.0%) stopped dabigatran primarily due to dyspepsia, and ~25% stopped dabigatran primarily due to other AEs (64 [7.7%] SAEs, 62 [7.5%] non-serious AEs, 58 [7.0%] bleeding events, 22 [2.7%] hypersensitivity to agent, 2 [0.2%] bruising, and 2 [0.2%] due to concomitant medication interactions). The majority of respondents cited “other” (reason not otherwise specified) as the primary reason for discontinuation (n = 495, 59.8%) (**Table 3**). Upon further investigation of the proportion of patients who discontinued treatment citing a primary reason due to AEs

(including bleeding, bruising, dyspepsia, hypersensitivity or interactions with the agent, or other AEs/SAEs), more than half of these discontinuations occurred in the first 6 months (58.3%). For the individual adverse events, 65.0% of bleeds/bruising, 57.8% of dyspepsia, 72.7% of hypersensitivity to agents and 62.9% of general adverse drug reactions were reported in the first 6 months. For SAEs which were not necessarily related to dabigatran, 43.8% were reported in the first 6 months.

Overall, primary discontinuation due to cost of treatment was reported relatively infrequently with less than 3% of all primary reasons for discontinuation cited due to cost (**Table 3**). When evaluating the main reasons for discontinuation in North America compared to Europe, for example, where we might expect higher rates of reimbursement, the proportion of primary reasons for discontinuation due to cost were not markedly different (North America 1.0%; Asia 4.0%; Europe 3.1%; Latin America 0.0%).

Upon further investigation of patients who discontinued treatment with a primary reason documented as “other”, only a small proportion of the patients overall (8.1%) had adverse drug reactions or serious adverse events that were reported within 30 days prior to discontinuation (not necessarily related to treatment discontinuation). Furthermore, there were no thromboembolic events observed within 30 days prior to discontinuation in this group of patients.

PREDICTORS OF DABIGATRAN TREATMENT PERSISTENCE. Factors associated with dabigatran non-persistence were region, type of AF, type of site, categorization of AF, physician specialty, and prior proton pump inhibitor use. In particular, patients in North America were at higher risk of dabigatran discontinuation

(hazard ratio [HR] 1.66; 95% confidence interval [CI] 1.35 to 2.04) when compared with Europe, and patients in Latin America were at lower risk (HR 0.61; 95% CI 0.40 to 0.90) (**Table 4**). Patients with asymptomatic/minimally symptomatic AF were more likely to be persistent (HR for Non-persistence 0.78; 95% CI 0.66 to 0.91) versus symptomatic. Those with permanent AF were similarly less at risk for non-persistence versus paroxysmal/persistent AF patients (HR 0.73; 95% CI 0.56 to 0.93) (**Table 4**), as were patients followed by a primary care physician compared with those followed at a community hospital (HR 0.71; 95% CI 0.50 to 0.98). Prior proton pump inhibitor use was predictive of dabigatran non-persistence (HR 1.26; 95% CI 1.04 to 1.51).

Patients that were enrolled at a specialist's office had a similar risk for discontinuation as compared to those at a community hospital (HR 0.99, 95% CI 0.80 to 1.23); patients enrolled at a university hospital did not appear to be markedly at higher risk of discontinuation (HR 1.16, 95% CI 0.94 to 1.44). (**Table 4**). Other factors included in the model are shown in **Supplementary Table 2**.

PREDICTORS OF DABIGATRAN TREATMENT PERSISTENCE—SUBGROUP WITHOUT SWITCH TO ANOTHER OAC. Region was the strongest predictor of non-persistence without switch, with North America having the greatest risk of dabigatran non-persistence. In this subgroup analysis, patients in Asia appeared to have similar rates of discontinuation as Europe, but were at higher risk of discontinuing without switching (HR 1.64; 95% CI 1.20 to 2.21). Latin America and the Middle East/Africa had the lowest risk of dabigatran non-persistence in this subgroup (HR 0.62; 95% CI 0.35 to 1.03 and HR 0.86; 95% CI 0.33 to 1.84, respectively) versus Europe (**Table 4**). The main

clinical variables associated with a lower risk of dabigatran non-persistence without switch in the Cox model were prior stroke/transient ischemic attack (HR 0.66; 95% CI 0.46 to 0.93) and permanent AF versus paroxysmal/persistent AF (HR 0.66; 95% CI 0.46 to 0.93) (**Table 4**). Prior myocardial infarction (MI) was associated with a higher risk of non-persistence (HR 1.43; 95% CI 0.95 to 2.11) as was treatment at a university hospital compared to a community hospital (HR 1.35; 95% CI 1.00 to 1.81). Other factors included in the model are shown in **Supplementary Table 2.**

The sensitivity analysis considering patients as switchers if they had started another OAC after remaining untreated for more than 30 days (28 patients identified) led to similar results.

DISCUSSION

In this prospective assessment of clinical practice data from a global registry program, overall dabigatran persistence in an incident AF population was high, with the probability of remaining on dabigatran treatment after 1 year at ~75% and ~70% after 2 years. Of clinical importance is that about half of those patients who discontinued treatment during follow-up did not start another OAC within 30 days, leaving patients at risk for stroke, at least in the early period after initial discontinuation. To our knowledge, this is the first global, prospective study cohort describing regional differences in persistence patterns, specifically with a NOAC, dabigatran.

PUBLISHED STUDIES OF OAC PERSISTENCE. Previous evaluations of persistence have consistently demonstrated relatively poor persistence with warfarin

treatment, with 1-year discontinuation rates ranging from about 25% (17,18) to over 60% (7).

Some publications defined discontinuation as a treatment gap of 45 to 60 days, a definition less stringent than the one used here (30 days). Comparing persistence across studies is difficult, because even those focused on the same OAC may differ with respect to the patient populations, study designs, and definitions of non-persistence.

In another prospective registry of patients treated with another NOAC, rivaroxaban (XANTUS), persistence over a 1-year period was high with discontinuation rates of approximately 20% (19). A database study by Jackevicius et al. evaluating NOAC treatment persistence defined non-persistence as >14-day gaps between prescriptions. Persistence was described at 6-month follow-up and approximately one-third of patients were non-persistent to dabigatran and rivaroxaban. This population was considerably older, had a higher prevalence of comorbidity, and did not represent an incident AF population, with just over half of the population with prior warfarin use (20). Importantly, in this study, the risk of stroke/transient ischemic attack/death was significantly higher in those non-persistent to dabigatran or rivaroxaban compared with those who were persistent (20).

Better persistence with NOACs may result from better overall acceptance of NOAC therapies resulting from a lower burden of monitoring and fewer food and drug interactions compared with VKAs. It could also be posited that persistence with NOACs could be less favorable, due to fewer overall visits with healthcare providers resulting in fewer opportunities to have the importance of treatment persistence emphasized.

Risk of discontinuation is highest in the early period following treatment initiation (6 months to 1 year), after which point discontinuation rates level off or decline more gradually (17,18,21). Therefore, studies evaluating treatment persistence for only limited periods after treatment initiation may not predict accurately the discontinuation rates over the long term. Persistence should therefore be measured directly for at least a period of 1 year, or longer where possible.

REASONS FOR DISCONTINUATION. The data from this analysis suggest that the reasons for discontinuation of treatment are complex and may not be fully explained solely by examining adverse drug reactions such as bleeding or other AEs. About one-third of all reasons for primary dabigatran discontinuation were cited as due to an AE or SAE. The majority of primary reasons cited for treatment discontinuation or switch were "other," that is, not related to AEs or SAEs or to AEs associated with OAC treatment, such as bleeding or dyspepsia. A separate analysis in this group of patients showed only a small number of any adverse events reported within 30 days prior to discontinuation confirming that the responses indicated under the "other" reasons for discontinuation did not seem to include adverse events.

There may be an influence of patient or physician preference, potentially a higher perceived risk for outcomes that prompt changes in treatment, or other factors that were not directly explored. Indeed, in a review of adherence to NOACs, the importance of the patient's perspective was emphasized for making decisions around anticoagulant choice (22), and these preferences could also have strong implications for treatment persistence or switching to an alternative OAC.

PREDICTORS OF TREATMENT DISCONTINUATION. In this study, clinical factors predicted which patients were most likely to discontinue dabigatran treatment, with or without switching to an alternative OAC. The multivariable analyses showed that factors such as region (North America), and prior proton pump inhibitor use may be associated with dabigatran non-persistence, and measures that may be markers of disease severity, such as permanent AF, are associated with persistence.

This pattern is also seen in predictors of the subgroup that discontinue dabigatran but do not switch to another OAC within 30 days. In this group, which better reflects those who are at risk of complications stemming from lack of prophylaxis, the factors associated with a lower risk of non-persistence included permanent AF (vs. paroxysmal/persistent AF), and prior stroke/transient ischemic attack. Prior myocardial infarction was associated with a higher risk of non-persistence. Patients from Asia and North America had a higher risk of non-persistence with dabigatran compared with Europe.

Treatment-related AEs such as dyspepsia or hypersensitivity reactions were a more prevalent reason for switching than for discontinuing treatment. In cases of discontinuation without switching, SAEs and bleeding events were more often cited compared with those who switched, suggesting that patients who have more serious OAC-related side effects would more often remain untreated.

Clinical factors such as permanent AF, prior stroke, and low symptom burden, which are associated with treatment persistence, may be important clinical surrogates for disease severity. Physicians may provide more vigorous reminders or directives around the

importance of OACs in stroke prevention for patients with these markers, or patients themselves could be more committed to remaining on treatment after suffering a prior stroke or transient ischemic attack or experiencing more longstanding episodes of AF. Longer episodes of AF duration could, indeed, relate to the perception that a higher AF burden increases stroke risk and thus work to maintain patients on OAC therapy.

STRENGTHS. To our knowledge, this is the first prospective study to describe regional differences in persistence patterns. These regional differences may be secondary to differences in clinical standards, patient preferences, or patient management. Of note, the predictors of increased risk for treatment non-persistence appear to relate to factors associated with lower disease severity and to geographic differences.

LIMITATIONS. Our study has several limitations that should be noted. Patients consented to participate in the study, and physicians were aware that persistence to treatment would be recorded, potentially modifying behaviors (Hawthorne effect (23)). There could be increased attention from the treating physician, influencing patients to remain on treatment and patients likelier to have good adherence may agree to participate in a registry, resulting in higher overall rates of treatment persistence.

Patients were not followed up in the VKA group in this phase of the registry, which limited our ability to make comparisons. Another limitation is that only 1 primary reason was ascertained for treatment discontinuation. Furthermore, for a large proportion of patients, no specific information on the reason for discontinuation is available as the "other" category of reason for discontinuation was chosen without an option for

additional free field text. Finally, phase II started later in certain regions (Latin America and Africa/Middle East) and are thus less well represented in the data.

CONCLUSIONS

In this analysis of newly diagnosed AF patients, we found evidence for long-term persistence with dabigatran with ~30% probability of discontinuing index dabigatran treatment after 2 years. About half of those who discontinued dabigatran received another OAC within 30 days. Most of the primary reasons noted for treatment discontinuation did not directly relate to AEs, which implies that other factors such as perceived thromboembolic and bleeding risks or patient preferences may play an important role in decisions to persist with treatment. Surrogate markers of AF severity such as permanent AF were associated with lower risk of treatment discontinuation, suggesting that patients without these characteristics may be an important group to target to increase treatment persistence.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Persistence with oral anticoagulation treatment in patients with AF remains a challenge and a significant barrier to achieving optimal outcomes in patients. Information on long-term persistence with non-VKA oral anticoagulants is limited. This study describes long-term persistence with dabigatran etexilate over 2 years of follow-up and explores predictors of treatment persistence.

COMPETENCY IN PATIENT CARE: Factors associated with treatment discontinuation should be considered in patients prescribed long-term oral anticoagulation for stroke prevention in order to improve treatment persistence.

TRANSLATIONAL OUTLOOK: Future studies should evaluate reasons for treatment discontinuation in long-term follow-up with the aim to develop interventions to improve oral anticoagulant treatment persistence.

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Figure Legends

FIGURE 1 Distribution of Patients Initiated on Dabigatran

Regional distribution of patients initiated on dabigatran as their index therapy

FIGURE 2 Kaplan-Meier Curve of Time to Treatment Discontinuation Over 2 Years

Central Illustration

*Patients remaining on DE or switching to another OAC are considered persistent, and only those who discontinue are considered non-persistent. †Patients remaining on DE are considered persistent, and patients who switch or discontinue are considered non-persistent.

All eligible patients excluding those prescribed but not treated.

DE = dabigatran etexilate; OAC = oral anticoagulant.

Figure 1 Distribution of Patients Initiated on Dabigatran

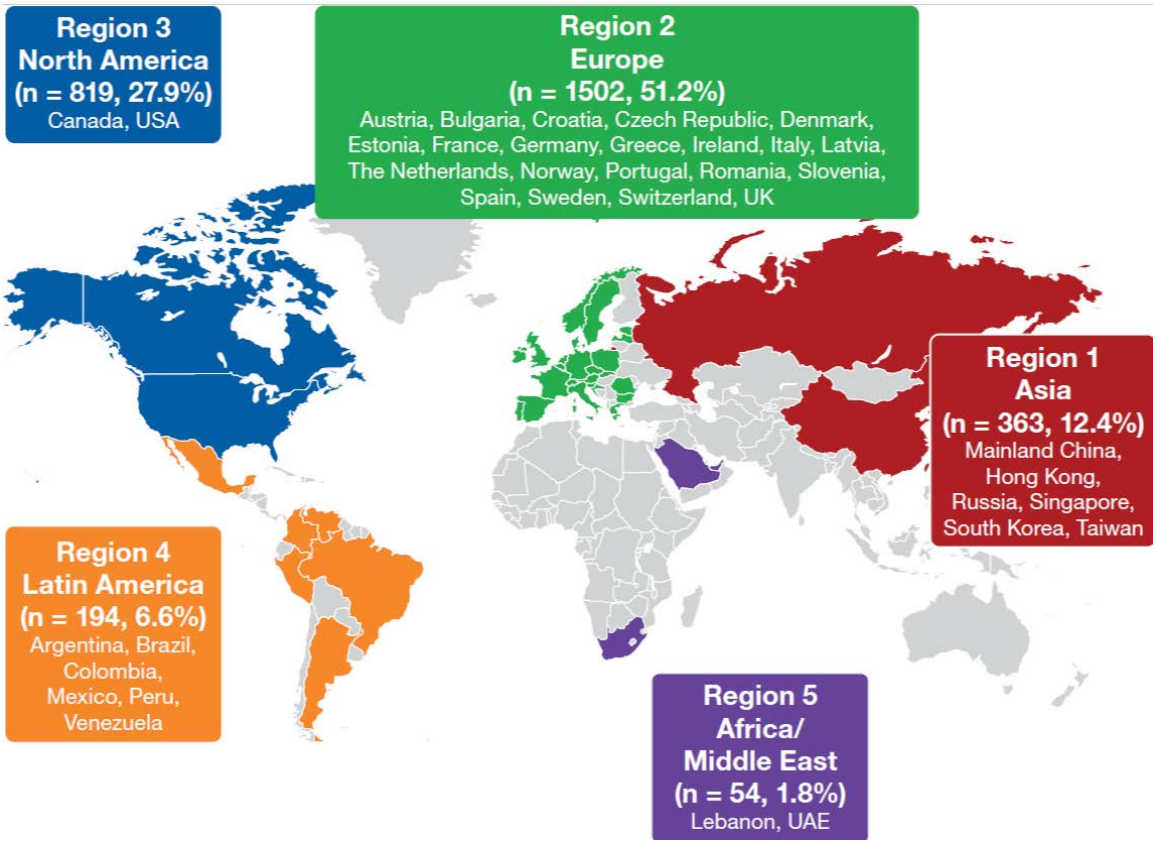

Figure 2 Kaplan-Meier Curve of Time to Treatment Discontinuation Over 2 Years

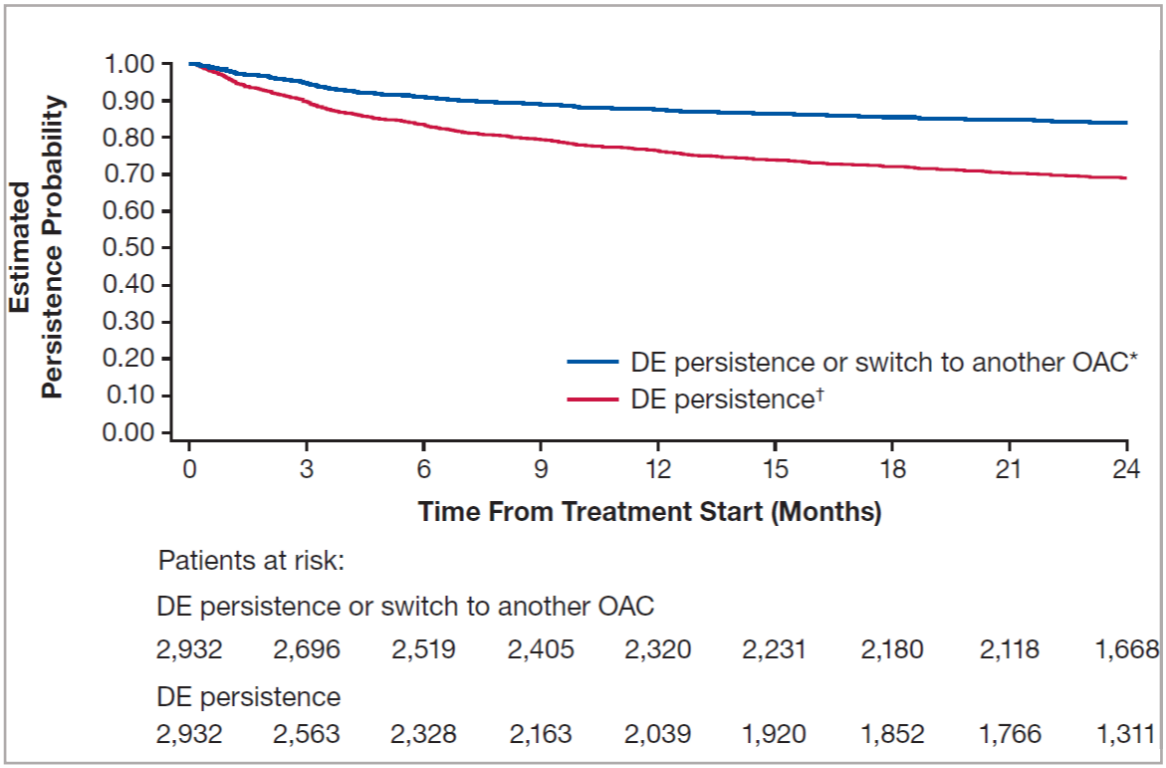

TABLE 1 Patient Characteristics and Predictors of Non-persistence

Patient Characteristics	Previous Stroke/TIA*		PPI Use		AF Type		AF Symptoms		Total N=2,932
	Yes n=414	No n=2,517	Yes n=572	No n= 2,360	Paroxysmal/ Persistent n=2,544	Permanent n=388	Minimally/ Asymptom. n=2,155	Symptom. n=777	
Age, mean (SD), years	72.6 (9.6)	69.9 (10.2)	71.8 (9.4)	69.9 (10.3)	69.9 (10.2)	73.1 (9.9)	70.5 (9.9)	69.8 (10.9)	70.3 (10.2)
Age ≥75 years, n (%)	184 (44.4)	891 (35.4)	235 (41.1)	841 (35.6)	890 (35.0)	186 (47.9)	780 (36.2)	296 (38.1)	1,076 (36.7)
BMI, mean (SD), kg/m^2†	28.1 (5.6)	29.4 (6.2)	29.4 (6.2)	29.2 (6.1)	29.3 (6.2)	28.9 (5.6)	29.2 (6.0)	29.4 (6.5)	29.2 (6.1)
Male, n (%)	224 (54.1)	1,395 (55.4)	286 (50.0)	1,334 (56.5)	1,410 (55.4)	210 (54.1)	1,237 (57.4)	383 (49.3)	1,620 (55.3)
MI, n (%)‡	45 (10.9)	203 (8.1)	62 (10.8)	186 (7.9)	215 (8.5)	33 (8.5)	191 (8.9)	57 (7.3)	248 (8.5)
Coronary artery disease, n (%)x	102 (24.6)	489 (19.4)	138 (24.1)	454 (19.2)	517 (20.3)	75 (19.3)	441 (20.5)	151 (19.4)	592 (20.2)
Congestive heart failure, n (%)§	68 (16.4)	664 (26.4)	139 (24.3)	593 (25.1)	591 (23.2)	141 (36.3)	473 (21.9)	259 (33.3)	732 (25.0)
History of hypertension, n (%)‖	325 (78.5)	1,896 (78.9)	466 (81.5)	1,846 (78.2)	2,003 (78.7)	309 (79.6)	1699 (78.8)	613 (78.9)	2,312 (78.9)
Diabetes mellitus, n (%)	93 (22.5)	572 (22.7)	157 (27.4)	508 (21.5)	580 (22.8)	85 (21.9)	503 (23.3)	162 (20.8)	665 (22.7)

CHA_2DS_2-VASc risk score, mean (SD)	5.0 (1.3)	2.9 (1.2)	3.6 (1.5)	3.1 (1.4)	3.2 (1.4)	3.6 (1.4)	3.2 (1.4)	3.3 (1.4)	3.2 (1.4)
Prior bleeding, n (%)#	41 (9.9)	106 (4.2)	48 (8.4)	99 (4.2)	133 (5.2)	14 (3.6)	111 (5.2)	36 (4.6)	147 (5.0)
HAS-BLED score, mean (SD)**	2.0 (0.9)	1.1 (0.7)	1.4 (0.9)	1.2 (0.8)	1.2 (0.8)	1.3 (0.8)	1.3 (0.9)	1.2 (0.8)	1.2 (0.8)
Renal impairment, n (%)††	1 (0.2)	11 (0.4)	1 (0.2)	11 (0.5)	10 (0.4)	2 (0.5)	9 (0.4)	3 (0.4)	12 (0.4)
Physician specialty‡‡									
Cardiology, n (%)	341 (82.4)	2,328 (92.5)	506 (88.5)	2,164 (91.7)	2,325 (91.4)	345 (88.9)	1,934 (89.7)	736 (94.7)	2,670 (91.1)
General practitioner/ geriatrician, n (%)	12 (2.9)	92 (3.7)	24 (4.2)	80 (3.4)	93 (3.7)	11 (2.8)	83 (3.9)	21 (2.7)	104 (3.5)
Internist, n (%)	6 (1.4)	57 (2.3)	12 (2.1)	51 (2.2)	43 (1.7)	20 (5.2)	54 (2.5)	9 (1.2)	63 (2.1)
Neurologist, n (%)	46 (11.1)	2 (0.1)	33 (1.4)	2 (0.1)	45 (1.8)	3 (0.8)	47 (2.2)	1 (0.1)	48 (1.6)
Other, n (%)	9 (2.2)	36 (1.4)	13 (2.3)	32 (1.4)	37 (1.5)	8 (2.1)	35 (1.6)	10 (1.3)	47 (1.6)

Percentages are expressed as the number of patients with the condition present divided by the total number of patients with data available.

*Unknown in 1 patient. †Unknown or missing in 20 patients. ‡Unknown in 1 patient. xUnknown in 74 patients. §Unknown in 32 patients. ||Unknown in 7 patients. #Unknown in 52 patients. **Unknown or missing in 300 patients. ††Unknown in 26 patients. ‡‡Unknown in 2 patients.

AF = atrial fibrillation; BMI = body mass index; MI = myocardial infarction; PPI = proton pump inhibitor; SD = standard deviation; TIA = transient ischemic attack.

TABLE 2 Patient Characteristics by Geographic Region

Patient Characteristics	Region					Total (N = 2,932)
	Europe (n = 1,502)	North America (n = 819)	Asia (n = 363)	Latin America (n = 194)	Middle East/Africa (n = 54)	
Age, mean (SD), years	70.7 (10.0)	70.8 (10.2)	67.1 (10.6)	71.3 (10.1)	70.4 (9.5)	70.3 (10.2)
Age ≥75 years, n (%)	574 (38.2)	315 (38.5)	88 (24.2)	81 (41.8)	18 (33.3)	1,076 (36.7)
BMI, mean (SD), kg/m^2*	28.6 (5.4)	30.9 (7.3)	28.3 (5.7)	28.3 (5.1)	29.6 (6.1)	29.2 (6.1)
Male, n (%)	811 (54.0)	484 (59.1)	195 (53.7)	109 (56.2)	21 (38.9)	1,620 (55.3)
MI, n (%)†	113 (7.5)	86 (10.5)	31 (8.5)	14 (7.2)	4 (7.4)	248 (8.5)
Coronary artery disease, n (%)‡	237 (15.8)	220 (26.9)	101 (27.8)	21 (10.8)	13 (24.1)	592 (20.2)
Congestive heart failure, n (%)x	396 (26.4)	132 (16.1)	139 (38.3)	57 (29.4)	8 (14.8)	732 (25.0)
History of hypertension, n (%)§	1,145 (76.2)	665(81.2)	303 (83.5)	151 (77.8)	48 (88.9)	2,312 (78.9)
Diabetes mellitus, n (%)	318 (21.2)	211(25.8)	81 (22.3)	36 (18.6)	19 (35.2)	665 (22.7)
CHA_2DS_2-VASc risk score, mean (SD)	3.2 (1.4)	3.2 (1.5)	3.2 (1.4)	3.3 (1.4)	3.6 (1.4)	3.2 (1.4)
Prior bleeding, n (%)‖	57 (3.8)	64 (7.8)	16 (4.4)	9 (4.6)	1 (1.9)	147 (5.0)
HAS-BLED score, mean (SD)#	1.2 (0.8)	1.4 (0.9)	1.1 (0.8)	1.2 (0.8)	1.2 (0.7)	1.2 (0.8)
Renal impairment, n (%)**	4 (0.3)	6 (0.7)	0 (0.0)	2 (1.0)	0 (0.0)	12 (0.4)

Physician specialty††						
Cardiology, n (%)	1,447 (96.3)	661 (80.7)	334 (92.0)	175 (90.2)	54 (100.0)	2,670 (91.1)
General practitioner/ geriatrician, n (%)	11 (0.7)	65 (7.9)	15 (4.1)	13 (6.7)	0 (0.0)	104 (3.5)
Internist, n (%)	10 (0.7)	47 (5.7)	0 (0.0)	6 (3.1)	0 (0.0)	63 (2.1)
Neurologist, n (%)	8 (0.5)	40 (4.9)	0 (0.0)	0 (0/0)	0 (0.0)	48 (1.6)
Other, n (%)	25 (1.7)	6 (0.7)	14 (3.9)	0 (0.0)	0 (0.0)	47 (1.6)

Percentages are expressed as the number of patients with the condition present divided by the total number of patients with data available.

*Unknown or missing in 20 patients. †Unknown in 1 patient. ‡Unknown in 74 patients. xUnknown in 32 patients. §Unknown in 7 patients. ||Unknown in 52 patients. #Unknown or missing in 300 patients. **Unknown in 26 patients. ††Unknown in 2 patients.

BMI = body mass index; MI = myocardial infarction; SD = standard deviation.

TABLE 3 Reasons for Discontinuation of DE Treatment at 2 Years

Reasons for DE Discontinuation, n (%)	Patients Who Discontinued DE and Did Not Use Another OAC After Stopping n = 438	Patients Who Switched from DE to Another OAC Within 30 Days* n = 390	Total n = 828
Other†	285 (65.1)	210 (53.8)	495 (59.8)
Dyspepsia	10 (2.3)	56 (14.4)	66 (8.0)
Adverse events‡	27 (6.2)	35 (9.0)	62 (7.5)
Serious adverse events‡	43 (9.8)	21 (5.4)	64 (7.7)
Bleeding	40 (9.1)	18 (4.6)	58 (7.0)
Hypersensitivity to agent	6 (1.4)	16 (4.1)	22 (2.7)
Cost of treatment	10 (2.3)	9 (2.3)	19 (2.3)
Social reason (drug, alcohol abuse)	7 (1.6)	6 (1.5)	13 (1.6)
Bruising	0 (0.0)	2 (0.5)	2 (0.2)
Bridging therapy start	7 (1.6)	2 (0.5)	9 (1.1)
Dementia	2 (0.5)	2 (0.5)	4 (0.5)
Severe interaction with concomitant medication	1 (0.2)	1 (0.3)	2 (0.2)

*Data are missing for 12 patients who switched from DE to another OAC.

†Reason was not specified.

‡Does not include adverse events listed in the table.

DE = dabigatran etexilate; OAC = oral anticoagulant.

TABLE 4 Main Predictors of Dabigatran Non-persistence in a Multivariable Cox Regression Model

Variable (n)	No. (%) of Dabigatran Non-persistent Patients (n = 828)	Adjusted* HR (95% CI)	No. (%) of Dabigatran Non-persistent Patients Without Subsequent OAC† (n = 438)	Adjusted* HR (95% CI)
Region				
Europe (1,502)	383 (25.5)	Ref. group	187 (12.5)	Ref. group
North America (819)	303 (37.0)	1.66 (1.35 to 2.04)	156 (19.0)	1.53 (1.15 to 2.03)
Asia (363)	101 (27.8)	1.18 (0.92 to 1.50)	72 (19.8)	1.64 (1.20 to 2.21)
Latin America (194)	30 (15.5)	0.61 (0.40 to 0.90)	17 (8.8)	0.62 (0.35 to 1.03)
Africa/Middle East (54)	11 (20.4)	0.72 (0.36 to 1.27)	6 (11.1)	0.86 (0.33 to 1.84)
Categorization of AF				
Symptomatic (777)	248 (31.9)	Ref. group	132 (17.0)	Ref. group
Minimally symptomatic/ asymptomatic (2,155)	580 (26.9)	0.78 (0.66 to 0.91)	306 (14.2)	0.84 (0.67 to 1.05)
Previous TIA or stroke				
No/missing (2,518)	726 (28.8)	Ref. group	398 (15.8)	Ref. group
Yes (414)	102 (24.6)	0.84 (0.66 to 1.06)	40 (9.7)	0.66 (0.46 to 0.93)
Type of AF				

Paroxysmal/persistent AF (2,544)	749 (29.4)	Ref. group	401 (15.8)	Ref. group
Permanent AF (388)	79 (20.4)	0.73 (0.56 to 0.93)	37 (9.5)	0.66 (0.46 to 0.93)
Proton pump inhibitors				
No (2,360)	640 (27.1)	Ref. group	350 (14.8)	Ref. group
Yes (572)	188 (32.9)	1.26 (1.04 to 1.51)	88 (15.4)	1.04 (0.80 to 1.36)
Type of site				
Community hospital (866)	220 (25.4)	Ref. group	105 (12.1)	Ref. group
University hospital (635)	187 (29.4)	1.16 (0.94 to 1.44)	100 (15.7)	1.35 (1.00 to 1.81)
Specialist office (1,065)	332 (31.2)	0.99 (0.80 to 1.23)	182 (17.1)	1.31 (0.97 to 1.76)
GP/primary care (226)	51 (22.6)	0.71 (0.50 to 0.98)	31 (13.7)	1.10 (0.70 to 1.69)
Outpatient health care/ anticoagulation clinic (117)	31 (26.5)	0.88 (0.57 to 1.31)	17 (14.5)	0.89 (0.49 to 1.51)
Myocardial infarction				
No/missing (2,684)	748 (27.9)	Ref. group	395 (14.7)	Ref. group
Yes (248)	80 (32.3)	1.10 (0.81 to 1.47)	43 (17.3)	1.43 (0.95 to 2.11)
CHA_2DS_2-VASc score class				

High (score ≥2) (2,587)	715 (27.6)	Ref. group	365 (14.1)	Ref. group
Moderate (score = 1) (345)	113 (32.8)	1.13 (0.88 to 1.45)	73 (21.2)	1.31 (0.94 to 1.80)
Age class				
<75 years (1,856)	536 (28.9)	Ref. group	303 (16.3)	Ref. group
≥75 years (1,076)	292 (27.1)	0.95 (0.80 to 1.12)	135 (12.5)	0.84 (0.66 to 1.06)
Congestive heart failure				
No/missing (2,200)	639 (29.0)	Ref. group	325 (14.8)	Ref. group
Yes (732)	189 (25.8)	0.96 (0.80 to 1.15)	113 (15.4)	1.16 (0.92 to 1.46)
History of hypertension				
No/missing (620)	183 (29.5)	Ref. group	93 (15.0)	Ref. group
Yes (2,412)	645 (26.7)	0.90 (0.75 to 1.08)	345 (14.3)	1.01 (0.79 to 1.31)
Coronary artery disease				
No/missing (2,340)	646 (27.6)	Ref. group	352 (15.0)	Ref. group
Yes (592)	182 (30.7)	1.05 (0.84 to 1.30)	86 (14.5)	0.79 (0.57 to 1.06)
Chronic gastrointestinal diseases				
No/missing (2,526)	690 (27.3)	Ref. group	359 (14.2)	Ref. group
Yes (406)	138 (34.0)	1.08 (0.87 to 1.33)	79 (19.5)	1.25 (0.94 to 1.64)
Medical treatment reimbursed by				
Statutory/federal insurance (1,999)	559 (28.0)	Ref. group	283 (14.2)	Ref. group
Private insurance (578)	183 (31.7)	1.06 (0.88 to 1.29)	96 (16.6)	1.06 (0.81 to 1.38)
Self-pay/no coverage /unknown (355)	86 (24.2)	1.01 (0.78 to 1.28)	59 (16.6)	1.24 (0.90 to 1.66)
BMI, kg/m^2				

BMI <30 (1,832)	518 (28.3)	Ref. group	279 (15.2)	Ref. group
BMI ≥30 (1,080)	307 (28.4)	0.95 (0.81 to 1.12)	158 (14.6)	0.84 (0.67 to 1.04)
DE mono vs. combination				
DE mono (2,539)	704 (27.7)	Ref. group	360 (14.2)	Ref. group
DE combination (393)	124 (31.6)	1.00 (0.80 to 1.25)	78 (19.8)	1.27 (0.95 to 1.70)

333 patients from other types of site, or having missing values for body mass index or HAS-BLED score were excluded from the multivariable analyses.

*Adjusted HRs were estimated from a multivariable Cox model including all variables listed in this table and in **Supplementary Table 2**.

†Represents patients who discontinue DE but do not start another OAC within 30 days.

AF = atrial fibrillation; CI = confidence interval; DE = dabigatran etexilate; GP = general practice; HR = hazard ratio; OAC = oral anticoagulant; Ref. = reference; TIA = transient ischemic attack.

APPENDIX: SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE 1 Baseline Characteristics of Dabigatran Persistent versus Non-persistent Patients at 24 months

	DE Persistent Patients n= 1859	**DE Non-persistent Switchers n = 390**	**DE Non-persistent Non-switchers n = 438**
Age, mean (SD), years	70 (10)	71.4 (9.4)	68.8 (11.1)
Age ≥75 years, n (%)	649 (34.9)	157 (40.3)	135 (30.8)
BMI, mean (SD), kg/m^2	29.4 (6.0)	29.1 (5.9)	28.9 (6.2)
Male, n (%)	1014 (54.5)	210 (53.8)	245 (55.9)
Previous stroke, n (%)*	187 (10.1)	46 (11.8)	27 (6.2)
MI, n (%)†	140 (7.5)	37 (9.5)	43 (9.8)
Coronary artery disease, n (%)‡	345 (18.6)	96 (24.6)	86 (19.6)
Congestive heart failure, n (%)	450 (24.2)	76 (19.5)	113 (25.8)
History of hypertension, n (%)	1468 (79.0)	300 (76.9)	345 (78.8)
Diabetes mellitus, n (%)	406 (21.8)	98 (25.1)	90 (20.5)
CHA_2DS_2-VASc risk score, mean (SD)	3.2 (1.4)	3.3 (1.4)	3.0 (1.5)

*Data are missing for 12 patients who switched from DE to another OAC.

†Reason was not specified. ‡Does not include adverse events listed in the table.

BMI = body mass index; DE = dabigatran etexilate; MI = myocardial infarction; OAC = oral anticoagulation; SD = standard deviation.

SUPPLEMENTARY TABLE 2 Adjusted Multivariable Cox Regression Model - Estimates of the HR for Dabigatran Non-persistence

Variable (n)	No. (%) of Dabigatran Non-persistent Patients (n = 828)	Adjusted* HR (95% CI)	No. (%) of Dabigatran Non-persistent Patients Without Subsequent OAC† (n = 438)	Adjusted* HR (95% CI)
Region				
Europe (1,502)	383 (25.5)	Ref. group	187 (12.5)	Ref. group
North America (819)	303 (37.0)	1.66 (1.35 to 2.04)	156 (19.0)	1.53 (1.15 to 2.03)
Asia (363)	101 (27.8)	1.18 (0.92 to 1.50)	72 (19.8)	1.64 (1.20 to 2.21)
Latin America (194)	30 (15.5)	0.61 (0.40 to 0.90)	17 (8.8)	0.62 (0.35 to 1.03)
Africa/Middle East (54)	11 (20.4)	0.72 (0.36 to 1.27)	6 (11.1)	0.86 (0.33 to 1.84)
Categorization of AF				
Symptomatic (777)	248 (31.9)	Ref. group	132 (17.0)	Ref. group
Minimally symptomatic/ asymptomatic (2,155)	580 (26.9)	0.78 (0.66 to 0.91)	306 (14.2)	0.84 (0.67 to 1.05)
Previous TIA or stroke				
No/missing (2,518)	726 (28.8)	Ref. group	398 (15.8)	Ref. group
Yes (414)	102 (24.6)	0.84 (0.66 to 1.06)	40 (9.7)	0.66 (0.46 to 0.93)
Type of AF				
Paroxysmal/ persistent AF (2,544)	749 (29.4)	Ref. group	401 (15.8)	Ref. group
Permanent AF (388)	79 (20.4)	0.73 (0.56 to 0.93)	37 (9.5)	0.66 (0.46 to 0.93)
Proton pump inhibitors				
No (2,360)	640 (27.1)	Ref. group	350 (14.8)	Ref. group
Yes (572)	188 (32.9)	1.26 (1.04 to 1.51)	88 (15.4)	1.04 (0.80 to 1.36)
Age class				
<75 years (1,856)	536 (28.9)	Ref. group	303 (16.3)	Ref. group

≥75 years (1,076)	292 (27.1)	0.95 (0.80 to 1.12)	135 (12.5)	0.84 (0.66 to 1.06)
Sex				
Male (1,620)	455 (28.1)	Ref. group	245 (15.1)	Ref. group
Female (1,312)	373 (28.4)	1.03 (0.87 to 1.21)	193 (14.7)	1.05 (0.83 to 1.31)
Hyperlipidemia				
No/missing (1,628)	434 (26.7)	Ref. group	247 (15.2)	Ref. group
Yes (1,304)	394 (30.2)	1.02 (0.87 to 1.20)	191 (14.6)	0.92 (0.74 to 1.14)
Congestive heart failure				
No/missing (2,200)	639 (29.0)	Ref. group	325 (14.8)	Ref. group
Yes (732)	189 (25.8)	0.96 (0.80 to 1.15)	113 (15.4)	1.16 (0.92 to 1.46)
History of hypertension				
No/missing (620)	183 (29.5)	Ref. group	93 (15.0)	Ref. group
Yes (2,412)	645 (26.7)	0.90 (0.75 to 1.08)	345 (14.3)	1.01 (0.79 to 1.31)
Prior bleeding				
No/missing (2,785)	778 (27.9)	Ref. group	414 (14.9)	Ref. group
Yes (147)	50 (34.0)	1.12 (0.80 to 1.53)	24 (16.3)	0.88 (0.54 to 1.36)
Diabetes mellitus				
No (2,267)	640 (28.2)	Ref. group	348 (15.4)	Ref. group
Yes (665)	188 (28.3)	0.96 (0.80 to 1.15)	90 (13.5)	0.90 (0.69 to 1.16)
Type of site				
Community hospital (866)	220 (25.4)	Ref. group	105 (12.1)	Ref. group
University hospital (635)	187 (29.4)	1.16 (0.94 to 1.44)	100 (15.7)	1.35 (1.00 to 1.81)
Specialist office (1,065)	332 (31.2)	0.99 (0.80 to 1.23)	182 (17.1)	1.31 (0.97 to 1.76)
GP/primary care (226)	51 (22.6)	0.71 (0.50 to 0.98)	31 (13.7)	1.10 (0.70 to 1.69)
Outpatient health care/anticoagulation clinic (117)	31 (26.5)	0.88 (0.57 to 1.31)	17 (14.5)	0.89 (0.49 to 1.51)
Myocardial infarction				

No/missing (2,684)	748 (27.9)	Ref. group	395 (14.7)	Ref. group
Yes (248)	80 (32.3)	1.10 (0.81 to 1.47)	43 (17.3)	1.43 (0.95 to 2.11)
CHA_2DS_2-VASc score class				
High (score ≥2) (2,587)	715 (27.6)	Ref. group	365 (14.1)	Ref. group
Moderate (score = 1) (345)	113 (32.8)	1.13 (0.88 to 1.45)	73 (21.2)	1.31 (0.94 to 1.80)
HAS-BLED risk score class				
Low (score <3) (2,449)	694 (28.3)	Ref. group	374 (15.3)	Ref. group
High (score ≥3) (183)	57 (31.1)	1.17 (0.84 to 1.61)	32 (17.5)	1.37 (0.87 to 2.10)
Coronary artery disease				
No/missing (2,340)	646 (27.6)	Ref. group	352 (15.0)	Ref. group
Yes (592)	182 (30.7)	1.05 (0.84 to 1.30)	86 (14.5)	0.79 (0.57 to 1.06)
Chronic gastrointestinal diseases				
No/missing (2,526)	690 (27.3)	Ref. group	359 (14.2)	Ref. group
Yes (406)	138 (34.0)	1.08 (0.87 to 1.33)	79 (19.5)	1.25 (0.94 to 1.64)
Medical treatment reimbursed by				
Statutory/federal insurance (1,999)	559 (28.0)	Ref. group	283 (14.2)	Ref. group
Private insurance (578)	183 (31.7)	1.06 (0.88 to 1.29)	96 (16.6)	1.06 (0.81 to 1.38)
Self-pay/no coverage /unknown (355)	86 (24.2)	1.01 (0.78 to 1.28)	59 (16.6)	1.24 (0.90 to 1.66)
BMI, kg/m^2				
BMI <30 (1,832)	518 (28.3)	Ref. group	279 (15.2)	Ref. group
BMI ≥30 (1,080)	307 (28.4)	0.95 (0.81 to 1.12)	158 (14.6)	0.84 (0.67 to 1.04)

DE mono vs. combination				
DE mono (2,539)	704 (27.7)	Ref. group	360 (14.2)	Ref. group
DE combination (393)	124 (31.6)	1.00 (0.80 to 1.25)	78 (19.8)	1.27 (0.95 to 1.70)
Smoking status				
No/missing (1,902)	525 (27.6)	Ref. group	272 (14.3)	Ref. group
Yes (1,030)	303 (29.4)	0.96 (0.81 to 1.12)	166 (16.1)	0.96 (0.77 to 1.19)
Alcohol abuse				
No/missing (2,770)	774 (27.9)	Ref. group	406 (14.7)	Ref. group
Yes (162)	54 (33.3)	1.07 (0.78 to 1.44)	32 (19.8)	1.17 (0.77 to 1.70)

333 patients from other types of site, or having missing values for BMI or HAS-BLED score were excluded from the multivariable analyses.

*Adjusted HRs were estimated from a multivariable Cox model including all variables listed in this table.

†Represents patients who discontinue DE but do not start another OAC within 30 days.

BMI = body mass index; CI = confidence interval; HR = hazard ratio; OAC = oral anticoagulant; Ref. = reference.

CHAPTER 3: Dabigatran Persistence and Outcomes Following Discontinuation in Atrial Fibrillation Patients from the GLORIA-AF Registry

PREFACE TO CHAPTER 3

The manuscript entitled, “Dabigatran Persistence and Outcomes Following Discontinuation in Atrial Fibrillation Patients from the GLORIA-AF Registry” was submitted to the American Journal of Cardiology on 15 August, 2019, with revisions submitted and accepted on 30 October, 2019. The final manuscript was electronically published on 7 November, 2019 and published in full on 1 February, 2020 (Feb 1;125(3):383-391; https://doi.org/10.1016/j.amjcard.2019.10.047). This dissertation includes the final revised submitted version.

Contributions of Authors

Miney Paquette wrote the first draft of the manuscript, addressed critical revisions, and incorporated all author and reviewer comments into the final accepted version of the manuscript. She also contributed to the design and conduct of the study, analysis plan, interpretation of the data, and writing of results.

Lionel Riou França, Christine Teutsch, Shihai Lu, and Kristina Zint contributed to the design and conduct of the study, interpretation of the data, and writing of results. Shihai Lu conducted the analysis. Professor Chris Diener, Dr. Sergio Dubner, Professor Changsheng Ma, Dr. Kenneth Rothman, Dr. Jonathan Halperin, Dr. Menno Huisman, and Professor Gregory Y.H. Lip contributed to the design of the study, interpretation of the data, and writing of the manuscript. Dr. Robby Nieuwlaat contributed to the interpretation of the data and writing of the manuscript.

All authors reviewed and approved the final version of the accepted manuscript.

Dabigatran Persistence and Outcomes Following Discontinuation in Atrial Fibrillation Patients from the GLORIA-AF Registry

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Drs Huisman and Lip are co-chairs of the GLORIA-AF registry, and Dr Nieuwlaat is principal supervisor of this analysis; all 3 are joint senior authors.

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Abstract

Prospective studies evaluating persistence to non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation (AF) are needed to improve our understanding of drug discontinuation. The study objective was to evaluate if and when patients with newly diagnosed AF stop dabigatran treatment and to report outcomes following discontinuation. Patients prescribed dabigatran in diverse clinical practice settings were consecutively enrolled and followed for 2 years. Dabigatran persistence over time, reasons for discontinuation, and outcomes post discontinuation were assessed. Of 4,859 patients, aged 70.2 ± 10.4 years, 55.7% were male. Overall 2-year dabigatran persistence was 70.9% (95% confidence interval [CI], 69.6 to 72.2). Persistence probability was lower in the first 6-month period (83.7% [82.7 to 84.8]) than in subsequent periods for patients on dabigatran at the start of each period (6–12 months, 92.5% [91.6 to 93.3]; 12–18 months, 95.1% [94.3 to 95.8]; 18–24 months, 96.3% [95.6 to 96.9]). Of 1,305 patients (26.9%) who discontinued dabigatran, adverse events were reported as the reason for discontinuation in 457 (35.0%). Standardized stroke incidence rate post discontinuation (per 100 patient-years) in patients discontinuing without switching to another oral anticoagulant was 1.76 (95% CI, 0.89 to 2.76) and 1.02 (95% CI, 0.43 to 1.76) in those who switched, consistent with the expected benefit of remaining on treatment. Patients persistent with treatment at 1 year had >90% probability of remaining persistent at 2 years suggesting clinical interventions to improve persistence should be focused on the early period following treatment initiation.

Key Words: atrial fibrillation ■ stroke prevention ■ dabigatran ■ persistence

Introduction

Atrial fibrillation (AF) is well recognized as an important independent risk factor for stroke.[1] Although current guidelines recommend long-term oral anticoagulation (OAC) for stroke prevention in AF patients with at least 1 additional stroke risk factor,[2] high rates of OAC discontinuation have posed a barrier to achieving optimal outcomes. Discontinuation has been especially noteworthy in the era before the availability of non–vitamin K antagonist OACs (NOAC) with 1 year discontinuation rates exceeding 50%[3-5]; and investigations examining persistence or adherence have primarily been based on claims databases,[6,7] national health registers,[8-11] or commercial databases[12]. While some evidence indicates discontinuation rates may be lower with NOACs versus vitamin K antagonists,[5,7,13] periods of risk and reasons for NOAC discontinuation remain poorly understood. Reasons for early discontinuation may differ from reasons patients discontinue after more enduring periods of stable treatment and this information may be informative for clinicians implementing management strategies to address the important clinical barrier of treatment persistence. The objectives of this analysis from a large prospective global registry of clinical practice settings were to investigate in newly diagnosed AF patients initiating dabigatran: treatment persistence over 2 years; predictors of discontinuation; reported reasons for discontinuation as a function of time; and stroke, bleeding and mortality outcomes following discontinuation.

Methods

Analyses were conducted using data from phase 2 of the GLORIA-AF registry program (registration at https://clinicaltrials.gov/ct2/home: NCT1468701; NCT01671007; NCT01937377) whereby newly diagnosed AF patients from various outpatient settings (including hospitals and specialist and general practice offices) from 44 countries and 5 regions were prospectively and consecutively enrolled at 982 sites between 2011 and 2014 (Figure 1). Patients with at least 1 additional stroke risk factor (CHA_2DS_2-VASc[14] criteria, including female sex) were eligible for inclusion; patients with >60 days of prior vitamin K antagonist use were excluded. Patients prescribed dabigatran per routine clinical practice who took at least 1 dose were followed for 2 years, with the last patient follow-up visits conducted in December 2016. Baseline data only were collected for those prescribed other anticoagulation therapies in phase 2. Further details on the GLORIA-AF registry design have been previously published,[15] and clinical characteristics of all patients enrolled to phase 2 have been reported.[16] Patients provided informed consent and the study was approved by research ethics boards where required.

Baseline characteristics, including stroke and bleeding risk factors used to calculate CHA_2DS_2-VASc[14] and HAS-BLED[17] scores, as well as AF type (paroxysmal, persistent, permanent), AF-related symptom burden based on the European Heart Rhythm Association classification,[18] antithrombotic treatment, medical history, concomitant medications, and reimbursement status of prescribed OAC, were collected, and follow-up occurred approximately 3, 6, 12, and 24 months after baseline. Changes to medical conditions, serious adverse events (SAEs), AEs related to any OAC treatment, and

start/stop dates of medications (including antithrombotic treatments) were documented. Physicians could choose 1 main reason from a pre-specified list for stopping oral anticoagulation treatment including AEs or "other reasons." As physicians could only select 1 reason, they were requested to select the main (and most specific) reason for discontinuation. If there was > 1 reason (for example, major bleeding, also classified as an SAE), physicians were requested to select the more specific option—in this case, the bleeding event.

Baseline data were summarized descriptively, with continuous variables reported as means (± standard deviation [SD]) and categorical variables reported as absolute frequencies and percentages.

To assess persistence, patients were followed from dabigatran initiation until study withdrawal, death, end of study, or dabigatran discontinuation, whichever came first. Discontinuation was defined as either a switch to another OAC from dabigatran or stopping dabigatran for ≥30 days (to exclude temporary treatment interruptions due to medical procedures [e.g., percutaneous coronary intervention]). Dose adjustments were not considered in determination of discontinuation for this analysis. Kaplan-Meier time-to-event analyses were used to calculate probabilities and 95% confidence intervals (CIs) for dabigatran persistence over 2 years and for 6-month increments from the time of treatment initiation (for subsets of patients remaining on treatment at the start of each interval).

Reported reasons for dabigatran discontinuation were summarized descriptively and grouped into events representing AEs or SAEs, and other events (Table 1). Reported

reasons for dabigatran discontinuation were described for 4 periods: following treatment initiation (0–3 and 3–6 months), stabilizing (6–12 months), and more enduring treatment (≥12 months). A sensitivity analysis to evaluate the potential effect of misclassifying discontinuation due to AEs/SAEs as "other" reasons was carried out by exploring whether any AEs/SAEs were reported 14 days before discontinuation in this group.

Two Cox-regression model approaches were used. To identify overall predictors of dabigatran discontinuation during follow-up, a multivariable Cox-regression model, including region and patient clinical and sociodemographic characteristics was used to explore predictors of nonpersistence. Variables included in the model were variables denoting region and patient characteristics such as CHA_2DS_2-VASc score, age, hypertension, categorization of AF, prior transient ischemic attack/stroke, and AF type. Hazard ratios (HR) and 95% CIs were calculated for these predictors. In addition, as patient clinical characteristics may not have constant effect on persistence over time, time-dependent effects of patient clinical characteristics on nonpersistence were evaluated with a separate multivariable Cox-regression model that included interactions between covariates and indicator functions of time for the 4 following time intervals: 0 to 3, 3 to 6, 6 to 12, and ≥12 months.

Stroke, major bleeding, vascular, and all-cause death were assessed from discontinuation until end of study in those who discontinued without switching and in those who switched to another OAC within 30 days of discontinuation. Stroke was defined as an acute onset of a focal neurological deficit of presumed vascular origin, lasting for 24 hours or more, or resulting in death. Major bleeding was defined as overt

bleeding associated with a hemoglobin reduction of at least 20 g/l or leading to a transfusion of at least 2 units of blood or packed cells, symptomatic bleeding in a critical area or organ, or life-threatening or fatal bleeding. Incidence rates following discontinuation were standardized using averages of the stratum-specific incidence rates (4 strata using cut-offs for low and moderate HAS-BLED scores and CHA_2DS_2-VASc scores ≤ 3 or >3), weighted by total patient-years in each. Missing data were handled using multiple imputation to provide unbiased estimates of missing values, with added random error to compensate for the imputed information.[19] The imputation model was constructed upon 54 baseline patient characteristic variables including those used in the multivariable analyses (refer to footnote in Table 2 for information on missing data). Imputed datasets were analyzed separately, and results combined to provide estimates under the missing at random assumption. CIs of standardized incidence rates were constructed using the bootstrap method.[20] SAS version 9.4 (SAS Institute, Cary, NC) was used for all data analyses.

Results

A total of 15,308 patients were enrolled from 5 regions, of whom 4,873 were prescribed dabigatran (Figure 1) and the majority (n = 4,859; 99.7%) took $\geq$ 1 dose (14 patients who did not take any dose were excluded). The mean number of patients per site was 15.9 (SD $\pm$ 18.6) and median was 10 (interquartile range: 17). Baseline characteristics and medical history of patients are shown in Table 2.

The overall probability of dabigatran treatment persistence was 77.5% (CI: 76.2% to 78.6%) at 1 year and 70.9% (CI: 69.6% to 72.2%) at the end of follow-up (2 years). At end of follow-up, 1,305 patients (26.9%) stopped dabigatran, with 621 (12.8%) switching

to another OAC and 684 (14.1%) not starting another OAC within 30 days. Of those switching, 260 (41.9%) switched to a vitamin K antagonist, 358 (57.6%) to a factor Xa inhibitor, and 3 (0.5%) to an antiplatelet drug with bridging therapy.

The evaluation of treatment persistence over time revealed that over half of the total discontinuations occurred in the first 6 months (n = 756; 57.9%). The estimated probability of persistence was lowest in the first 6-month interval following treatment initiation and was successively higher for each subsequent 6-month interval for those on treatment at the start of each respective period (Figure 2). For patients persistent at 1 year, the estimated probability of continuing treatment for an additional year was >90% (2-year persistence conditional on 1-year persistence [95.1*96.3]).

In the overall multivariable Cox-regression analyses to evaluate predictors of dabigatran persistence, relative to patients in Europe, patients in North America and Asia had higher discontinuation, and patients in Latin America and Africa/Middle East had lower discontinuation (Figure 3). Patients with symptomatic AF, prior bleeding, and proton pump inhibitor (PPI) use had higher discontinuation and those with a higher body mass index (BMI) and prior stroke or transient ischemic attack had lower discontinuation (Figure 3). An increase in BMI of 10 units was associated with a 15% lower rate of discontinuation (HR 0.85 [95% CI, 0.77 to 0.94]).

When evaluating predictors of discontinuation by time (0–3, 3–6, 6–12, and ≥12 months) (Supplementary Table S1), the effect of symptomatic AF on discontinuation was observed in earlier periods (0–3 or 3–6 months), but less visible in the later period (≥12 months) (HR [95% CI], 1.36 [1.13 to 1.65]; 1.48 [1.15 to 1.89]; 1.07 [0.83 to 1.40],

respectively). PPI use was associated with higher risk for discontinuation in the later period (≥12 months) with HR (95% CI) 1.54 (1.17 to 2.06); in the earlier period (0–3 months), HR was 1.03 (0.82 to 1.29). The effect of private insurance compared with federal/statutory insurance was associated with greater discontinuation in the later period (≥12 months: HR [95% CI], 1.35 [1.00 to 1.82]), but not in the earlier period (0–3 months: 0.98 [0.76 to 1.26]).

Reasons reported for stopping dabigatran over 2 years of follow-up are presented in Table 1 and were further categorized into primary reasons related to AEs (including SAEs) or not related to AEs. These reasons for discontinuation reported to be due to AEs/SAEs were not directly linked to AEs reported in the system. AEs such as bleeding, bruising, dyspepsia, hypersensitivity to agents, or severe interactions with concomitant medication were reported as the reason for discontinuation in approximately a third of cases with the remaining 2 thirds being reported as “other reasons” (Table 1).

In the sensitivity analysis examining the extent to which discontinuation with the primary reason documented as “other” (n = 756) followed an SAE or AE/adverse drug reaction within 14 days, 44 (5.8%) had an SAE and 14 (1.9%) an AE/adverse drug reaction in the 14 days before discontinuation.

Patient death was a censoring point for discontinuation, and therefore these patients did not have a reason for discontinuation (n = 173). Of these patients who died, 135 (78.0%) had an SAE within 14 days and 5 (2.9%) had an AE. As these were not reported by treating physicians as due to AEs/SAEs, they were not combined with AE/SAE attributed discontinuations.

Standardized incidence rates per 100 patient-years for stroke, major bleeding, vascular and all-cause death following discontinuation are presented for patients who permanently discontinued with and without switching; higher stroke and mortality rates were observed in the latter group (Figure 4). The average follow-up duration was ~1.3 years for different patient groups and different outcomes. For the full cohort of patients evaluated as part of a separate investigation, incidence rates for the period on treatment, censored at the point of discontinuation (per 100 patient-years, 95% CI) for stroke, major bleeding, vascular death, and all-cause death were lower than both groups of patients who discontinued (0.65 [0.48 to 0.87], 0.97 [0.76-1.23], 0.85 [0.65-1.09] and 2.48 [2.13-2.87] respectively][21].

Discussion

This prospective study of patients on dabigatran showed the probability of persistence over 2 years exceeded 70%, which is higher than previously reported persistence rates to warfarin[3,4] and claims-based estimates of persistence to NOACs.[8,10] Furthermore, it was also shown that the greatest risk for discontinuation is in the early period following treatment initiation. There are limited prospective studies of NOAC persistence and to our knowledge, this is the first investigation in clinical practice settings examining discontinuation over long-term follow-up.

Patients in Asia and North America had greater discontinuation than patients in Europe, and patients in Latin America had less discontinuation. Patients with symptomatic AF, prior bleeding, and PPI use had more discontinuation and those with higher body mass index and prior stroke/transient ischemic attack had lower discontinuation. These factors may be related to perceived differences in stroke or bleeding risk factors, or due to AEs.

Patients with certain characteristics may simply be more prone to discontinue earlier, due to factors such as lifestyle, low treatment satisfaction, or poor tolerance among others (i.e., patients remaining persistent over time become less susceptible to discontinue; the concept of "depletion of susceptibles"[22]). Closer clinical management in the early period could be warranted to improve commitment to treatment or to help manage side effects and identification of characteristics associated with discontinuation could support targeted interventions in these patients.

Discontinuations attributed to AEs occurred with lower frequency than discontinuations reported due to other reasons. For patients who remained persistent at 1 year, the probability of remaining on treatment for an additional year exceeded 90%, suggesting that this is a period of stable management where less intensive follow-up may be justified, at least in terms of mitigating poor persistence. It may be that once tolerance is established (i.e., absence of early AEs), patients are more likely to continue anticoagulation, although AEs alone did not account for the majority of reasons for discontinuation.

The reasons for discontinuation are complex. Fewer than half of all reported

reasons for discontinuation were directly related to AEs. Although specific details are not available for these "other" reasons for discontinuation reported by clinicians, they are still informative as they represent discontinuations not attributed to bleeding or other AEs that would be considered clinically appropriate. This finding has important implications for practice, as well as future research. It remains an open question whether these "other" reasons represent potential opportunities to reduce discontinuations through education or other interventions. These other reasons could relate to patient or physician preference, or perceived higher risk for outcome events that prompt changes in treatment. These are not likely discontinuations prompted through 'curative' interventions such as ablation as earlier data in this cohort (presented at the European Heart Rhythm Association [2017]), reported that >90% of interventions were conducted with an uninterrupted anticoagulation regimen.

The importance of the patient's perspective for making decisions around anticoagulant choice has been reported in other studies,[23] and these preferences could also have implications for treatment persistence or switching to an alternative OAC. Furthermore, if patients' knowledge of their AF and risk for thromboembolic outcomes is limited, perceptions surrounding treatment necessity may affect their motivation to continue treatment. Indeed, studies have demonstrated that many patients have poor knowledge of AF and its treatment.[24] There may be an opportunity to improve treatment persistence through education or patient decision aids with shared decision making.

The incidence of post-discontinuation stroke, vascular, and all-cause death was higher (albeit with broad 95% CIs) in patients who discontinued without switching to

another OAC compared with those who switched, and both groups had higher stroke and mortality outcomes following discontinuation than overall patient outcome rates prior to discontinuation. This finding is consistent with the expected benefit of remaining on oral anticoagulation and similar to retrospective studies of dabigatran and rivaroxaban prophylaxis.[10] However, it should be noted that the decision not to restart an anticoagulant after discontinuation of dabigatran could have been due to patients being moribund, resulting in higher mortality rates in patients not switching, independent from the effect of discontinuing OAC use. Although outcome numbers were small, major bleeding rates post discontinuation were similar between those discontinuing with or without switching to another OAC.

The use of reported start/stop dates of dabigatran may provide greater accuracy, compared with claims database analyses that rely on prescription fill dates. Furthermore, estimated rates of persistence to NOACs can vary even between studies focused on the same treatment due to differences with respect to patient characteristics, timing of investigation relative to treatment initiation, retrospective compared with prospective evaluations, study design, and definitions of nonpersistence. For example, defining nonpersistence by a treatment gap of 14 days[10] could include temporary discontinuations due to procedures, which has been shown in 1 study to represent almost a quarter of their patient population.[25] As the risk of nonpersistence appears to stabilize within a year following treatment initiation, clinicians may consider this early period most critical for evaluation and intervention.

There are some limitations of this analysis including the fact that data were

collected as part of an observational registry, which could modify behavior of both treating physicians and patients based on awareness that data would be reviewed and monitored ("Hawthorne effect"[26]). Despite this, there may be benefits of prospective data collection compared with retrospective database studies in which risk of missing or inaccurate information is common. Furthermore, patients who consent to participate in a study may be more likely to persist with treatment than a general AF population. Notwithstanding this, the diverse selection of clinical practice sites, practitioners, and extensive geographical representation in this study suggest broad clinical applicability of the results. A further notable limitation is that no specific information on the "other" reasons for discontinuation was collected and start/stop dates were used as a surrogate marker for drug intake. Finally, interpretation of incidence rates of outcomes after dabigatran discontinuation according to presence or absence of switch to another OAC is limited by relatively high levels of random error as evidenced by the wide CIs, and potential for unmeasured confounding.

In conclusion, this prospective analysis of newly diagnosed patients with AF showed overall probability of 2-year persistence in patients taking dabigatran was 70.9%. The period of greatest risk for discontinuation was in the first 6 months following treatment initiation, and for those persistent at 1 year, the probability of remaining on treatment for an additional year was >90%. Thus, closer clinical management in the early period following treatment initiation could potentially enhance commitment to treatment, improve management of side effects, and ultimately support better patient outcomes through improved persistence.

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Figure Legends

Figure 1. Distribution of GLORIA-AF patients prescribed dabigatran by region

UAE = United Arab Emirates; USA = United States of America; UK = United Kingdom.

Figure 2. Risk of discontinuation

Risk of discontinuation is highest in the early period following dabigatran treatment initiation and most reasons for discontinuation are not due to adverse events. The figure shows probabilities and reasons for dabigatran discontinuation (with or without switching to another oral anticoagulant) over 2 years. * Cumulative incidence of persistence at the end of the time period for patients on treatment at the start of the period are shown as Kaplan-Meier estimates and 95% confidence intervals. † "Other" reasons for discontinuation included cost of treatment, bridging therapy start, social reason (e.g., drug/alcohol abuse), dementia, "other" reasons not specified or reason was missing.

Figure 3. Forest plot of multivariable predictors of dabigatran treatment persistence

Missing data were imputed using a multiple imputation approach (based on the eligible population) before the analysis. * Adjusted HRs were estimated from a multivariable Cox model including all variables listed here. AF=atrial fibrillation; BMI=body mass index; CI=confidence interval; HR=hazard ratio; Ref.=reference; TIA=transient ischemic attack.

Figure 4a. Standardized incidence rates of outcomes in patients who discontinued dabigatran treatment (Rates standardized by CHA_2DS_2-VASc and HAS-BLED).

In case of recurrent events after dabigatran discontinuation, the first event was considered. As death is a competing risk for discontinuation, patients who died without date of discontinuation reported were separately examined. CI = confidence interval; OAC = oral anticoagulant.

Figure 1. Distribution of GLORIA-AF patients prescribed dabigatran by region

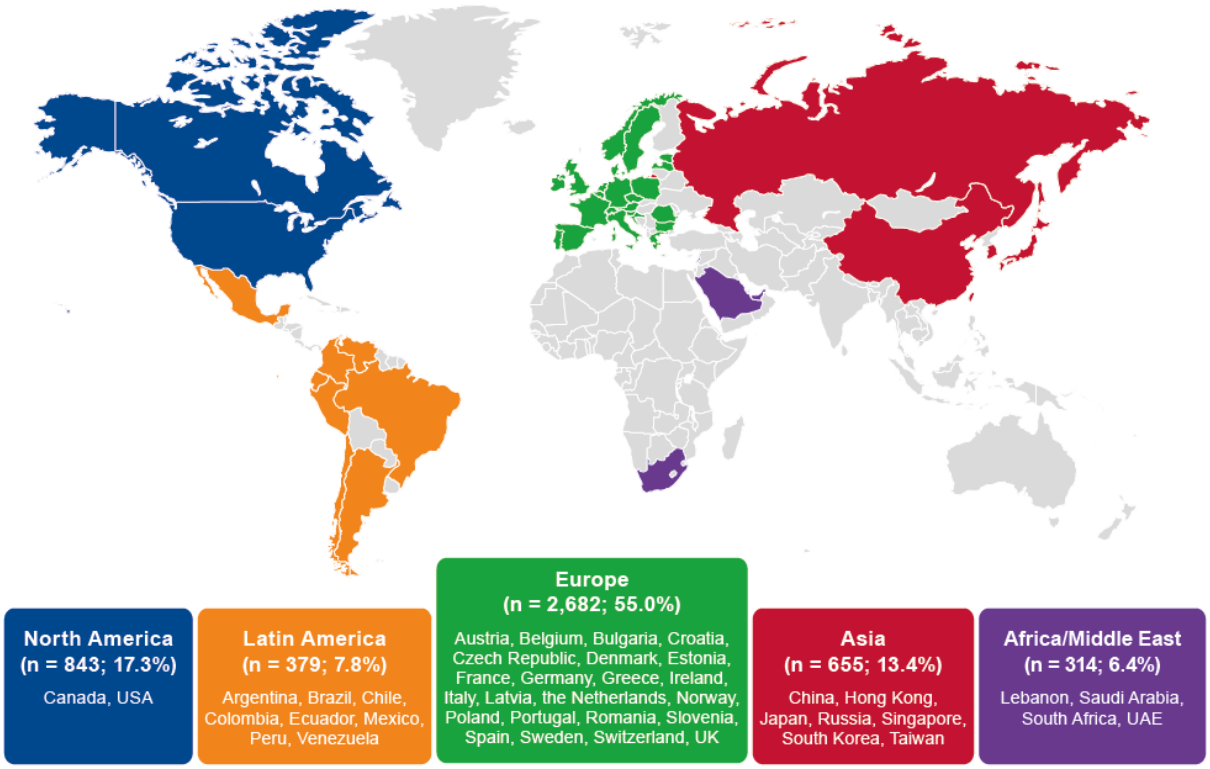

Figure 2. Risk of discontinuation

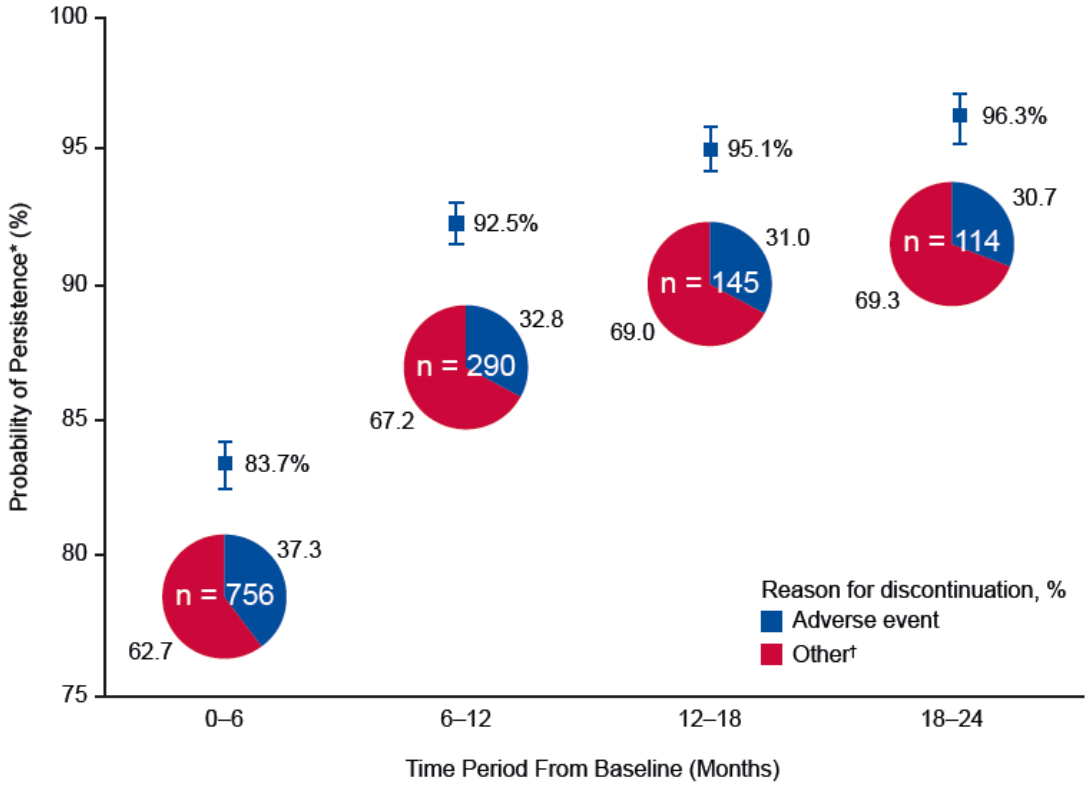

Figure 3. Forest plot of multivariable predictors of dabigatran treatment persistence

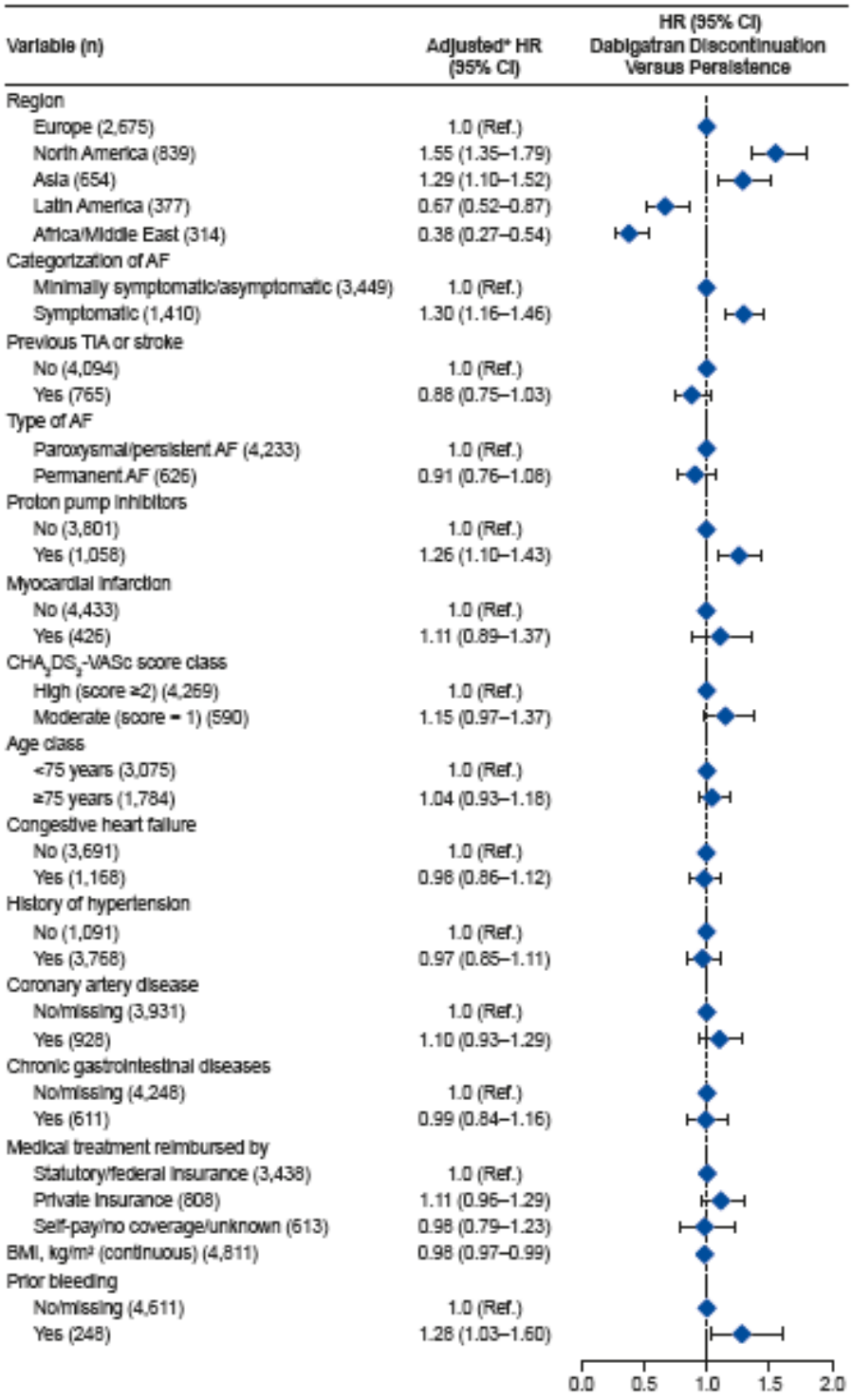

Figure 4. Standardized incidence rates of outcomes in patients who discontinued dabigatran treatment

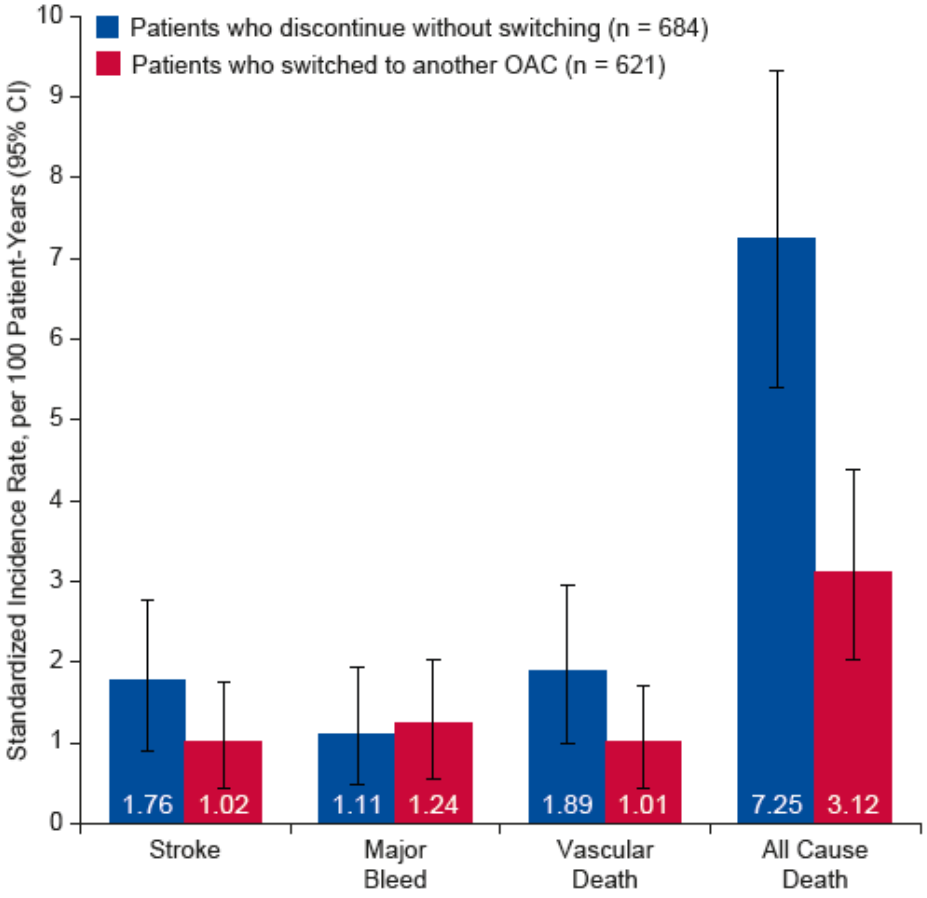

Table 1 Reported reasons for dabigatran discontinuation over 2 years according to time period

	Time (months) after initiation of dabigatran				
	0 to 3 months (n=474)	3 to 6 months (n=282)	6 to 12 months (n=290)	12 to 24 months (n=259)	Total (n=1305)
All adverse events*	189 (39.9%)	93 (33.0%)	95 (32.8%)	80 (30.9%)	457 (35.0%)
Serious adverse events	49 (10.3%)	17 (6.0%)	26 (9.0%)	25 (9.7%)	117 (9.0%)
Bleeding	39 (8.2%)	20 (7.1%)	14 (4.8%)	15 (5.8%)	88 (6.7%)
Dyspepsia	32 (6.8%)	20 (7.1%)	24 (8.3%)	10 (3.9%)	86 (6.6%)
Hypersensitivity to agents	17 (3.6%)	7 (2.5%)	6 (2.1%)	3 (1.2%)	33 (2.5%)
Severe concomitant medication interaction	4 (0.8%)	1 (0.4%)	2 (0.7%)	1 (0.4%)	8 (0.6%)
Bruising	1 (0.2%)	1 (0.4%)	2 (0.7%)	2 (0.8%)	6 (0.5%)
Other adverse events	47 (9.9%)	27 (9.6%)	21 (7.2%)	24 (9.3%)	119 (9.1%)
Other reasons	285 (60.1%)	189 (67.0%)	195 (67.2%)	179 (69.1%)	848 (65.0%)
Cost of treatment	4 (0.8%)	3 (1.1%)	1 (0.3%)	24 (9.3%)	32 (2.5%)
Bridging therapy start	5 (1.1%)	5 (1.8%)	5 (1.7%)	6 (2.3%)	21 (1.6%)
Social reason (e.g., drug/alcohol abuse)	2 (0.4%)	9 (3.2%)	4 (1.4%)	1 (0.4%)	16 (1.2%)
Dementia	1 (0.2%)	2 (0.7%)	1 (0.3%)	0 (0.0%)	4 (0.3%)
Other reasons not specified	266 (56.1%)	167 (59.2%)	178 (61.4%)	145 (56.0%)	756 (57.9%)
Missing reason for switching	7 (1.5%)	3 (1.1%)	6 (2.1%)	3 (1.2%)	19 (1.5%)

Time periods are based on planned visit time (e.g., 3 and 6 months). One category (reason for

discontinuation) could be selected per patient. Does not include 173 patients who died while on dabigatran.

* As physicians could only select 1 reason, they were requested to select the main (and most specific) reason for discontinuation.

Table 2 Patient characteristics

	Total (N = 4,859)
Age, mean ± standard deviation (years)	70.2 ± 10.4
Age ≥75 years	1,784 (36.7%)
Body mass index, mean ± standard deviation (kg/m^2)*	28.9 ± 5.9
Women	2,154 (44.3%)
Prior stroke†	765 (15.7%)
Prior myocardial infarction‡	426 (8.8%)
Coronary artery disease§	928 (19.1%)
Heart failure‖	1,168 (24.0%)
Hypertension (history)¶	3,768 (77.5%)
Diabetes mellitus	1,104 (22.7%)
CHA_2DS_2-VASC risk score, mean ± standard deviation	3.2 ± 1.5
Prior bleeding#	248 (5.1%)
HAS-BLED score, mean ± standard deviation**	1.2 ± 0.9
Renal impairment††	18 (0.4%)
Permanent atrial fibrillation	626 (12.9%)
Persistent/paroxysmal atrial fibrillation	4,233 (87.1%)
Asymptomatic/minimally symptomatic	1,410 (29.0%)
Symptomatic	3,449 (71.0%)
Physician specialty‡‡	
Cardiology	4,251 (87.5%)

General practitioner/geriatrician	164 (3.4%)
Internist	152 (3.1%)
Neurologist	194 (4.0%)
Other	96 (2.0%)

* Missing: 48 patients.

† Missing: 1 patient.

‡ Unknown: 1 patient.

§ Unknown: 135 patients.

‖ Unknown: 46 patients.

¶ Unknown: 9 patients.

Unknown: 95 patients.

** Unknown: 506 patients.

†† Unknown: 37 patients.

‡‡ Missing: 2 patients.

SUPPLEMENTAL MATERIAL

Table S1 Multivariate Cox Regression Analysis to Identify Predictors of Dabigatran Treatment Persistence

(All Eligible Patients Excluding Prescribed but Not Treated)

Variable	0 to 3 months HR (95% CI)	3 to 6 months HR (95% CI)	6 to 12 months HR (95% CI)	≥12 months HR (95% CI)
Region				
Europe	1.0 (Ref)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Asia	1.27 (0.98–1.66)	1.24 (0.87–1.77)	1.10 (0.78–1.56)	1.62 (1.13–2.32)
North America	1.61 (1.28–2.02)	1.28 (0.92–1.78)	1.21 (0.88 –1.68)	2.16 (1.60–2.91)
Latin America	0.63 (0.40–0.99)	0.57 (0.32–1.02)	0.66 (0.39–1.12)	0.88 (0.54–1.43)
Africa/Middle East	0.37 (0.20–0.67)	0.48 (0.25–0.91)	0.14 (0.04–0.43)	0.57 (0.32–1.04)
Categorization of AF				
Minimally symptomatic/ asymptomatic	1.0 (Ref)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Symptomatic	1.36 (1.13–1.65)	1.48 (1.15–1.89)	1.27 (0.99–1.64)	1.07 (0.83–1.40)
Previous TIA or stroke				
No	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Yes	0.99(0.77–1.28)	0.68 (0.46–0.99)	0.89 (0.63–1.25)	0.87 (0.63–1.21)
Type of AF				
Paroxysmal/persistent AF	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Permanent AF	0.79 (0.59–1.08)	0.89 (0.60–1.33)	0.86 (0.59–1.25)	1.19 (0.84–1.67)
Proton pump inhibitors				
No	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)

Yes	1.03 (0.82–1.29)	1.56 (1.19–2.06)	1.12 (0.84–1.50)	1.54 (1.17–2.02)
Myocardial infarction				
No	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Yes	1.00 (0.70–1.44)	1.06 (0.67–1.68)	0.94 (0.57–1.53)	1.57 (1.00–2.47)
CHA2DS2−VASc score class				
High (Score ≥2)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Moderate (Score =1)	1.24 (0.94–1.65)	1.11 (0.76–1.63)	1.13 (0.77–1.66)	1.09 (0.76–1.57)
Age class				
<75 years	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
≥75 years	1.21 (0.99–1.47)	0.90 (0.69–1.19)	1.12 (0.86–1.45)	0.87 (0.67–1.14)
Congestive heart failure				
No	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Yes	0.99 (0.80–1.23)	0.88 (0.66–1.18)	1.16 (0.88–1.53)	0.91 (0.68–1.21)
History of hypertension				
No	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Yes	0.87 (0.70–1.07)	1.03 (0.76–1.39)	1.01 (0.76–1.34)	1.09 (0.81–1.47)
Coronary artery disease				
No	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Yes	1.13 (0.87–1.47)	1.29 (0.91–1.81)	1.13 (0.79–1.61)	0.85 (0.59–1.23)
Chronic gastrointestinal diseases				
No	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Yes	1.03 (0.79–1.35)	1.03 (0.73–1.46)	0.89 (0.61–1.30)	0.96 (0.68–1.36)

Medical treatment reimbursed by				
Statutory/Federal insurance	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Private insurance	0.98 (0.76–1.26)	1.18 (0.84–1.64)	1.04 (0.74–1.46)	1.35 (1.00–1.82)
Self-pay/no coverage	0.86 (0.58–1.28)	1.21 (0.76–1.91)	0.96 (0.59–1.57)	1.02 (0.64–1.64)
BMI				
BMI (continuous)	0.99 (0.98–1.01)	0.99 0.97–1.01)	0.96 (0.94–0.98)	0.98 (0.96–1.00)
Prior bleed				
No	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Yes	1.26 (0.88–1.81)	1.35 (0.84–2.17)	1.41 (0.86–2.29)	1.16 (0.71–1.88)

AF indicates atrial fibrillation; BMI, body mass index; CI, confidence interval; HR, hazard ratio; Ref., reference; TIA, transient ischemic attack. Missing data were imputed using a multiple imputation approach (based on the eligible population) before the analysis.

CHAPTER 4: A Systematic Review and Meta-Analysis of Supplemental Education in Patients Treated with Oral Anticoagulation

PREFACE TO CHAPTER 4

The manuscript entitled, "A systematic review and meta-analysis of supplemental education in patients treated with oral anticoagulation" was submitted to Blood Advances on 24 February 2019, and accepted with revisions on 14 April 2019. The final manuscript was published on 28 May 2019 (https://doi.org/10.1182/bloodadvances.2019000067).

Contributions of Authors

Miney Paquette contributed to the study design, search strategy, study selection, data extraction, statistical analysis, and interpretation of findings. She wrote the first draft of the manuscript, addressed critical revisions, and incorporated all author and reviewer comments into the final submitted version of the manuscript.

Daniel M. Witt, Ann Holbrook, Jane Skov, Jack Answell, Holger J. Schünemann and Wojtek Wiercioch contributed to the study design, interpretation of findings, and writing of the report.

Robby Nieuwlaat contributed to the study design, search strategy, study selection, data extraction, statistical analysis, interpretation of findings, and writing of the report.

All authors reviewed and approved the final version of the submitted manuscript.

A Systematic Review and Meta-Analysis of Supplemental Education in Patients Treated with Oral Anticoagulation

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Short Title: Systematic review of education on oral anticoagulation

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Key Point (139 characters)

- Supplemental patient education does not have a clear benefit on mortality, bleeding or thromboembolism in patients on oral anticoagulants

Abstract (237 words):

Oral anticoagulants (OAC) are indicated for treatment and prevention of thromboembolic diseases. Supplemental patient education (education) has been proposed to improve outcomes and this systematic review assessed the effect of education on mortality, thromboembolic events (TEE) including venous thromboembolism (VTE), and bleeding in patients taking OAC. Randomized controlled trials were included and 2 authors independently screened articles and assessed risk of bias. In 9 trials (720 control; 646 intervention group patients), 4 trials assessed critical outcomes of mortality, TEE (VTE, stroke, and systemic embolism) and bleeding to estimate absolute risk ratios. When comparing education to usual care, in 1000 patients (95%CI): there may be 12 fewer deaths (19 fewer to 154 more) and 16 fewer bleeding events (34 fewer to 135 more) but this evidence is uncertain; and the evidence suggests 6 fewer VTE (10 fewer to 16 more), and 8 fewer TEE (16 fewer to 18 more). The mean difference in time in therapeutic range (TTR) may be 2.4% higher in the education group compared to usual care (2.79% lower to 7.58% higher). We also found very low certainty of evidence for a large increase in knowledge scores [SMD 0.84 SD units higher (0.51-1.16)]. Overall, the certainty of evidence was low to very low due to serious risk of bias and serious imprecision. Additional sufficiently powered trials or different approaches to education are required to better assess supplemental education effects on outcomes in patients taking OAC.

Introduction

Oral anticoagulants (OAC) are indicated for treatment and prevention of thromboembolic diseases including venous thromboembolism (VTE)[1] for prevention of stroke and systemic embolism in patients with atrial fibrillation (AF)[2], and increasingly for cardiovascular indications. Oral anticoagulants are considered to be 'high alert' medications because they also are one of the top drug-related causes of hospitalization in seniors[3,4]. OACs include traditional Vitamin K Antagonists (VKA) requiring monitoring and dose adjustment to maintain blood coagulation parameters within narrow therapeutic ranges to optimize the risk-benefit ratio as well as direct oral anticoagulants (DOACs). While the latter do not require monitoring, they still require education about the importance of adherence, proper dosing, bleeding risk, and drug interaction potential.

Supplemental patient education (education) provides information beyond what is typically provided by a health care provider as part of 'usual care'. Due to the complexity of patient management using OAC treatments, 'usual care' for patients initiating OAC is likely to involve more extensive education than is typical with other cardiovascular medications. The content of these educational interventions would be expected to cover information such as indications for treatment including chances of benefits and harms, drug intake information (e.g. dose, frequency, and timing of doses relative to food intake), drug interaction management, recognition and management of bleeding and therapeutic failure, the importance of medication adherence and strategies if doses are missed.

The effect of educational intervention strategies in patients taking DOACs is of major importance given their relatively shorter half-lives, and rapid onset and offset of action and absence of INR monitoring. Due to the pharmacokinetics of DOACs, missed doses may create critical transient gaps in OAC coverage, exposing patients to increased risk of thromboembolic events (TEE)[5]. Adherence is therefore potentially a more essential educational issue for DOACs than VKAs.

Improving patient OAC knowledge may result in better adherence to prescribed treatments (influencing both TEE and bleeding risks), or promote early recognition of signs and symptoms of adverse events such as bleeding. Patient education may modify other behaviors or lifestyle factors that could impact well-known and established cardiovascular risk factors such as hypertension, smoking, hypercholesterolemia and diabetes[6-8].

A previous systematic review (SR) on supplemental patient education for OACs found a lack of evidence of benefit for clinical outcomes[9], however this SR pre-dated the launch of DOACs. The objective of this SR was to evaluate the effect of supplemental patient education for OACs on patient important outcomes including death, TEE [VTE, stroke, myocardial infarction (MI), and systemic embolism], and bleeding. Secondarily, the impact of supplemental patient education on time in therapeutic INR range (TTR) and patient knowledge was assessed. Information from the earlier SR was critically appraised and synthesized together with new evidence including information about DOACs (which became available after the review by *Wong, et al.*[9] was published).

Methods

This systematic review was performed as part of the American Society of Hematology (ASH) guidelines on VTE, developed in partnership with McMaster University's Grading of Recommendations Assessment, Development and Evaluation (GRADE) Centre and investigates one of the questions prioritized for the new guidelines[10]. Review and meta-analysis methodology followed the Cochrane Handbook[11] with reporting according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[12].

Randomized controlled trials (RCT) of patients treated with OACs (including patients at risk for, or diagnosed with DVT/PE, AF or prosthetic heart valves), with any length of follow-up were included if they had at least 1 supplemental educational component as the intervention and at least one control group comprised of no supplemental education (usual care). Diverse approaches comprised 'usual care', with unstructured education, or unrestricted VTE education serving as controls. Supplemental education was defined as information in addition to basic drug information provided as part of usual care and varied in modality, content and intensity. Some education programs were more intensive such as visual material, augmented with daily visits by nurses and physicians to repeat some items[13] or in another program, sessions up to 2 hours were held three times a week, providing information about the blood coagulation system, and effects of some substances on treatments (alcohol, diet, medication, among others)[14]. One study provided targeted educational intervention based on knowledge gaps assessed in patients[15]. Other programs were less intensive and more self-directed such as sessions including a brief educational

video[16] or educational booklets[17]. A brief summary of interventions and description of control groups is presented in Table 1.

Broad types of supplemental educational interventions aimed at improving patient knowledge, TTR or clinical outcomes were considered, however, the ability to evaluate the educational component alone was required. For example, educational interventions only administered together with patient INR self-monitoring, whereby the effect of supplemental education could not be separated, were not considered for pooling in the meta-analysis.

There were no restrictions for co-interventions administered and in cases where different OACs were assessed for efficacy within the same study, treatments were pooled, and the educational component of the assessment across treatments was included in the meta-analysis. Cluster RCTs were eligible for inclusion but observational and quasi-randomized studies (e.g. allocation of treatments by non-random methods such as date of birth, or randomization after delivery of the educational component) were excluded.

MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials were searched in addition to other sources (Clintrials.gov, article citations, ASH guideline panel experts and published guidelines[18]). Efforts were made to identify unpublished studies such as those identified only in abstracts, by contacting authors. Search terms aimed to identify all anticoagulant agents including synonyms, related terms and variants including DOAC agents, parenteral agents, and VKA, as well as educational interventions, patient compliance and health behaviours as potential targets of intervention. The initial search

was performed on 28 Jan 2017 and an updated search on 23 Oct 2018 using the identical search strategy (additional details found in Supplementary Table 1a and 1b).

Independent screening and review of titles and abstracts for inclusion eligibility was conducted by two reviewers. Authors were contacted to obtain information on studies, including two with only abstract proceedings available at the time of search[15,19], and another to obtain additional information on mean knowledge and TTR values[20]. As this review was an update of the review conducted by Wong et. al.[9], references before 2012 were excluded from the screening process. Studies identified for inclusion from the previous systematic review were reviewed and considered for inclusion in the data synthesis.

One reviewer independently extracted data for review by the second reviewer who verified the information with discrepancies resolved by discussion. Risk of bias (RoB) was assessed using the recommended categories in the Cochrane Handbook for Systematic Reviews of Interventions[11]. RoB was assessed separately for two cluster RCTs using the Risk of Bias 2.0© tool assessing the effect of assignment to intervention. Evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for the primary and secondary outcomes of interest.

Primary outcomes rated as 'Critical' using the GRADE approach included all-cause mortality, TEE [including VTE (DVT and PE), stroke, MI, peripheral embolism], and bleeding events of any severity. Secondary outcomes rated as 'Important' using the GRADE approach included TTR and knowledge based measurements related to the disease

condition and/or anticoagulation treatment. Outcomes were pooled and analyzed by meta-analytic techniques using RevMan software version 5.3 released June 2014.

For dichotomous outcomes (mortality, TEE, and bleeding events), the Mantel-Haenszel method was used for analyzing and pooling the data for risk ratios (RR) of total patient events for each group and calculating 95% confidence intervals (CI). For secondary outcomes with continuous variables (TTR and knowledge measures), results were analysed as (standardized) mean differences with higher TTR and higher knowledge scores indicating better outcomes. Individual VTE outcomes, PE and/or DVT, were not assessed as studies did not include sufficient detail to present this information and no MIs were reported. Bleeding events irrespective of location or severity were pooled together for calculation of risk. Only one study provided a definition for 'major' bleeding[21] so major bleeding was not separately analyzed.

For studies in patients who were using a VKA, TTR means and standard deviations were pooled to compare mean differences using a random effects model. For one study which only presented median and interquartile ranges for TTR[20], data analysis was completed with means imputed using the method described by Hozo[22].

For the two cluster RCTs[21,23], adjustments were made to correct both the sample size (effective sample size) and event number for the dichotomous outcomes by dividing the sample size and event number by the design effect as described in the Cochrane handbook[11]. For continuous variables, only the effective sample size was corrected using the design effect[23].

Authors were contacted to obtain data identified from abstract screening however the data were not published at the time of the analysis[19]. Two authors were contacted to provide mean and standard deviation for knowledge scores and data was obtained for one study[15] but not the other[20].

Heterogeneity of the eligible studies was assessed using the Chi-squared test with significance at $P<0.10$, and the I^2 statistic[11] which was the primary measure used to assess degree of heterogeneity. I^2 values between 50-90% were considered substantially heterogeneous and values between 30-60% considered moderately heterogeneous[24]. For the purposes of the analysis in this investigation, random effects models were utilized. The Mantel-Haenszel method was used for analyzing risk ratios for the pooled results of the dichotomous outcomes. Effect estimates for comparisons were calculated using median risks from pooled event rates from the control group of patients from the included RCTs. Absolute effects were similarly based on the control group event rates from the included RCTs.

Results

The search retrieved a total 4392 articles from all sources. Studies to February 2012 were reviewed by the Wong et. al. SR[9], therefore were not screened (n=1544). Once the remaining titles and abstracts were screened and full text reviewed, a total of 25 studies were identified for potential eligibility. Details of the studies reviewed and reasons for exclusion are summarized in *Figure 1*.

A total of 9 studies were included (5 studies from the previous SR[9], 3 additional studies from the 28 Jan 2017 search and 1 from the 23 Oct 2018 search), and these studies recruited 1366 patients (720 patients in the control groups and 646 patients in the intervention groups). The Characteristics of Included Studies (Table 1) provides further information for the studies that comprised data for the meta-analyses which included patients ranging from 18-91 years of age who were followed up from 24-72 hours up to 12 months.

The studies included a mix of OAC indications including two studies that exclusively studied VTE patients[21,25], one study in patients with generally described thromboembolic events[13], two studies in mixed populations[14,23], two studies in AF populations[15,20] and two studies with unspecified indications[16,17]. All but one of the studies addressed VKAs, and one included DOACs[15]. Two of the studies were cluster randomized[21,23].

A brief summary of reasons for excluded studies are presented in Figure 1 and detailed reasons in Supplementary Table 2. Two studies previously included in the earlier systematic review[9] were excluded. One study was excluded as patients were randomized after delivery of the educational intervention, the control group was historical and adverse events were not monitored in the control group[26]. A second study was excluded as there was no qualifying education component (only a visual analog scale with a brief 'teach back' session of several minutes)[27]. One study presented only median knowledge scores at subsequent follow-up points and was excluded from the analysis of knowledge outcomes[20].

RoB using the Cochrane RoB tool was assessed in each of the eligible studies and is further detailed in Supplementary Table 3. *Figure 2* shows the assessment of risk of bias for each

of the studies and *Figure 3* summarizes the RoB for each domain assessed. Most studies had high RoB due to absence of blinding of participants or personnel[13-16,21,23,25], and 4 studies had identified high RoB with respect to incomplete outcome data[14-16,25]. The summary of findings table summarizing certainty of evidence for all outcomes is included in Supplementary Table 4: Summary of Findings.

There was only one death of unknown cause reported in the control group of a study including 97 participants[20]. The absolute risk reduction (ARR) was 12 fewer deaths per 1000 patients in the intervention group compared to the control (95% CI: 19 fewer to 154 more). Overall, the evidence was uncertain about the effect of supplemental education on mortality (due to very serious imprecision). The 95% CIs included appreciable benefit and harm with evidence of moderate heterogeneity (I^2=52%). The Forest plot is available in Supplementary Figure 1: Mortality.

Outcomes of VTE (Supplementary Figure 2: VTE) were assessed from four studies enrolling a total of 706 patients (631 after adjustment for cluster RCTs)[13,14,20,21]. From the pooled analysis, we calculated 6 fewer VTE per 1000 patients in the intervention group (95% CI: 10 fewer to 16 more); and 8 fewer TEE per 1000 patients (95% CI: 16 fewer to 18 more) with confidence intervals showing appreciable benefit and harm (Figure 4a). Events were only reported in one study so heterogeneity could not be assessed. The overall certainty of the evidence was low (primarily due to high risk of bias and imprecision).

Bleeding was assessed in four studies[13,14,20,21], enrolling a total of 706 patients (631 after adjustment for cluster RCTs). From the pooled analysis, we calculated 16 fewer bleeding

events per 1000 when supplemental education was provided (95% CI: 34 fewer to 135 more, Figure 4b). There was substantial heterogeneity in the studies for this outcome (I^2 = 65%), and confidence intervals included both substantial benefit and harm. The overall certainty of the evidence was very low due to high risk of bias, inconsistency and imprecision of estimates.

Four studies randomizing 749 patients (505 after adjustment for cluster randomization) measured the effect of supplemental education on TTR; the mean difference in TTR was 2.40% higher with education (95% CI 2.79% lower to 7.58% higher, Supplementary Figure 3: TTR). The mean TTR in the usual care group was 64.4%. Heterogeneity in the studies was moderate (I^2 = 31%). The overall certainty of the evidence was low due to high risk of bias and imprecision.

For knowledge scores, six studies (936 patients in total, 643 after adjustment for cluster RCTs) reported results which were pooled[15-17,20,21,23,25]. The standardized mean difference in knowledge score was 0.84 standard deviation (SD) units higher with supplemental education (95% CI 0.51 to 1.16 SD higher; absolute increase of 15.1% (8.4%); Supplementary Figure 4) compared to usual care (higher scores indicating better knowledge). Heterogeneity between studies however was substantial (I^2 = 70%). The certainty of evidence was very low primarily due to the high risk of bias, imprecision and inconsistency.

Discussion

Despite additionally searching the 6 most recent research intensive years, and including additional studies, there was low to very low certainty in the evidence for improving patient important outcomes with supplemental education. Although absolute risks of harms with education tended to be lower with supplemental education, we were very uncertain about this effect on critically important outcomes. The small magnitude of improvement (<3%) on TTR alone, is unlikely to be sufficient to improve critical patient outcomes[28]. Due to the small number of events and limited follow-up in some of the studies, there was serious to very serious concern with the overall precision of the estimated effects, precluding the possibility to draw conclusions of benefit with a high level of certainty. Consequently, recent guidelines have issued a conditional recommendation based on very low certainty evidence that health care practitioners consider incorporating supplemental patient education in addition to basic education as part of the management strategy for patients receiving oral anticoagulation for VTE treatment[10].

The main challenges to arrive at definitive conclusions around the impact of education on outcomes were related to methodological concerns with serious risk of bias and imprecision due to the small number of observed events, variability in duration of follow-up between studies (impacting the period of time over which to observe mortality, bleeding and thromboembolic outcomes, and may have also resulted in differential decay of knowledge based measures), as well as the variability in content, delivery and intensity of educational interventions. The challenges and methodological biases should be addressed in future

studies especially with respect to patient and health care provider blinding and allocation concealments.

In another systematic review of OAC treatment in AF patients evaluating the effect of self-monitoring plus education on the primary outcome of TTR, they concluded that the effect of these interventions was uncertain compared to usual care, in 11 trials of over 2000 AF patients with very low-quality evidence, citing similar challenges around the lack of standardization of interventions and differing conditions of education reflective of usual care[29].

Despite the paucity of evidence, belief in the inherent value of education and the low perceived risk of causing harm may lead some health systems to continue promoting the use of different forms of supplemental education in these patient groups. However, the opportunity cost of doing so may be underestimated. Studies included did not consider the cost-effectiveness, resource implication or potential patient burden of supplemental OAC education which could be significant depending on the format, frequency and intensity of patient education programs.

In patients taking DOACs[15], there was only one study evaluating supplemental education on knowledge and none which evaluated education on patient important outcomes such as mortality or bleeding. Therefore, additional information is needed as the uptake of DOACs and integration into clinical practice has become more widespread. Patient education may be even more important to promote treatment adherence and persistence due to the comparatively shorter half-life of these agents.

Strengths

Attempts to minimize bias in the review process were made by using multiple databases, not limiting the search by language and ensuring that the screening of studies to be included was done independently by two reviewers. We also contacted authors of unpublished studies and contacted other authors to obtain additional data. Data extraction and analysis was conducted by one researcher but was checked by a second, reducing potential bias in the review process.

Limitations

Although we did not detect publication bias, it is possible that bias exists that was not found. This is of particular importance with interventions such as supplemental education which may be particularly prone to subject selection, attrition and reporting bias.

There was significant heterogeneity in some measures, namely bleeding and knowledge score-based outcomes with variability that could not easily be controlled prior to comparing treatment groups. This underscores the importance of standard measures to improve interpretation and further highlights the importance of using standardized definitions for bleeding and validated measures for knowledge assessment outcomes. For TTR, moderate heterogeneity may also reflect systematic and important differences in the 'usual care' delivered between institutions as well as the intensity and/or effectiveness of the supplemental education interventions.

Furthermore, this review did not aim to assess patient values or preferences, or address the feasibility and acceptability of such programs by patients, health care providers, payers,

institutions or granting agencies. Finally, the resources to implement and sustain such programs were not addressed as part of this review and these are important to consider for any future recommendations.

Conclusion

Although absolute risks for outcomes with supplemental education were generally lower than with usual care, there was low to very low certainty in these effects on critical patient outcomes such as mortality, bleeding and thromboembolic events in patients taking oral anticoagulants. Longer follow-up, additional studies or different approaches to education are needed, and future studies should also examine potential harms and costs to make definitive conclusions around the benefit of supplemental patient education in OAC use, and particularly in patients using DOACs where information is lacking and follow-up may be less frequent in the absence of INR monitoring.

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AUTHORSHIP CONTRIBUTIONS:

MP contributed to study design, search strategy, study selection, data extraction, statistical analysis, interpretation of findings and writing of the report. DMW, AH, JS, JA, HJS and WW contributed to study design, interpretation of findings and writing of the report. RN contributed to study design, search strategy, study selection, data extraction, statistical analysis, interpretation of findings and writing of the report.

CONFLICTS OF INTEREST:

MP is an employee of Boehringer Ingelheim Ltd., which markets dabigatran etexilate, a direct oral anticoagulant. The review question focused on all available oral anticoagulants, and 8 of the 9 studies included in the review were exclusively in patients receiving a vitamin K antagonist, mainly warfarin. In our opinion, Boehringer Ingelheim will not be affected by this review regardless of its conclusions. MP's work on each step of this review has been supervised by RN who has no conflicts, and the other authors have no conflicts.

AH receives honoraria as a drug policy expert advisor from federal and provincial governments, as well as publicly funded peer reviewed grants to improve the quality of OAC management

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Table 1: Characteristics of Included Studies

Study	Indication	Setting	Follow-up Period	Interventions	Control	Outcomes and Description
Clark 1972[17]	Patients discharged on warfarin	Outpatient	24-72 hours after receiving educational materials	Educational program instruction booklet consisting of 5 sections including action and indication for use of drug, lab testing, calculation of dose, factors altering effect of drug and safety factors.	Group 1 received the programmed instruction booklets. Groups 2 and 3 (control groups) received a two-page handout information sheet and no specific printed or verbal instruction.	**Knowledge***: Knowledge of drug use (15 item quiz to assess objective understanding of drug use)
Clarkesmith 2013[20]	AF	Outpatient	3,6 and 12 months†	TREAT Intervention: disease-specific theory-driven educational intervention. Patients attended group sessions lasting 1 hour with DVD information about the need, risks and benefits of OAC, potential interactions with food, drugs, and importance of INR control	All patients received a standard booklet to identify them as taking OAC treatment. General topics included disease information and key safety information including dietary advice.	**Bleeding*, Mortality*, TEE*, TTR*, VTE*** Beliefs about medication, Anxiety and depression scale (HADS), illness representations and health related quality of life.
Desteghe 2018[15]	AF	Inpatient and Outpatient	1,3,6 and 12 months*	After completion of the Jessa Atrial Fibrillation Knowledge Questionnaire (JAKQ), the study team went through responses and further explained incorrect responses. No additional educational materials were used.	Patients received standard care with no extra focused reinforcements and only changes in knowledge score were monitored.	**Knowledge***: Atrial fibrillation knowledge assessment (JAKQ), symptom burden (using the Leuven ARrhythmia Questionnaire), quality of life and DOAC adherence.
Gadisseur 2003[14]	Patients requiring long term OAC (include:AF, and DVT)	Outpatient	6 months	Training consisted of 3 weekly sessions of 90-120 minutes. Information about diet, disease, dosing and training on the Coagucheck system was given.	Routine care, untrained patients.	**Bleeding*, Mortality*, TEE*, TTR*, VTE*** % of all INR values within TTR per patient based on linear interpolation.
Laporte 2003[13]	VTE and embolic cardiomyopathy	Inpatient	3 months	Daily visits by nurses and physicians and education given until hospital discharge. Intensive education group had emphasis on the necessity of strictly complying with information on maintaining	Standard education comprised of minimum information consistent with ethical management of OAC patients with no particular emphasis on compliance, or specific	**Bleeding*, Mortality*, TEE*, TTR*, VTE*** INR stability, compliance.

				anticoagulation stability, and additional visual material.	information about causes of OAC instability	
Marini 2014[25]	VTE	Inpatient	24-48 hours after randomization	A 5 minute educational video was shown on a tablet device after study admission.	All patients also received unrestricted VTE education as deemed appropriate by the healthcare team.	**Knowledge***, Satisfaction with VTE education, and perception of overall healthcare system.
Mazor 2007[16]	Adult patients receiving care from an anticoagulation clinic	Outpatient	Testing 3 weeks after baseline questionnaire	Random assignment to 1 of 4 groups. 1) Narrative evidence video 2) Statistical evidence video 3) Combined narrative + statistical evidence video or usual care. Videos showed physician–patient encounters about oral anticoagulant medication and included narrative or statistical evidence to support recommendations.	Usual care group received no video	**Knowledge***, Beliefs, Adherence (Warfarin related knowledge included belief in import of labs, benefit of warfarin, regimen confusing, intent to adhere, non-adherence, missed lab appointments)
Pernod 2008[21]	DVT or PE	Outpatient	3 months	Tailored educational intervention (20-30 min) consisting of one on one teaching. Patients were given a picture book describing their disease and treatment.	Physicians provided patients with the usual unstructured information about VKA treatment and a standard booklet published by the French Heart Association.	**Bleeding*, Knowledge***, **Mortality*. TEE*, VTE***
Vormfelde 2014[23]	VTE, PE, AF, or mechanical heart valve	Outpatient	6 months	One hour standardized patient education; information on 13 topics pertaining to OAC with phenprocoumon and 20-minute video presentation followed by a discussion, and an 8-page brochure and corresponding questionnaire.	Knowledge assessments only without standardized patient education	**Knowledge*, TTR***:

***** Outcomes in bold font represent those evaluated in meta-analyses
† 6 month follow-up time point was used in meta-analysis

AF= Atrial Fibrillation, DOAC=Direct Oral Anticoagulant, DVT=Deep Venous Thromboembolism; HADS=Hospital Anxiety and Depression Scale, INR=International Normalized Ratio, OAC=Oral Anticoagulant, PE=Pulmonary Embolism; TEE=Thromboembolic Events; TTR=Time in Therapeutic Range, VKA=Vitamin K Antagonist, VTE=Venous Thromboembolism

Figure Legend:

Figure 1. Study Flow Diagram

Figure 2. Risk of Bias Summary: Authors' Assessment for Risk of Bias of Included Studies

Figure 3. Risk of Bias Graph Illustrating Risk of Bias for Included Studies by Domain

Figure 4: Forest Plots: Supplemental Education vs. Usual Care

4a: Outcome Thromboembolic Events

4b: Outcome: Any Bleeding Events

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Figure 1. Study Flow Diagram

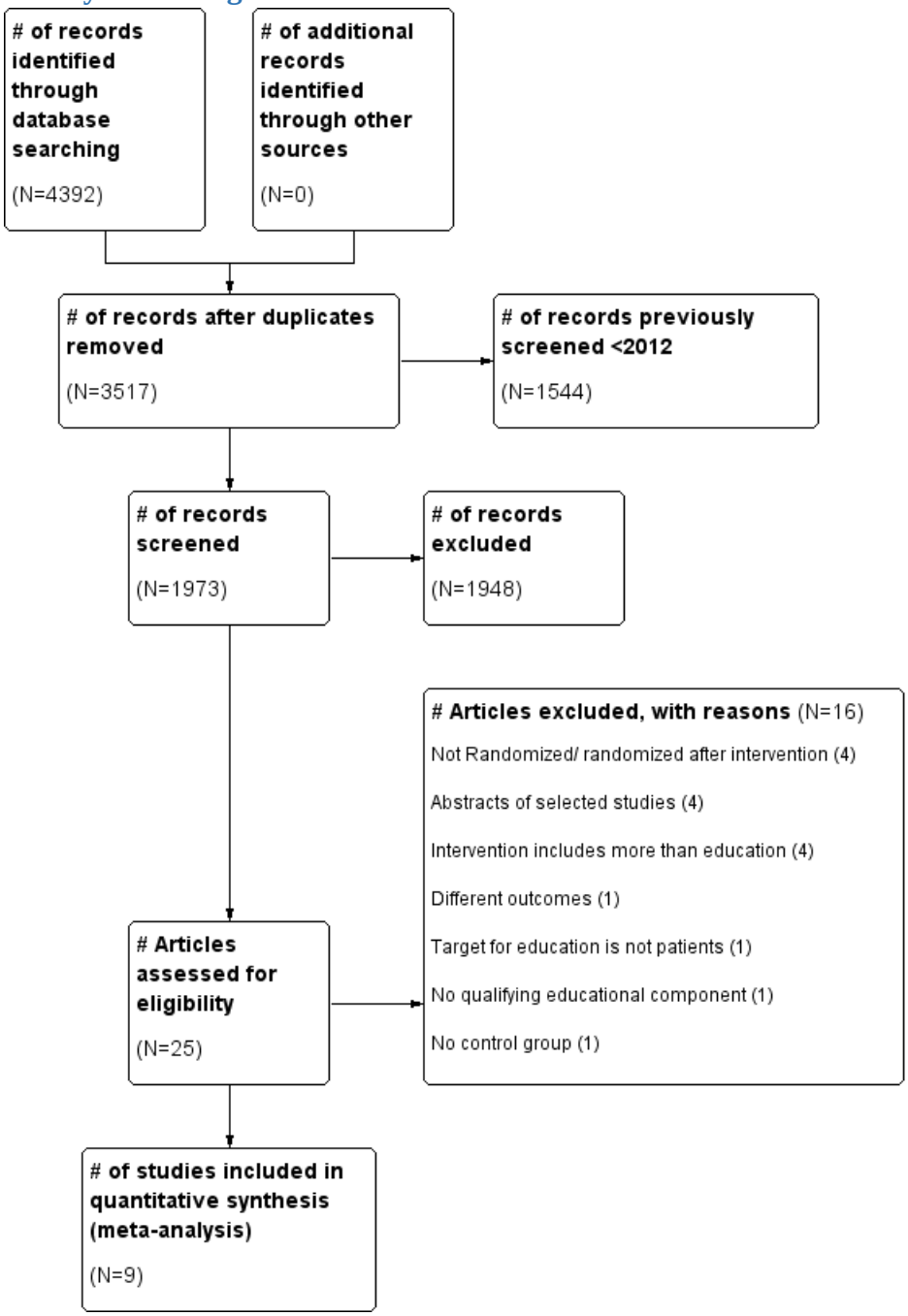


Figure 2. Risk of Bias Summary:

Authors' Assessment for Risk of Bias of Included Studies

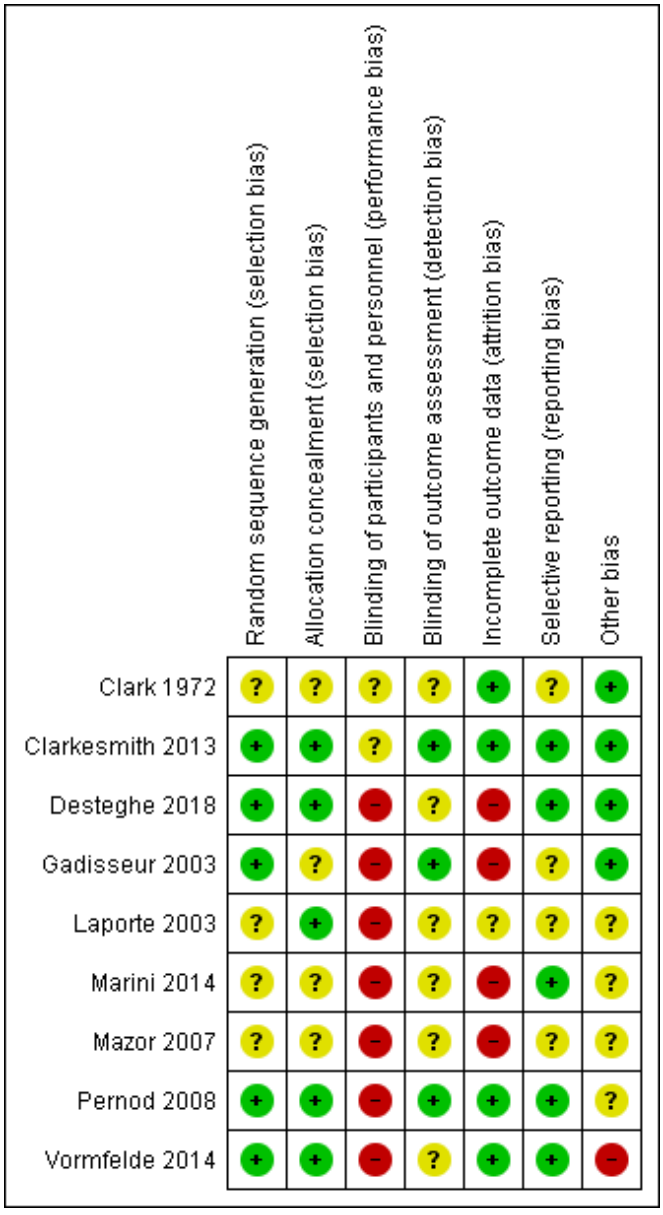


Figure 3. Risk of Bias Graph for Included Studies by Domain

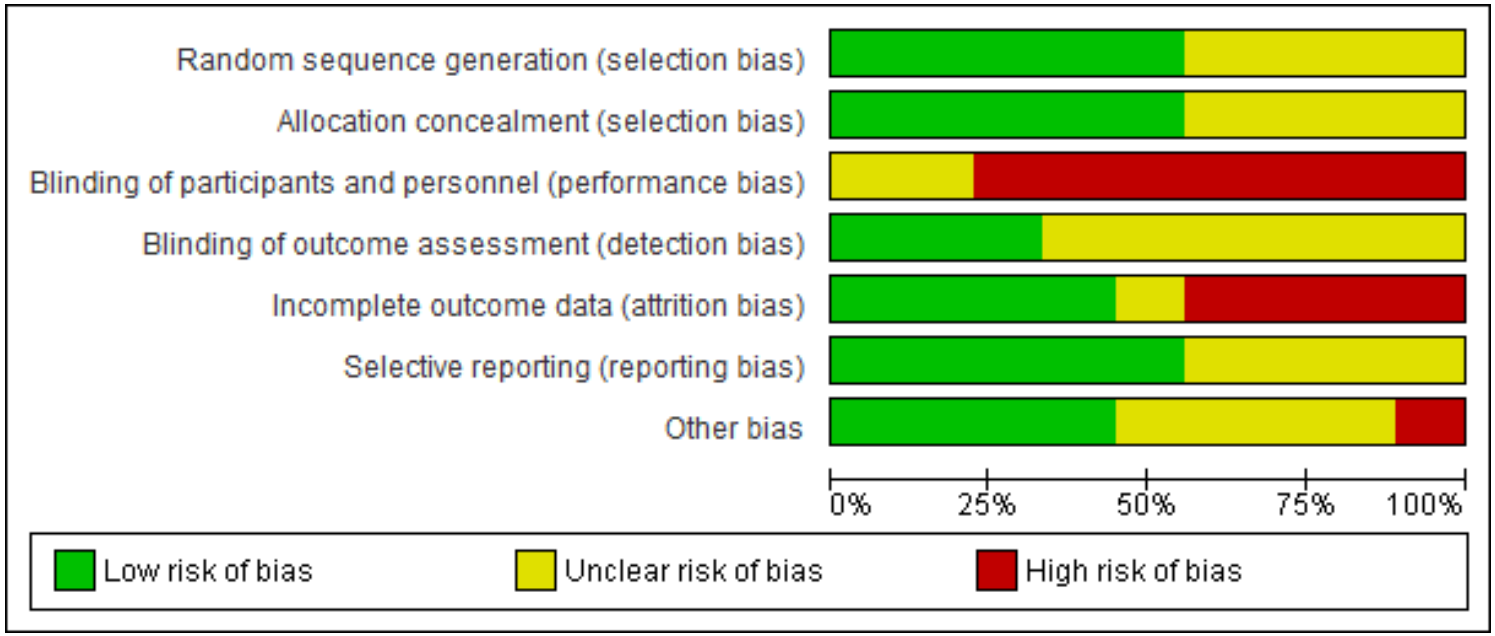
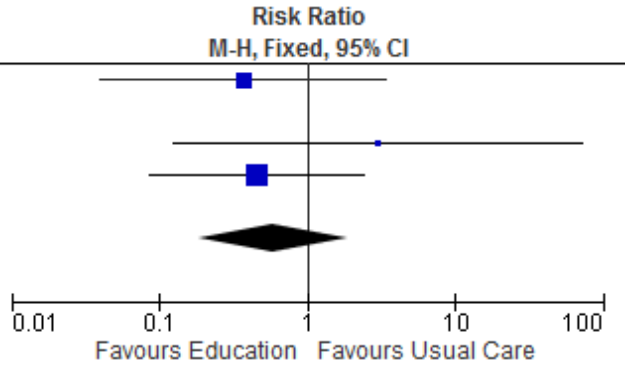


Figure 4. Forest Plots Supplemental Education vs. Usual Care

4a: Outcome Thromboembolic Events*

Study or Subgroup	Supplmental Education Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Clarkesmith 2013	1	46	3	51	37.7%	0.37 [0.04, 3.43]
Gadisseur 2003	0	60	0	161		Not estimable
Laporte 2003	1	43	0	43	6.6%	3.00 [0.13, 71.65]
Pernod 2008	2	119	4	108	55.6%	0.45 [0.08, 2.43]
Total (95% CI)		**268**		**363**	**100.0%**	**0.59 [0.19, 1.88]**
Total events	4		7			

Heterogeneity: Chi² = 1.27, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)



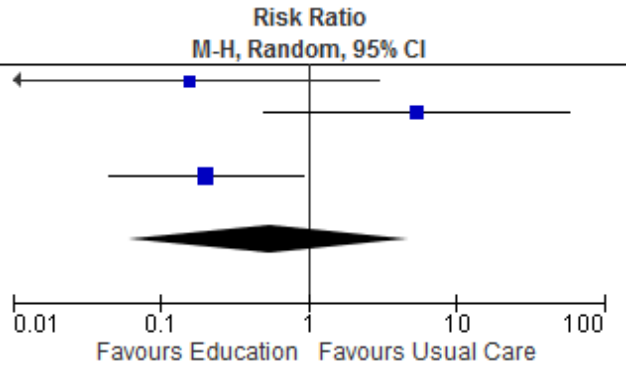
***Includes VTE, systemic embolism**

4b: Outcome: Any Bleeding Events

Study or Subgroup	Supplemental Education Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Clarkesmith 2013	0	46	3	51	26.7%	0.16 [0.01, 2.98]
Gadisseur 2003	2	60	1	161	31.9%	5.37 [0.50, 58.11]
Laporte 2003	0	40	0	43		Not estimable
Pernod 2008	2	119	9	108	41.4%	0.20 [0.04, 0.91]
Total (95% CI)		**265**		**363**	**100.0%**	**0.54 [0.06, 4.76]**
Total events	4		13			

Heterogeneity: Tau² = 2.39; Chi² = 5.74, df = 2 (P = 0.06); I² = 65%

Test for overall effect: Z = 0.56 (P = 0.58)



Supplementary Material

Supplementary Table 1a. Search Strategies and Results

Search Strategy

The search was conducted using the interface: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present. The search represents an update to the systematic review conducted by Wong et. al. in 2013[9].

The databases to be searched include Medline, Embase and Central. Additional resources to be searched included the following sources to identify new studies, or unpublished:

- The largest clinical trials database (Clintrials.gov) was searched which is run by the United States National Library of Medicine at the National Institutes of Health, estimated to include approximately 200,000 trials from more than 170 countries in the world. This was selected as this should include most trials including those that are industry or disease area specific.
- In addition, the citations of the selected articles will also be reviewed to ensure additional relevant studies are identified
- Reference lists of studies of educational intervention identified in an alternate indication (atrial fibrillation) will be checked from 2012 to current
- Guidelines of VTE will be searched for any additional studies which meet the criteria for inclusion
- Efforts will be made to identify unpublished studies such as those identified only in abstracts by reaching out to authors by email

The search was run on 28 Jan 2017 and repeated on 23 Oct 2018 in Medline using the search strategy noted below specifically targeting the following:

- Types of Studies
  - RCTs with >1 educational components as the intervention
  - RCTs published after February 2012
  - Any language; Any length of follow-up period
  - At least 1 control group comprised of 'usual care'
  - Patients at risk for or diagnosed with DVT/PE including:
    - Surgical patients,
    - Medical or ambulatory outpatients,
    - Critically/acutely ill in-patients; hospitalized or in a chronic care facility,
    - In or outpatients with other comorbid conditions,
    - Children or pregnant women

The search was organized by the following sets of terms:

1) Terms to identify all possible relevant anticoagulant agents used in VTE treatment including synonyms, related terms and variants.
   a. Direct oral anticoagulants, also referred to as non-VKA or target specific anticoagulants. These include generic names as well as terms which describe mechanism (eg. Factor Xa, thrombin inhibitor). Parenteral agents

such as the low molecular weight heparins are also included followed by the vitamin K antagonist medications.

2) Terms to identify educational interventions with patient identification as a topic as well as patient compliance and health behaviours
3) The last set of terms are modified from Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision), excluding terms to capture drug therapy as the intervention is not pharmacologic.

Search Date	**28-Jan-17**	**23-Oct-18**	**Total**
Total No. Retrieved:	**3745**	**647**	**4392**
Medline (no date limit):	851	76	927
Embase (2010-current):	2490	379	2869
Cochrane Library (no date limit):	404	192	596
Duplicates:	628	247	875
<2012:	1544	N/A	1544
Screening (Title and Abstract Review) (without duplicates)	**1847**	**400**	**2247**
No. Excluded:	**1828**	**394**	**2222**
Selection (Full Text Review)	**19**	**6**	**25**
Total No. Excluded:	11	5	16
Total Included:	**8**	**1**	**9**

Supplementary Table 1b. Search Terms

Medline

OVERVIEW	
Interface:	Ovid
Database:	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present Ovid MEDLINE(R) Daily Update February 25, 2016
Search Date:	January 28, 2017 and October 23, 2018
Study Types:	RCT
Limits:	Publication date: no limits

Search Strategy: search terms (number of results)

SEARCH NAME: z - GL4-Q1 - Patient education - RCT_Medline

Any Anticoagulant pharmac_(AC_ DOAC_ VKA_ LMWH_ UHF_ fondaparinux)

1 exp anticoagulant agent/ (226634)
2 Anticoagula$.mp. (116291)
3 or/1-2 (262142)
4 Antithrombins.mp. or expAntithrombins/ (20201)
5 thrombin inhibitor/ or thrombin inhibitor.mp. (2954)
6 Factor Xa Inhibitors.mp. or exp Factor Xa Inhibitors/ (4901)
7 rivaroxaban/ or dabigatranetexilate/ or apixaban/ or edoxaban/ or betrixaban/ or ximelagatran/ or hirudins/ (6600)
8 (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatranetexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban$ or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatroban or pradax or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp. (8758)
9 (TSOAC$ or NOAC$ or DOAC$).ti,ab,kw. (1658)
10 ((Target adj Specific adj Oral adj Anticoagulant$) or (oral adj anticoagulant$) or (novel adj anticoagulant$) or (new adj anticoagulant$) or (direc$ adj anticoagulant$)).mp. (10737)
11 ((new or novel or direct or direct-acting or target-specific or targeted or non-vitamin K) adj3 oral anticoagulant*).mp. (3716)
12 (factor Xa adj2 (antag* or inhibit*)).mp. (5017)
13 or/4-12 (33035)
14 exp Heparin/ or heparin.mp. (102644)
15 exp Heparin, Low-Molecular-Weight/ (11880)
16 dalteparin/ or enoxaparin/ or nadroparin/ or heparinoids/ (5277)
17 (LMWH or LMWHs or low molecular weight heparin or nadroparin or fraxiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin* or

danaproid or danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine).mp. (16315)
18 (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp. (134)
19 or/14-18 (104552)
20 exp 4-Hydroxycoumarins/ or warfarin/ or acenocoumarol/ or dicumarol/ or Coumarins/ or coumarin anticoagulant/ or ethyl biscoumacetate/ or phenprocoumon/ or phenindione/ (36472)
21 vitamin K antagonist$.mp. (4233)
22 (4-Hydroxycoumarins or warfarin or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Coumadin or Jantoven or vitamin K antagonist$ or VKA or fluindione or difenacoum or coumatetralyl).mp. (35921)
23 20 or 21 or 22 (49640)
24 (fondaparinux or Arixtra).mp. (1863)
25 exp Heparin/ (67207)
26 (un?fract* adj heparin).mp. (5597)
27 UFH.mp. (1967)
28 ((sodium or alpha) adj1 heparin).mp. (994)
29 (Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock or blockasol or celparin or hed or heparin).mp. (101242)
30 or/25-29 (103584)
31 3 or 13 or 19 or 23 or 24 or 30 (307138)

Patient Education
32 exp Patient Education as Topic/ or exp patient education/ or exp education/ or exp health education/ or exp attitude to health/ or expself care/ or exp patient care planning/ or exp self evaluation/ or expself monitoring/ (1115955)
33 Health Education/ (62292)
34 exp Patient Compliance/ (73061)
35 (((patient or patients) adj3 (education or educate or educating or information or literature or leaflet$ or booklet$ or pamphlet$)) or education or self monitoring* or self-testing*).mp. (773403)
36 or/32-35 (1364103)
37 31 and 36 (4482)

SR filter
38 meta-analysis/ (86348)
39 meta-analysis as topic/ (17511)

40 (meta analy* or metanaly* or metaanaly*).ti,ab. (121194)
41 (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. (38741)
42 ((systematic* or evidence*) adj2 (review* or overview*)).ti,ab. (139464)
43 (search strategy or search criteria or systematic search or study selection or data extraction).ab. (42280)
44 (search* adj4 literature).ab. (46765)
45 (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. (156274)
46 ((pool* or combined) adj2 (data or trials or studies or results)).ab. (49085)
47 cochrane.jw. (17437)
48 or/38-47 (368991)
49 animals/ not humans/ (4815030)
50 exp Animals, Laboratory/ (915053)
51 exp Animal Experimentation/ (9361)
52 exp Models, Animal/ (562802)
53 expRodentia/ (3364245)
54 (rat or rats or mouse or mice).ti. (1361127)
55 or/49-54 (5751006)
56 48 not 55 (352841)
57 37 and 56 (200)
RCT filter
58 randomized controlled trial.pt. (507130)
59 controlled clinical trial.pt. (98123)
60 Clinical Trials as topic.sh. (197690)
61 trial.ti,ab. (548970)
62 factorial*.ti,ab. (25503)
63 (crossover* or cross over* or cross-over*).ti,ab. (81458)
64 ((doubl* or singl*) adj blind*).ti,ab. (162983)
65 (assign* or allocat* or volunteer* or placebo*).ti,ab. (730256)
66 placebo.ab. (204571)
67 random*.ti,ab. (1018074)
68 or/58-67 (2000904)
69 animals/ not humans/ (4815030)
70 exp Animals, Laboratory/ (915053)
71 exp Animal Experimentation/ (9361)
72 exp Models, Animal/ (562802)
73 exp Rodentia/ (3364245)
74 (rat or rats or mouse or mice).ti. (1361127)
75 or/69-74 (5751006)
76 68 not 75 (1781504)
77 37 and 76 (851) →*Any Anticoagulant pharmacy and Patient education and RCT filter*
78 77 not 57 (778)

Embase

OVERVIEW	
Interface:	Ovid
Database:	Embase 1980 to 2018
Search Date:	January 28, 2017 and October 23, 2018
Study Types:	Systematic reviews; and RCT
Limits:	Publication date: no limits for SR. RCT from 2010-2018

Search Strategy: search terms (number of results)

GL4-Q1 - Patient education - RCT_Embase

Any Anticoagulant pharmac_(AC_ DOAC_ VKA_ LMWH_ UHF_ fondaparinux)

1 expantithrombin/ or Antithrombins.mp. (9962)
2 thrombin inhibitor/ or thrombin inhibitor.mp. (8161)
3 Factor Xa Inhibitors.mp. or exp blood clotting factor 10a inhibitor/ (18312)
4 rivaroxaban/ or dabigatranetexilate/ or apixaban/ or edoxaban/ or betrixaban/ or ximelagatran/ or Darexaban/ or Otamixaban/ or Razaxaban/ or Bivalirudin/ or Desirudin/ or Lepirudin/ or Melagatran/ or hirudin/ (24127)
5 (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatranetexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban$ or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatroban or pradax or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp. (21042)
6 (TSOAC$ or NOAC$ or DOAC$).ti,ab,kw. (3062)
7 ((Target adj Specific adj Oral adj Anticoagulant$) or (oral adj anticoagulant$) or (novel adj anticoagulant$) or (new adj anticoagulant$) or (direc$ adj anticoagulant$)).mp. (15987)
8 ((new or novel or direct or direct-acting or target-specific or targeted or non-vitamin K) adj3 oral anticoagulant*).mp. (5999)
9 (factor Xa adj2 (antag* or inhibit*)).mp. (4117)
10 or/1-9 (52770)
11 exp 4 hydroxycoumarin/ or exp 4 hydroxycoumarin derivative/ (792)
12 warfarin/ (79186)
13 acenocoumarol/ (5528)
14 coumarin/ or coumarin derivative/ (20256)
15 phenindione/ (1230)
16 dicoumarol derivative/ or dicoumarol/ (3363)
17 phenprocoumon/ (4630)
18 phepromaron/ (11)
19 ethyl biscoumacetate/ (550)
20 fluindione/ or difenacoum/ or coumatetralyl/ (970)
21 vitamin K antagonist.mp. or antivitamin K/ (11683)

22 (4 hydroxycoumarin or warfarin or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Coumadin or Jantoven or vitamin K antagonist$ or VKA or fluindione or difenacoum or coumatetralyl).mp. (96264)
23 or/11-22 (117119)
24 exp anticoagulant agent/ (593969)
25 Anticoagula$.mp. (187826)
26 24 or 25 (624906)
27 (fondaparinux or Arixtra).mp. (6491)
28 exp Heparin/ (136329)
29 (un?fract* adjheparin).mp. (7862)
30 UFH.mp. (3134)
31 ((sodium or alpha) adj1 heparin).mp. (1107)
32 (Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lockor or blockasol or celparin or hed-heparin).mp. (1636)
33 or/28-32 (137517)
34 exp heparin derivative/ or heparin*.mp. (195321)
35 nadroparin/ (4265)
36 enoxaparin/ (20308)
37 dalteparin/ (6990)
38 ardeparin/ (342)
39 tinzaparin/ (2856)
40 certoparin/ (694)
41 reviparin/ (916)
42 danaparoid/ (2624)
43 (LMWH or LMWHs or low molecular weight heparin or nadroparin or fraxiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine).mp. (54363)
44 (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp. (340)
45 or/34-44 (197363)
46 10 or 23 or 26 or 27 or 33 or 45 (665752)
Patient Education
47 exp Patient Education as Topic/ or exp patient education/ or exp education/ or exp health education/ or exp attitude to health/ or expself care/ or exp patient care planning/ or expself evaluation/ or expself monitoring/ (1538463)

48 Health Education/ (91413)
49 exp Patient Compliance/ (131966)
50 (((patient or patients) adj3 (education or educate or educating or information or literature or leaflet$ or booklet$ or pamphlet$)) or education or self monitoring* or self-testing*).mp. (1069260)
51 or/47-50 (1788359)
52 46 and 51 (28559)
SR filter
53 systematic review/ (151302)
54 meta-analysis/ (156413)
55 (meta analy* or metanaly* or metaanaly*).ti,ab. (139489)
56 (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. (39797)
57 ((systematic* or evidence*) adj2 (review* or overview*)).ti,ab. (152355)
58 (search strategy or search criteria or systematic search or study selection or data extraction).ab. (43556)
59 (search* adj4 literature).ab. (53525)
60 (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. (171634)
61 ((pool* or combined) adj2 (data or trials or studies or results)).ab. (55358)
62 cochrane.jw. (15262)
63 or/53-62 (436370)
64 animals/ not humans/ (1220996)
65 nonhuman/ (5056842)
66 exp Animal Experiment/ (2086480)
67 exp Experimental Animal/ (665421)
68 animal model/ (1040424)
69 exp Rodent/ (3366330)
70 (rat or rats or mouse or mice).ti. (1413188)
71 64 or 65 or 66 or 67 or 68 or 69 or 70 (7348315)
72 63 not 71 (392374)
73 52 and 72 (1586)
RCT filter
74 random*.ti,ab. (1169187)
75 trial.ti,ab. (632382)
76 factorial*.ti,ab. (29529)
77 (crossover* or cross over* or cross-over).ti,ab. (86745)
78 ((doubl* or singl*) adj blind*).ti,ab. (194069)
79 (assign* or allocat* or volunteer* or placebo*).ti,ab. (827022)
80 placebo.ab. (242943)
81 crossover procedure/ (54668)
82 single blind procedure/ (28771)
83 randomized controlled trial/ (473357)
84 double blind procedure/ (139893)

85 or/74-84 (2082240)
86 animals/ not humans/ (1220996)
87 nonhuman/ (5056842)
88 exp Animal Experiment/ (2086480)
89 exp Experimental Animal/ (665421)
90 animal model/ (1040424)
91 exp Rodent/ (3366330)
92 (rat or rats or mouse or mice).ti. (1413188)
93 86 or 87 or 88 or 89 or 90 or 91 or 92 (7348315)
94 85 not 93 (1764922)
95 52 and 94 (4811)
96 95 not 73 (4185)→*Any Anticoagulant pharmacy and Patient education and RCT filter*
97 limit 96 to yr="2010 -Current" (2490)→*Any Anticoagulant pharmacy and Patient education and RCT filter <2010*

Cochrane Library

OVERVIEW	
Interface:	Cochrane Library
Database:	Cochrane Database of Systematic Reviews
Date of Search:	*28/01/17 and 23/10/18*
Study Types:	RCT
Limits:	Publication date: no limits

Search Strategy: search terms (number of results)

Search Name: GL4-Q1_patient education-
Date Run: 22:51:02.441
Description: complete 20170128

ID	Search Hits
#1	MeSH descriptor: [Patient Education as Topic] explode all trees 7775
#2	MeSH descriptor: [Education] explode all trees 22675
#3	MeSH descriptor: [Self Care] explode all trees 4843
#4	MeSH descriptor: [Health Knowledge, Attitudes, Practice] explode all trees 4761
#5	MeSH descriptor: [Patient Care Planning] explode all trees 1675
#6	MeSH descriptor: [Patient Care Team] explode all trees 1654
#7	MeSH descriptor: [Health Education] this term only 3441
#8	MeSH descriptor: [Patient Compliance] explode all trees 10372
#9	(((patient or patients) near/3 (education or educate or educating or information or literature or leaflet* or booklet* or pamphlet*)) or (information near/3 pack*) or education* or self-testing* or self-monitoring*) 58156

#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 74352
#11 MeSH descriptor: [Anticoagulants] explode all trees 4543
#12 (Anticoagulant or anticoagulation) 6495
#13 #11 or #12 9058
#14 MeSH descriptor: [Heparin] explode all trees 4375
#15 MeSH descriptor: [Heparin, Low-Molecular-Weight] explode all trees 1861
#16 MeSH descriptor: [Heparinoids] this term only 55
#17 MeSH descriptor: [Dalteparin] this term only 233
#18 MeSH descriptor: [Enoxaparin] this term only 679
#19 MeSH descriptor: [Nadroparin] this term only 101
#20 (LMWH or LMWHs or low molecular weight heparin or heparin* or nadroparin or fraxiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine) 11209
#21 (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216) 132
#22 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 11246
#23 MeSH descriptor: [Heparin] explode all trees 4375
#24 (UFH or Unfractionated Heparin or Heparin, Unfractionated or Sodium Heparin or Heparin, Sodium or Heparin Sodium or alpha-Heparin or alpha Heparin or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock or blockasol or celparin or hed or heparin) 9896
#25 #23 or #24 10225
#26 MeSH descriptor: [Antithrombins] explode all trees 612
#27 MeSH descriptor: [Factor Xa Inhibitors] explode all trees 305
#28 MeSH descriptor: [Rivaroxaban] explode all trees 148
#29 MeSH descriptor: [Dabigatran] explode all trees 103
#30 MeSH descriptor: [Hirudins] explode all trees 284
#31 (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatranetexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban$ or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatroban or pradax or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b) 1913
#32 ((Target adj Specific adj Oral adj Anticoagulant$) or (oral adj anticoagulant$) or (novel adj anticoagulant$) or (new adj anticoagulant$) or (direc$ adj anticoagulant$)) 149
#33 ((new or novel or direct or direct-acting or target-specific or targeted or non-vitamin K) near/3 oral anticoagulant*) 442
#34 (factor Xa adj2 (antag* or inhibit*)) 8

#35	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34	2540
#36	MeSH descriptor: [Warfarin] explode all trees	1386
#37	MeSH descriptor: [Acenocoumarol] explode all trees	112
#38	MeSH descriptor: [Phenindione] explode all trees	27
#39	MeSH descriptor: [Coumarins] explode all trees	1893
#40	MeSH descriptor: [Dicumarol] explode all trees	22
#41	MeSH descriptor: [Phenprocoumon] explode all trees	89
#42	MeSH descriptor: [Ethyl Biscoumacetate] explode all trees	2
#43	MeSH descriptor: [4-Hydroxycoumarins] explode all trees	1571
#44	MeSH descriptor: [Phenprocoumon] explode all trees	89
#45	(4 hydroxycoumarin or warfarin or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Coumadin or Jantoven or vitamin K antagonist$ or VKA or fluindione or difenacoum or coumatetralyl)	4217
#46	#36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45	4534
#47	fondaparinux or Arixtra	377
#48	#13 or #22 or #25 or #35 or #46 or #47	18851
#49	#10 and #48	896

Supplementary Table 2. List of Excluded Studies

List of Excluded Studies		
First author (Surname)	**Year of Publication**	**Reason for Exclusion**
Abu A[29]	2013	**Abstract only:** Abstract from included study (Vormfelde 2014)
Al-Meshal, N[30]	2013	**Randomization:** Patients were allocated in a consecutive fashion and not randomized
Guo, Y[31]	2017	**Intervention extends beyond education only.** Mobile app intervention includes 8 components for educational intervention as well as clinical decision aids and structured follow-up.
Falamic, S[32]	2018	**Intervention extends beyond education only.** Included general practitioner (GP) contacts.
Khan TI[25]	2004	**Randomization:** Included in Wong 2013 but excluded in current analysis; patients randomized after education was already delivered. Control group was historical and they did not monitor adverse events in control group.
Hendriks[33]	2012	**Intervention extends beyond education only.** Includes "nurse led care/comprehensive management" which was comprised of diagnostics, education and psychosocial support.
Machtinger EL[26]	2007	**No qualifying education:** Included in Wong 2013 but no qualifying education component. Only a visual analog scale with a brief 'teach back' session of several minutes.
Maikrainz, V[34]	2017	**Intervention extends beyond education only.** Practices randomized to intervention group received a complex intervention, including additional tools and guidelines to GPs and their practice teams.
Moore, SJ[35]	2013	**Abstract only:** Abstract only and content is in included study.
Nuziale, B[36]	2015	**Different Outcome:** Outcome is only adherence.
Polek, C[37]	2012	**Randomization:** All patients had education before randomization. Only nursing assessments followed by phone contacts.
Tang, T[38]	2017	**Randomization:** Sites were not randomized to intervention.
Verret, L[39]	2012	**No control group:** The comparison is self-management vs. no self-management, and all participants receive the same education regarding OAC.
Vormfelde, SV[40]	2013	**Abstract only:** Conference abstract of same study as Vormfelde 2014 included in review.
Ware, KB[41]	2015	**Target is not patients:** Delivery is to students not to patients. Coumadin RAP song vs. oral delivery of same information.
Yildirim, JG[42]	2015	**Abstract only:** Effect of nurse home visits on self-care.

Supplementary Table 3. Risk of Bias

Risk of Bias	
Random Sequence Generation:	One of the domains assessed to have the lowest risk of bias was 'Random Sequence Generation'. More than half of the studies included information suggesting low risk of bias for this domain, explicitly noting computer generated sequences[14,15,23], in addition to block randomization[20,21] but the remaining studies did not have sufficient information to assess this domain.
Allocation Concealment:	Three of the studies included sufficient information and were assessed to have low risk of bias for allocation concealment of randomization[13,20,23]. Selection bias due to foreknowledge of cluster allocation was a potential concern for the two cluster RCTs[21,23] as patients could have been preferentially selected to derive benefit from an educational intervention or conversely, patients could be excluded if there was a perceived risk to derive no benefit. Furthermore, patients could opt not to participate with prior knowledge of intervention and there was some evidence of this type of bias for one study which showed a higher rate of declined participation in the intervention group compared to the control[23]. This same study showed baseline differences in the opposite expected direction of effect with baseline education levels in the control group higher than in the intervention group. Furthermore, a Zelen design where patients were consented after randomization, giving patients an opportunity to opt out of participating with foreknowledge of the treatment assignment was used in this study. In the second of the cluster RCTs[21] and the remaining studies, allocation concealment could not be explicitly ascertained[14,16,17,24]
Blinding of Participants and Personnel:	Two studies had insufficient information to assess risk of bias associated with blinding[17,20]. The other studies indicated that the design was open and that either participants or personnel were aware of the treatment groups[13-16,21,23,24]. Due to the nature of the intervention, it was not surprising that this domain was assessed to have the greatest risk of bias with no studies judged to have low risk. It would be difficult to blind patients to supplemental education, especially with delivery of a structured type of education, and there could be a risk of bias on the part of both patients and personnel, particularly when evaluating less objective outcomes such as knowledge based outcomes. For example, personnel not blinded to patient status may inadvertently treat patients differently or could influence outcomes directly such as in the scoring of measurements of

	patient knowledge. For the main outcomes of mortality, TEE and VTE recurrence, the risk of bias due to lack of participant/personnel blinding is less problematic due to the more objective nature of these outcomes.
Incomplete Outcome Data:	Four studies had evidence for low patient attrition and complete reporting of outcomes[17,20,21,23]. Four studies had evidence suggesting high risk of bias on this domain[14-16,24]. One study had high risk of bias due to a relatively large proportion of drop outs in the interventional group (~15%) and a large proportion that did not respond in the control group[14]. In another study, only 77% of randomized patients provided data at 3 weeks with important differences in retention between groups of patients. Approximately one third of the invited sample either explicitly opted out or did not respond to at least one of the mailings[16]. In the last study judged to have high risk of bias on this domain >40% of randomized patients did not provide outcome data[24]. One study had unclear risk of bias for incomplete outcome data with 9% lost to follow-up in the intervention group and 2% of the control group[13].
Selective Reporting:	Five studies were assessed to have low risk of bias for selective reporting of outcomes. Three studies had a protocol available[20,21,23], two studies did not have a protocol available but the primary outcome was used for calculating the sample size[15,24]. The remaining studies did not publish protocols or have sufficient information to assess risk of bias for this domain[13,14,16,17].
Other Potential Sources of Bias:	Risk of other biases was judged to be low for three studies which reported no commercial funding source[14,15,17], or involvement by study sponsors in design, collection, analysis, writing or decision to publish[20]. The remaining 4 studies did not have sufficient information to assess risk of publication bias and did not have information suggesting there were other sources of bias[13,16,21,24].

Supplementary Table 4. Summary of Findings

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Other consider-ations	Supplement. patient education	Usual Care	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: mean 12 months)												
4 [1,2,3,4]	RCT	not serious	not serious [a]	not serious	very serious [b]	none	0/46 (0.0%)	1/51 (2.0%)	**RR 0.37** (0.02 to 8.83)	**12 fewer per 1,000** (from 19 fewer to 154 more)	⨁⨁◯◯ LOW	CRITICAL
Venous Thromboembolism (follow up: range 3 months to 12 months)												
4 [1,2,3,4]	RCT	serious [c]	not serious	not serious	serious [b]	none	2/268 (0.7%)	4/363 (1.1%)	**RR 0.45** (0.08 to 2.43)	**6 fewer per 1,000** (from 10 fewer to 16 more)	⨁⨁◯◯ LOW	CRITICAL
All Thromboembolic Events (follow up: range 3 months to 12 months)												
4 [1,2,3,4]	RCT	serious [c]	not serious	not serious	serious [b]	none	4/268 (1.5%)	7/363 (1.9%)	**RR 0.57** (0.17 to 1.95)	**8 fewer per 1,000** (from 16 fewer to 18 more)	⨁⨁◯◯ LOW	CRITICAL
Bleeding Events (follow up: range 3 months to 12 months)												
4 [1,2,3,4]	RCT	serious [c]	serious [d]	not serious	serious [b]	none	4/265 (1.5%)	13/363 (3.6%)	**RR 0.54** (0.06 to 4.76)	**16 fewer per 1,000** (from 34 fewer to 135 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Other consider-ations	Supplement. patient education	Usual Care	Relative (95% CI)	Absolute (95% CI)		
Time in Therapeutic INR Range (follow up: range 3 months to 12 months; Scale from: 0 to 100)												
5 [1,3,4,5]	RCT	serious [c]	not serious	not serious	serious [b,e]	none	196 [e]	303 [e]	-	MD **2.4 % higher** (2.79 lower to 7.58 higher)	⨁⨁◯◯ LOW	IMPORTANT
Knowledge Scores - Supplemental Education vs. Usual Care (NOT prioritized) (follow up: range 1 days to 6 months)												
5 [1,2,5,6,7,8]	RCT	very serious [f]	serious [g]	not serious	not serious [h]	none	313 [h]	330 [h]	-	SMD **0.84 SD higher** (0.51 higher to 1.16 higher)	⨁◯◯◯ VERY LOW	NOT IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **RCT**: Randomized Clinical Trial; **SMD:** Standardised mean difference

Explanations

a. Cannot be determined
b. Lower and upper bound of 95% CI will lead to different recommendations
c. All RCTs had high RoB, primarily due to lack of blinding of participants, providers and outcome assessors, as well as lack of details on random sequence generation and allocation concealment.
d. Unexplained inconsistency with widely different point estimates and I2=65%
e. Results adjusted for design effect of cluster RCT (Vormfelde 2014)
f. In addition to the RoB issues as noted for the other outcomes, the outcome of knowledge was measured using non-validated questionnaires
g. Unexplained inconsistency with widely different point estimates and I2=70%
h. Results adjusted for design effect of cluster RCTs (Pernod 2008, Vormfelde 2014)

References for Summary of Findings

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Supplementary Figures. Forest Plots of Supplemental Education vs. Usual Care

Figure 1: Outcome - Mortality

Study or Subgroup	Supplemental Education Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Clarkesmith 2013	0	46	1	51	100.0%	0.37 [0.02, 8.83]
Gadisseur 2003	0	0	0	0		Not estimable
Laporte 2003	0	0	0	0		Not estimable
Pernod 2008	0	0	0	0		Not estimable
Total (95% CI)		**46**		**51**	**100.0%**	**0.37 [0.02, 8.83]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.54)

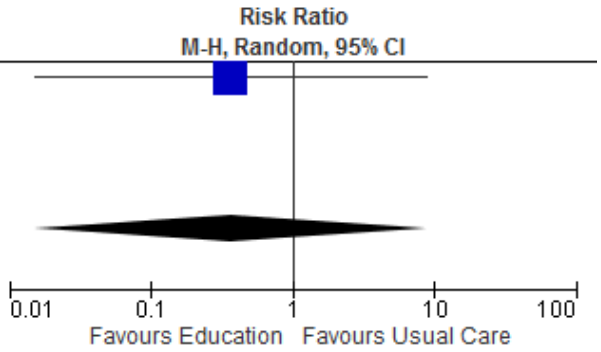


Figure 2: Outcome - Venous Thromboembolism

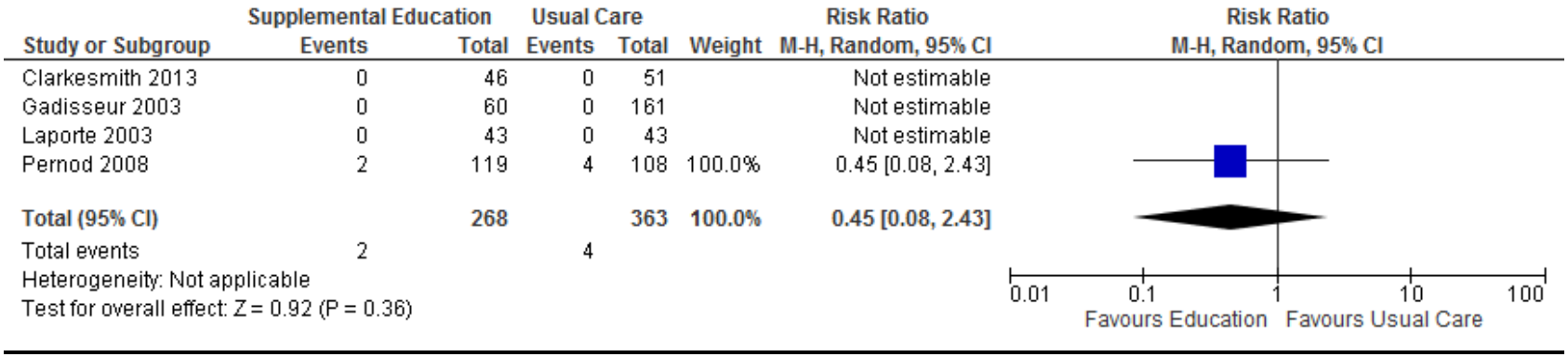
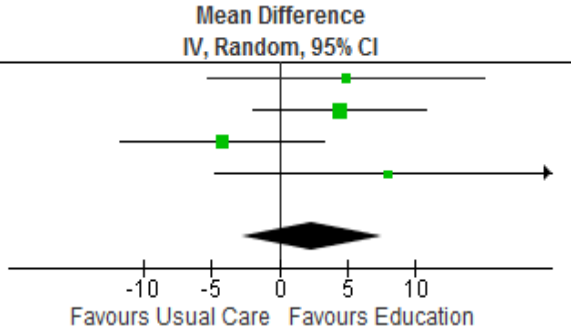


Figure 3: Outcome - Time in Therapeutic Range

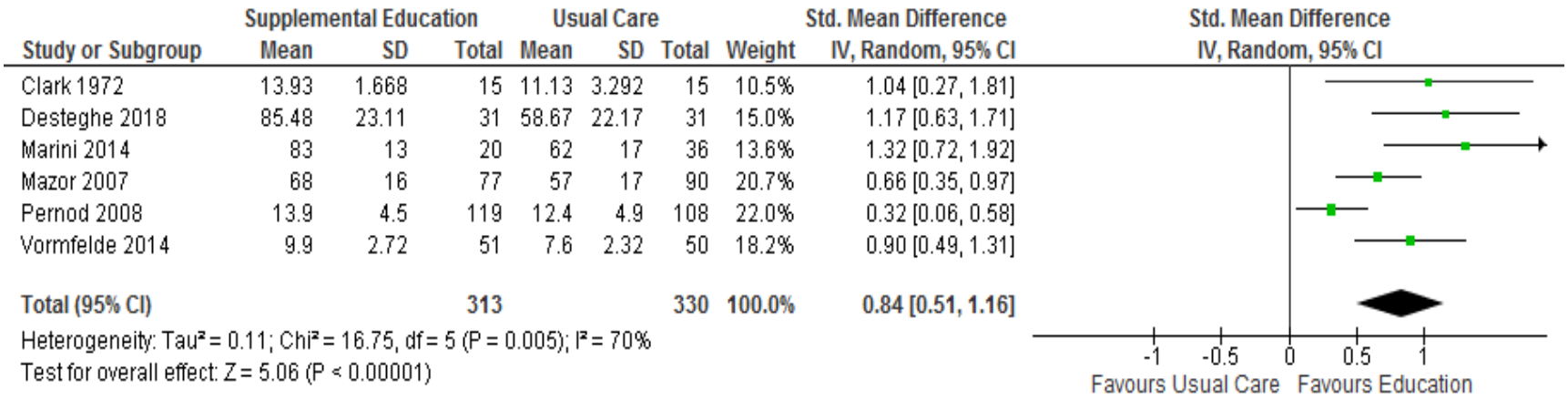
	Usual Care			Supplmental Education				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Clarkesmith 2013 (1)	76.2	24.6	42	71.3	24.8	49	19.6%	4.90 [-5.28, 15.08]
Gadisseur 2003	67.9	20	60	63.5	24.6	161	36.6%	4.40 [-1.93, 10.73]
Laporte 2003	61.6	17.6	43	65.8	17.7	43	30.2%	-4.20 [-11.66, 3.26]
Vormfelde 2014	72	27.9	51	64	36.9	50	13.7%	8.00 [-4.78, 20.78]
Total (95% CI)			**196**			**303**	**100.0%**	**2.40 [-2.79, 7.58]**

Heterogeneity: Tau² = 8.72; Chi² = 4.35, df = 3 (P = 0.23); I² = 31%
Test for overall effect: Z = 0.91 (P = 0.37)



Footnotes
(1) Excluding Clarkesmith

Figure 4: Outcome - Knowledge Scores



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CHAPTER 5: Methodological Considerations for Investigating Oral Anticoagulation Persistence in Atrial Fibrillation

PREFACE TO CHAPTER 5

The manuscript entitled, “Methodological Considerations for Investigating Oral Anticoagulation Persistence in Atrial Fibrillation” was submitted to the European Heart Journal on 1 February 2020, and was under review at the time this thesis was compiled. This dissertation includes the final revised submitted version.

Contributions of Authors

Miney Paquette conceived the paper and conducted the review. She wrote the first draft of the manuscript, addressed critical revisions, and incorporated all author comments into the final submitted version of the manuscript.

Dr. Lawrence Mbuagbaw, Dr. Alfonso Iorio, and Dr. Robby Nieuwlaat conceived the paper, provided critical revisions and approved the final version of the submitted manuscript.

Methodological Considerations for Investigating Oral Anticoagulation Persistence in Atrial Fibrillation

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Word Count: 4659 (text), 2073 (references), 243 (table)

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Abstract

Aims: Reports of long-term oral anticoagulant (OAC) therapy for atrial fibrillation (AF) reveal highly variable, and generally suboptimal estimates of medication persistence. The objective of this review is to summarize current literature and highlight important methodological considerations for interpreting persistence research and designing studies of persistence on OAC treatment.

Methods and Results: We summarize differences in study methodology, setting, timing, population, treatment and other factors associated with reports of better or worse persistence. For example, prospective study designs compared to retrospective study designs are associated with higher reported persistence. Similarly, patient factors such as permanent AF or high stroke risk, and non-vitamin K oral antagonists (NOACs) relative to vitamin K antagonists are associated with higher persistence. Persistence has also been reported to be higher in Europe compared to North America and higher when the treating physician is a general practitioner compared to a specialist.

We propose a framework for assessing and designing persistence studies. This framework includes aspects of patient selection, reliability and validity of measures, definitions of persistence used, clinical utility of measurements, follow-up periods and analytic approaches.

Conclusions: Differences in study design, patient selection, treatments and other factors such as the countries/regions where studies are conducted or the type of treating physician may help explain the variability in OAC persistence estimates. A framework is proposed

to assess persistence studies, which may have utility to compare and interpret published studies as well as for planning of future studies.

Key words: atrial fibrillation, oral anticoagulation, persistence, methodology

Introduction

Medication persistence, an important facet of managing disease, has been linked to patient important outcomes[1], and may be especially germane for chronic illnesses requiring long term treatments. Persistence, the focus of this discussion refers to "the duration of time from the initiation to discontinuation of therapy", which is one end of the spectrum within the concept of adherence which comprises the period from initiation, through implementation (reflecting the accurate intake of medications inclusive of dose, frequency and required schedule) to discontinuation[2,3]. Drug discontinuation and it's opposite, drug persistence are terms used interchangeably to measure how long patients remain on treatment.

A comprehensive understanding of the factors linked to discontinuation and how this affects clinical outcomes will be meaningful to patients and clinicians. This is especially true for treatments unrelated to symptom relief with a substantial risk of adverse events, such as oral anticoagulants (OAC) for atrial fibrillation (AF). AF is an arrhythmia with growing prevalence[4] which requires long term anticoagulation for those with additional stroke risk factors. Suboptimal OAC persistence in AF is a recognised concern, as the absolute risk of discontinuation is high[5,6].

Poor persistence to warfarin has been well established in the literature with estimates of <50% of patients remaining on treatment after 2 years[7]. When absolute rates of discontinuation are high, investigating persistence as a first step is reasonable, especially given the relative ease in persistence measurement compared to more complex

measurements of adherence that include dosage, timing and frequency of use[3]. However, measuring adherence may also have merit, especially with the case of medications such as non-vitamin K OACs (NOAC) which have a relatively short half life whereby even single missed doses could represent important gaps in treatment[8-11].

While NOACs are increasingly being prescribed over VKA for anticoagulation initiation, whether persistence is improved due to ease of use or worsened due to absence of routine monitoring has not yet been clearly established[12]. The estimates of discontinuation even in large randomized clinical trials (RCTs) are highly variable and inconsistent (ranging from 2.3-37%)[13] which make comparisons less reliable and lowers assurance that we have an adequate understanding of the problem; and in the extreme case, confidence to assert whether there is a problem at all.

Furthermore, understanding the reasons and predictors of non-persistence is essential to establish; the former which are imperative for developing constituents of effective interventions (appreciating that some reasons may be more amenable to intervention than others), and the latter to target our attention on the patients who are most vulnerable to discontinuation, thereby maximizing the potential benefit of delivered interventions. Failure to focus interventions on the group of least adherent patients has been put forth as a potential explanatory factor for the absence of important effects detected in many intervention trials to improve adherence[14].

Methodological differences in the way OAC persistence is explored require consideration to ensure appropriate interpretation of results. Variability in study designs, definitions of

persistence and assessment of outcomes, patient factors and environmental considerations, may at least partially explain the differences observed.

We aim to describe some of the main considerations for OAC persistence research in AF, by elaborating on 3 broad areas related to study, patient or other external factors (Figure 1), summarizing factors that may be associated with higher or lower persistence (Figure 2), and finally, providing a framework for assessing reliability, validity, outcome measures and clinical utility for designing interventions, in studies of persistence (Table 1).

Study Factors

Study Designs: Much of the current knowledge of NOAC persistence comes from retrospective analyses of available data such as those from established national health registries[15-18], surveys[19], electronic medical databases[20], and prescription claims databases[6,21,22]. While exploring and synthesizing information from these typically large datasets provides extensive and systematically collected information around patterns of use and discontinuation, there are limitations to keep in mind. One of the main limitations is missing data [23]. Furthermore, critical information may not be available such as explicit reasons why medications are discontinued, and important biases may exist that affect selection of patients and controls, thereby introducing substantial risk for unmeasured confounding[24]. These studies may be further restricted to certain patient segments such as databases comprising older patients (eg. Medicare[25]), or target a sociodemographic subset

of patients such as those with continuous health coverage[6,26], or those based in certain geographic locations[17,27].

As the nature of these studies are retrospective, treatment exposure and pre-specified collection of important outcomes cannot be controlled, and the accuracy or comprehensiveness of information cannot be fully substantiated. However, these databases offer an important opportunity to evaluate large, representative patient groups relatively efficiently from a cost and resource perspective and thus offer a powerful source of information to evaluate persistence. Generally, measurements of persistence in retrospective clinical practice studies are reported to be lower than their prospective counterparts[28].

Prospective studies offer some advantages which can include determining: when and how treatments will be administered; which patients, and respective controls, if applicable, will be enrolled; how outcomes will be measured in advance of measurement (for example including actual intake and discontinuation dates); and additional critical information to be collected, such as reasons for discontinuation without which, studies will have limited utility to enact effective interventions. Although documenting discontinuation dates in a prospective context may have greater precision and less missing data, such measurements are generally less objective and require relatively more time, resources and cost to conduct these studies. Patients and their health care providers may also potentially modify their behaviors as a consequence of knowing their behaviors are being monitored (Hawthorne effect)[29], with the effect of patients remaining on medication longer or health care providers providing additional support to enhance drug continuation.

Certain objectives and clinical questions may be inherently better answered by prospective studies, as is the case when the aim is to assess effectiveness of clinical interventions.

Randomized controlled trials (RCTs) can effectively mitigate the potential for unmeasured confounding and allow us to more confidently state that observed differences between groups are due to the presence or absence of an intervention. However, RCTs are designed to test interventions which may independently influence persistence. Furthermore, the ecological validity of measurement is compromised in such controlled settings where contact will likely be more intensive than would be the case in routine clinical practice and follow-up of relatively shorter duration. The patients included in RCTs typically represent a narrow segment of the overall population of patients who may eventually receive the treatment. As drugs are provided free of cost to the patients, the cost element which may drive discontinuation is eliminated. Prospective observational studies in clinical practice can lend greater generalizability and clinical utility than RCTs in this regard.

Discontinuation rates reported are generally lower in RCTs than in observational studies. For example, discontinuation rates in an RCT for one of the NOACs (dabigatran), were <15% at 1 year[9] and ~20% at 2 years of follow-up[8,10] but prospective observational studies of the same NOAC reported higher discontinuation rates in clinical practice settings at approximately 30% at 2 years [30]. For retrospective observational studies of the same NOAC, 1 year discontinuation rates ranged from 30%-51%[31,32].

Definitions of Persistence and Measurement of Outcomes: Researchers may be interested in persistence, defined as "the act of continuing the treatment for the prescribed duration" or "the duration of time from initiation to discontinuation of therapy"[2] or in it's related counterpart, discontinuation, defined as the termination of medication[33] by some period in which the medication is not taken. The stringency of the definitions will affect estimates.

The strengths and limitations of varying definitions of persistence or discontinuation require consideration when interpreting rates or comparing across studies. For example, defining discontinuation by treatment gaps of 14 days[34] or less could include temporary discontinuations due to procedures or other brief interruptions resulting from acute illness, which may inflate estimates of discontinuation. In contrast, defining discontinuation by significantly longer intervals to allow for periodic dose adjustments or variable timing of prescription refills (such as those defined by prescription refill gaps of 60 days or longer [6,35]) may be less clinically meaningful or may produce overly liberal and unrealistically optimistic estimates of persistence. In one study, which defined warfarin non-persistence by gaps of 180 days, the 1 year persistence estimate was relatively high compared to other estimates, with close to 3 quarters of patients identified as persistent after 1 year[36]. Even seemingly minor differences in definitions or different approaches to analyses could potentially create significant variability in persistence outcomes which need to be considered. Interpretation of results should be made with due caution applied when comparing studies with variable measurements of persistence.

Of critical importance is also how persistence is defined. For example, if persistence only measures the time to first discontinuation and does not consider patients who switch to

equally efficacious therapies to be persistent, the predicted clinical course may be assumed to be unnecessarily bleak. An investigation of patients who discontinued dabigatran in fact showed that approximately half of discontinuations were associated with re-start of other NOACs or VKAs[30]. Considering these issues, general persistence measures of all anticoagulation treatments (considering patients who switch as persistent) may be more clinically relevant.

Some definitions of persistence may inadvertently include competing outcomes such as mortality which can inflate discontinuation estimates as is the case when using claims databases which rely exclusively on prescription refills for which failure to re-fill a script may not only encompass periods of 'immeasurable time' when patients are hospitalized[37], but may be combined with patient death[38-40]. A propensity score matched analysis comparing rivaroxaban patients to those on warfarin illustrated fewer VTE events and better persistence for patients on rivaroxaban[39], however mortality data were unavailable and lower persistence and higher VTE events with VKA may have been confounded with lower mortality in this group.

Analytic Considerations: Analyses of comparative studies should consider the impact of differential censoring between drugs that could lead to populations with differing probabilities for outcomes[22]. If patients are more prone to switch with one medication compared to another, one might appear to have fewer outcome events but be confounded by censoring of more vulnerable patients at the point of switching to another medication. Hence more advanced modeling techniques to consider time varying confounders may be

appropriate[22]. Issues such as these are mainly problematic when persistence measures are drug specific.

Finally, in order to define clinically relevant targets for improving persistence with an intervention, it is fundamental to establish the relationship between some magnitude of effect (i.e. change in persistence) to rates of clinically important outcomes such as stroke or mortality, and studies that report outcomes following discontinuation meet the first important step to establish if there is a relationship at all [41,42].

Timing of Assessment and Duration of Follow-up: Exploring medication persistence has an implicit requirement for establishing an effective period for which patients should remain on treatment. For guideline adherent OAC for AF patients, this is an indefinite period which requires clinical judgement to weigh the stroke prophylactic benefits of OACs against their inherent risks for bleeding (which are dependent on evolving patient co-morbidities and characteristics that largely overlap with stroke risk factors). To understand the trajectory of treatment persistence over the disease course requires longer term follow-up to illustrate the complex relationships of patient characteristics, and drug effects over time yet some study designs offer only a cross-sectional description of patients with heterogeneous characteristics at diverse points following treatment initiation such as one investigation of adherence to dabigatran[43].

One potential issue seen with adherence measurements, which has a related issue for persistence measurement is the potential for confounding by timing or duration of follow-up. Adherence to medication has been shown to be inversely associated with the total

time of follow-up[44,45] [as the proportion of days covered (PDC) is a ratio of estimated total days on medication over the total number of follow-up days], and with a constant PDC, longer follow-up will dilute this ratio resulting in lower adherence estimates than those with shorter follow-up. This has further implications when comparing medications with differential timing for market availability in that these differences will favor the most recent medication introduced to the market if follow-up remains unadjusted[45]. For persistence measurements, shorter follow-up periods may produce lower estimates if extrapolated to reflect long-term persistence, as the early period following drug initiation may be the most vulnerable for discontinuation. Including longer follow-up would improve the expected probability of remaining on treatment[46].

The timing of persistence measurement relative to diagnosis may introduce additional variability that should be considered in the interpretation of findings. For example, in incident populations assessed soon after diagnosis and drug initiation (inception cohort[47]), patients may have higher inherent risk for discontinuation by virtue of starting measurement before sufficient time has transpired for detection of any important adverse drug reactions or drug interactions that drive discontinuation[48]. In contrast, starting assessment in patients on medication at a later point following diagnosis and drug initiation (prevalent AF patients) may look more favorable as patients with certain characteristics reflective of those with higher discontinuation risk will have dropped treatment at an earlier time point (a concept referred to as “depletion of susceptibles”[49]).

Following patients from the time of treatment initiation can help characterize *when* patients may be most likely to discontinue, an aspect of high importance when

considering how to maximize the impact of interventions (especially those that come with high cost and/or resource burden) to optimize persistence[30,41].

Inception cohort study designs measuring persistence from the time of diagnosis and treatment initiation to discontinuation, may be instrumental for differentiating drug and patient factors that contribute to discontinuation. A well-designed cohort study with enough follow-up time to evaluate long-term persistence using reliable and ecologically valid measurements of persistence with reasonable precision could be informative to clinicians. Restricting enrollment to patients newly diagnosed with atrial fibrillation (for example within 3 months), with documented stroke risk and without prior long-term exposure to anticoagulants (total duration < 30 days) would reduce risk of confounding. The primary outcome could be time to discontinuation defined by stopping of all OAC medication for a period of 30 days or more to reduce the impact of temporary discontinuations. Sensitivity analyses examining different cut-points could be conducted to confirm the optimal interval without medication for classification of discontinuation. Patients switching to an alternative OAC could be considered persistent. Ideally, reasons for discontinuation should be comprehensively assessed to improve understanding.

Patient and Treatment Factors

Factors such as patient sampling, treatment exposure and disease characteristics may further affect the generalizability of results and will be addressed next.

Patient Clinical Predictors of Discontinuation: In addition to considering the broad selection of patients included in studies of persistence, there are additional patient level

clinical characteristics that have been associated with OAC persistence which should be acknowledged, such as lower persistence reported in younger males[6], those with higher bleeding risk[50] and lower stroke risk [30,40]. In contrast, certain AF characteristics which may be surrogate markers for disease severity such as asymptomatic or minimally symptomatic AF and permanent AF[30] have been associated with higher persistence. Use of concomitant medications which may address common OAC side effects such as proton pump inhibitors prescribed for dyspepsia may also be predictive of those more likely to be non-persistent[30]. These groups identified as being most prone to be non-persistent are perhaps the groups to preferentially target to deliver interventions (Figure 2).

The reasons reported for discontinuing NOACs have not been primarily due to adverse events[30], suggesting that other reasons based on patient risk, or patient or physician preference may have an important role in driving discontinuations. In support of this hypothesis is the attribution of warfarin discontinuations to patient centric reasons such as patient preference or refusal to continue medication, patient frailty and frequent falls, high bleeding risk and inability to adhere to or monitor their treatment[48]. The complexity of reasons for discontinuation, those made unilaterally by patients as well as those jointly made with treating physicians, has highlighted the need for a multi-level approach incorporating both patients' treatment preferences as well as physicians' prescription and management determinants (including associated healthcare systems) to improve overall adherence to anticoagulant treatments[44].

Finally, awareness of other issues such as selection practices at the patient level may also affect the results and potentially limit generalizability of findings. For example, studies

that require patients to consent to participate may naturally represent a subset of patients more likely to persist with treatment or they may represent a selected sociodemographic subset of the overall population. The act of providing consent itself could act as implicit agreement to improve patient commitment to persist with treatment. Furthermore, including chronic medication users only (defined by > 2 prescriptions filled) could result in higher estimates of adherence and persistence than if 'non-chronic' users were also included[45]. These differences can produce variability that should be recognized in interpretation of results.

Treatment Factors: As treatments evolve and new options become available, reported persistence rates may improve simply due to availability of better, more tolerable or easier to manage therapies. This appears to be the case with the introduction of NOACs which are becoming the preferred OACs in newly diagnosed AF patients with guidelines highlighting the importance of treatment adherence[51].

The availability and endorsement of NOACs for stroke prophylaxis[51] have diminished some of the challenges inherently seen with warfarin such as those associated with the drug's narrow therapeutic window, possible interactions with other drugs and diet, and highly varied individual patient dose responses requiring frequent drug monitoring to maintain optimal anticoagulation[52]. Prospective, comparative persistence data with these agents is limited but there is some evidence that patients remain on NOACs longer than warfarin[30,40,53].

The availability of different doses to manage bleeding risk, such as seen with some of the NOACs, as well as once a day formulations[54,55] may impact adverse drug reactions and overall likelihood to persist with drug regimens. Although not directly demonstrated for persistence outcomes, less frequent dosing has generally been associated with better adherence in other chronic illnesses[56]. Similarly, fewer overall number of medications has generally been associated with better adherence in other conditions[57,58]. In AF patients, while polypharmacy and direct impact on persistence or adherence have not been reported, a higher number of comorbidities has been associated with lower adherence suggesting this may be a potentially explanatory factor driving non-adherence and by extension, non-persistence[59].

These associations between patient characteristics and persistence suggest there is room for enhancing clinician-patient decision making to initiate and maintain treatment with selected anticoagulants[60]. Patient groups who are most susceptible to discontinue should be preferentially targeted with interventions that may be developed to improve OAC persistence such as those who are newly diagnosed, those with low stroke risk, and those with symptomatic AF (Figure 2). Interventions such as patient education or other patient management interventions such as instituting more frequent follow-up in high-risk patients, engagement of associated health care professionals such as nurses or pharmacists or technological interventions could be potential options to explore[61].

The next broad area to consider when examining persistence is related to external or environmental factors including the impact of different treating physicians, treatment settings and country or regional considerations.

Other External Factors

The settings in which persistence to anticoagulation are measured can vary by geography as well as the types of settings such as institutions, clinics or private offices where patients are followed, or the infrastructure of the healthcare system itself. In addition, the type of healthcare provider such as a specialist or general practitioner may be associated with different observed rates of patient persistence to medication. These factors may be confounders if comparing persistence (e.g. between interventions or different drugs), without settings balanced between groups.

Healthcare Infrastructure and Treating Physician: Differences in healthcare infrastructure have been noted as a potential factor which could impact treatment persistence[60]. Patient management through specialized anticoagulation clinics for warfarin dosing for instance showed lower rates of non-persistence compared to studies without anticoagulation clinics[36,62]. While there is no explicit requirement for monitoring of NOACs, there may still be differences between health care settings with some preliminary evidence showing a trend for patients followed in university hospital settings to have higher non-persistence than community hospitals[30]. This may be directly related to the predominant type of treating physicians in these settings (e.g. higher proportion of specialty care physicians associated with large academic institutions) and the associated patient contact patterns for appropriate disease management. For example, cardiologists may not keep patients treated with NOACs under frequent and regular surveillance unless there are precipitating disease factors necessitating it, such as renal dysfunction. Thus, patients may not be seen by their cardiologist for longer intervals or until an outcome

event or other complication arises[63]. Supporting this hypothesis, is the higher persistence reported to a NOAC in AF patients followed by general practitioners (GP) compared to specialists[41] which has similarly been reported for other patient groups such as those taking bone sparing drugs[64]. There may be opportunities to improve persistence through encouragement of certain patient management practices such as cardiologist referral to GPs for follow-up after initial diagnosis as one example.

Regional and Country Differences: Important regional differences in guideline adherent prescribing of anticoagulants have been reported with significantly lower rates of treatment initiation in regions such as Asia[65]. It has similarly been reported that relative to patients in Europe, Asian patients (and those in North America) had higher discontinuation, and patients from Latin America had lower discontinuation[30]. The explanations for these regional differences and in particular the lower persistence seen in Asia are complex and not fully understood, although they could relate to higher perceived risk for catastrophic outcomes such as intracerebral hemorrhage[66], perceived lower stroke risk[67,68], potential for interactions with more frequently used herbal remedies[69] or simply issues related to access to care.

Regional differences have also been observed in OAC uptake and persistence within a country such as in Denmark[18]. Although the reasons for the observed differences were not clear, the authors suggested that variability in health care delivery and in 'attitude and attention' in AF patient management could have been contributing factors.

Cost of Medications and Coverage: While the availability of NOACs has introduced efficacious agents with greater convenience, they have come with an increased cost to patients and the health care system. Cost of medications may be an access barrier, and this has been reported as a reason for not persisting with anticoagulation (albeit in a minority of cases)[30,70]. Coverage through private insurance compared with federal or statutory insurance has also been associated with higher non-persistence rates over time suggesting that those drugs without public reimbursement may be more prone to discontinuation[41].

Assessing Persistence Studies and Considerations for Future Research

In reviewing the variability of approaches in measuring persistence to OACs in AF patients, the utility of a framework to guide interpretation of current research as well as planning for future research becomes clear. The assessment domains proposed (Table 1), relate to strengths and limitations for patient selection (i.e. those with confirmed AF at risk for stroke, or those newly initiating treatment), as well as definitions of persistence measurements. While studies blinded to the objectives of persistence measurement (with health care providers and patients not explicitly informed) may have less motivated or inadvertently modified drug-taking or drug-monitoring behaviours, revealing study objectives in an open design may be more ethically sound and produce more precisely documented information.

In addition, reliable measurements with low degree of missing data and high precision (e.g. medication start and stop dates as opposed to surrogate measures such as

prescription refill dates), are important considerations. While objective and reliable measures (e.g. retrospective chart abstraction) have value, these can be prone to limitations such as missing data or inaccuracies. Ecologically valid studies conducted in clinical practice settings rather than more contrived environments of RCTs have obvious strengths but also limitations if representativeness of settings or patients is not adequately demonstrated.

Measurements of persistence should ideally classify patients that switch to other equally efficacious agents as persistent (for example patients who switch to generic versions of NOACs) and should not include the competing outcome of mortality with non-persistence[38]. Outcomes should include follow-up beyond 6 months as the probability of non-persistence is observed to be non-linear over time[41], and patient important outcomes following discontinuation should be measured. Studies designed with these considerations may have higher utility and lend more confidence to draw conclusions.

Optional assessment domains related to analyses are further proposed. For example, comparative analyses of different drugs should adjust for important patient co-morbidities or other potential confounders such as differences in follow-up time, settings or differences in drug formulation or dosing.

Scoring of Classification Scheme: In total, this proposed classification scheme includes 16 mandatory assessment domains and 3 optional ones for a total of 19 potential domains. For all applicable items, a simplified scoring schema would allocate one point for affirmative responses, and no points if not affirmative, unknown or not reported. The final

percentage would be calculated by dividing the total number of affirmed responses over the total denominator of applicable items (to produce estimates ranging from 0-100%). Studies could thus be compared to assess in a comprehensive and consistent way, their methodological strengths and clinical utility. Testing of this schema is warranted in further research.

Conclusions:

Estimates of oral anticoagulation persistence may vary due to study methodology or design, patient, treatment or other factors linked to higher or lower persistence estimates. We identified multiple factors and summarized them in a pragmatic diagram.

We also identified important methodological heterogeneity and to our knowledge, this is the first framework to interpret OAC persistence research. The importance of selecting appropriate patients, outcomes with high reliability, objectivity and validity is emphasized. Definitions of persistence and important aspects of the definition that impact outcomes are included in this framework as well as considerations of clinical utility. This framework can be used to comparatively assess persistence research but also has applications for designing future research in OAC persistence.

Examining persistence in AF patients indicated for long term anticoagulation has important implications for improving patient outcomes and allocating resources efficiently. Researchers and clinicians still have work to provide sound, reliable and comprehensive measures of OAC persistence that can form the basis for developing cost-effective interventions to improve persistence.

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Figures

Figure 1: Factors Associated with Oral Anticoagulation Persistence

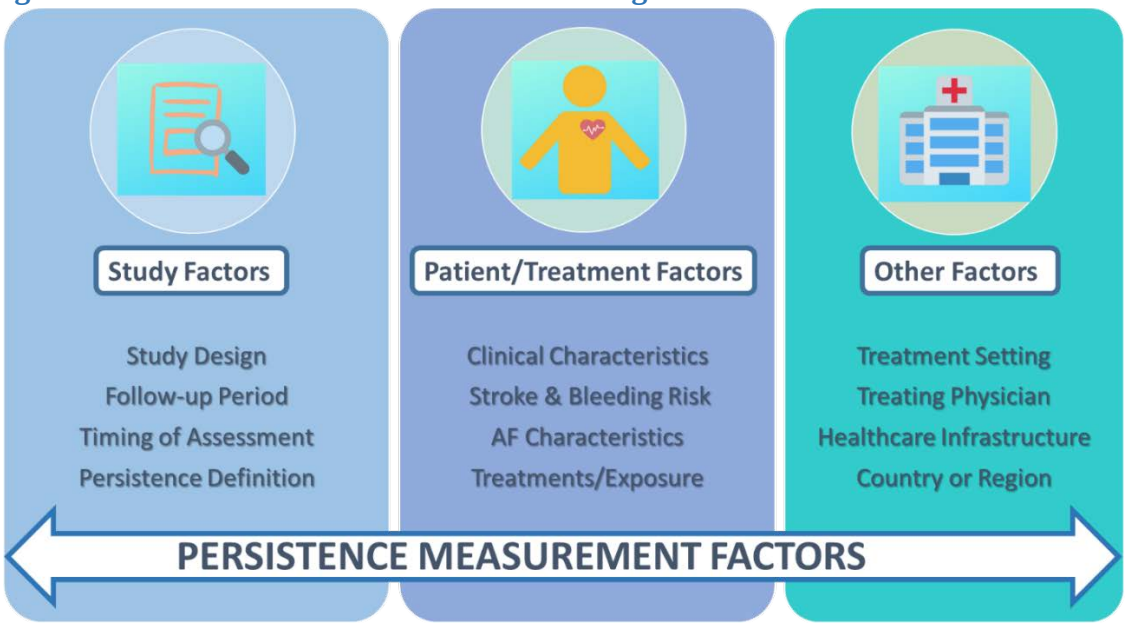
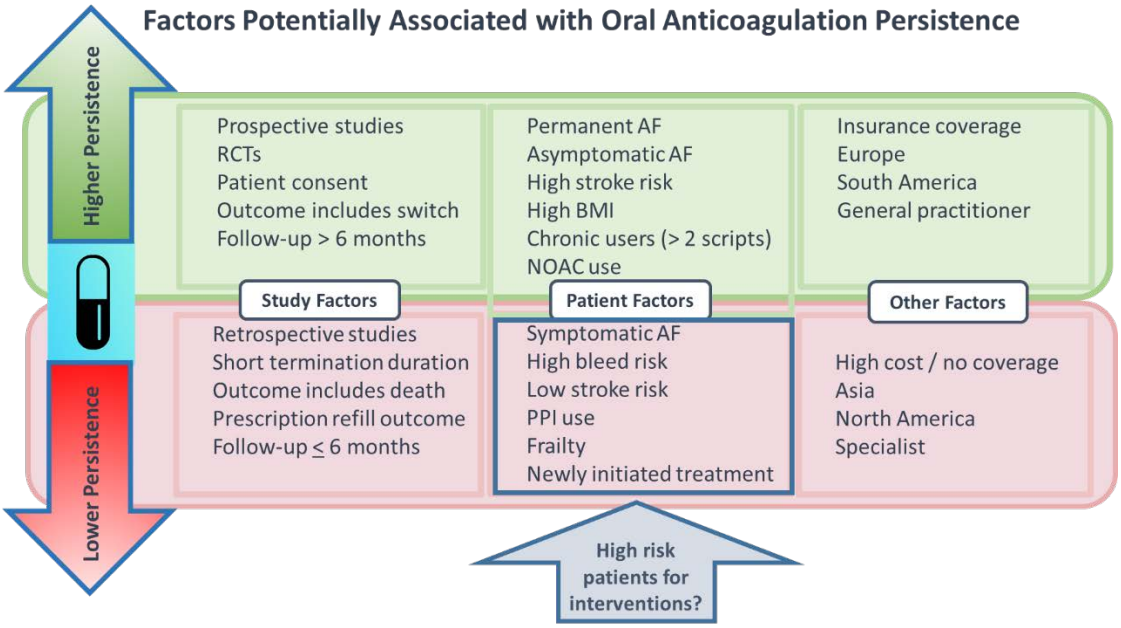


Figure 2: Factors Associated with Higher or Lower Oral Anticoagulation Persistence

Take Home Figure

Study, treatment and patient factors are associated with persistence estimates and patient groups with lower persistence should be considered for interventions.



RCT: randomized clinical trial, AF: atrial fibrillation, BMI: body mass index, NOAC: Non-Vitamin K Oral Anticoagulant, PPI: proton pump inhibitor

Table 1: Classification of Oral Anticoagulant Persistence Studies (Methodology, Patient Selection and Utility)

Assessment Domains						
Mandatory Domains						**Optional Domain**
Patient Selection	**Reliability**	**Validity**	**Definition of Persistence**	**Clinical Utility to Develop Interventions**	**Outcome and Follow-up**	**Analyses**
Includes patients with confirmed atrial fibrillation at risk for stroke with indication for oral anticoagulants	Complete: Low 'missingness' (estimate <10% missing data)	Ecological validity (clinical practice or 'real world' setting)	Includes switchers as persistent	Includes predictors of discontinuation	Includes follow-up > 6 months	Comparative analyses control for important patient co-morbidities
Studies incident population, newly diagnosed and starting treatment	Precise: High precision for medication start and stop (exact dates not ranges)	Concurrent measure of medication intake and not only prescription (eg. patient confirmation of intake)	Discusses or controls for impact of temporary discontinuations	Includes reasons for discontinuation	Patient important outcomes after discontinuation measured (eg. stroke, bleeding, mortality)	Adjusts for time dependent factors (eg. follow-up time) if study has follow-up
Unobtrusive (patient not aware and no consent required)	Objective: Consistent/objective measures (eg. prescriptions, chart reviews)		Excludes competing outcome of death	Considers health care delivery or infrastructure such as treating physician and reimbursement or medication cost		Considers and analyses differences in formulation or dosing

The number of applicable areas is summed to comprise the denominator (mandatory, n=16 + optional, n=3).
For all applicable items, allocate 1 if affirmative, 0 if not affirmative or unknown/not reported.
The percentage is the total affirmed responses over the total denominator of applicable items (range 0-100%).

CHAPTER 6: Summary and Future Direction

This chapter summarizes learnings, and highlights strengths, and limitations of the methods in the included studies with implications for design of future studies. In addition, clinical practice, research and policy implications of the findings are discussed.

6.1 Anticoagulation Persistence in the Non-Vitamin K Antagonist Era

With the availability of NOACs, is there reason to be optimistic that the problem of anticoagulation persistence has improved? Chapters 2 and 3 of this thesis explored this question in a large, prospective, global registry that provided some evidence that long term persistence with a NOAC (dabigatran) may be better than previously reported for warfarin where 1 year persistence estimates range widely from 39%[1] to as high as 68%[2] to 74%[3]. The latter estimates were based on prescription refill gaps of $\geq$60 and 180 days respectively.

The first investigation in over 2900 newly diagnosed AF patients estimated 1-year persistence at 76.6%[4] and the second, larger evaluation of over 4900 patients (including the original 2900 patients) showed a consistent 1-year persistence estimate of 77.5%[5]. The persistence outcomes for these analyses were based on reported stop dates of medication obtained by treating physicians.

Long-term follow-up is of value with chronic medications and this registry provides a more comprehensive picture of long-term persistence with a NOAC. Over 2 years of follow-up, these investigations showed that approximately 70% of patients will remain on the NOAC (dabigatran) initiated for treatment[4,5] and an even higher proportion will

continue to derive clinical benefit, as they will switch to another OAC[4]. Consistent with the expected benefit of anticoagulation for stroke prophylaxis, patients who discontinue without switching to another OAC have higher rates of ischemic stroke and mortality than those who switch[5].

Another important finding was the identification of the high risk period for NOAC discontinuation in the first 6 months following therapy initiation where probability for persistence was estimated at 83.7% [95%CI: 82.7 to 84.8]), with lower persistence than in subsequent periods[5]. The observation that patients persistent with treatment at 1 year had >90% probability of continuing treatment to 2 years strongly compels clinicians as well as researchers to focus on the early period following medication initiation to improve persistence, as treatment appears to remain relatively stable after 1 year.

The majority of reasons indicated for discontinuation were not primarily related to adverse events (AE). AEs accounted for approximately a third of discontinuations[4,5]. Cost of treatment, start of bridging therapy or other reasons such as excessive alcohol use or dementia, collectively considered, comprised a small minority of the reasons (<6%) for discontinuation. More than half of the reasons (58%) were attributed to 'other reasons not further specified', which could potentially include reasons related to patient or physician preferences, based on factors such as perceived risk of bleeding or perceived low stroke risk[5].

Although precise reasons for discontinuation were not fully elucidated, the finding that AEs do not explain the majority of discontinuations was in and of itself important. If discontinuations were attributed primarily to AEs, the value of certain interventions such

as patient education to improve persistence would be obviated. However, as this was not the case, supplemental education applied at the right time may be a potential avenue to improve patient persistence and outcomes.

Furthermore, preferentially targeting the highest risk patients for discontinuation, who may be suitable for delivery of interventions, should be considered. For patients newly initiating dabigatran, our studies have shown that this would include patients with symptomatic AF, prior bleeding, use of proton pump inhibitors and patients without prior stroke or transient ischemic attack[4,5].

When patients at risk for discontinuation are identified, whether interventions are likely to ameliorate overall persistence should first be assessed, followed by careful consideration of which interventions would be most effective. The distinction of modifiable (e.g. patient beliefs or knowledge) versus unmodifiable (e.g. patient age, co-morbidities, co-medications) determinants of non-persistence is an important consideration[6]. The recommendation has been made that interventions should be designed to target modifiable factors but be tailored to unmodifiable factors[6]. Intentional mapping of general adherence interventions (including persistence) to address specific patient determinants of non-adherence is put forth as a way to improve effectiveness of interventions[6,7] and lack of congruence has been suggested as one reason why previous studies may have failed to show improvements with interventions[8,9].

In chapter 4, the systematic review of randomized clinical trials of supplemental patient education in patients taking OAC did not reveal any clear benefit to outcomes such as thromboembolic events or mortality. Some possible explanations may include suboptimal

timing of delivery, intensity, modality, and general effectiveness of interventions, as well as patient selection, insufficient power due to follow-up time, or other methodological considerations in the way such studies were designed. There was heterogeneity in the settings, follow-up period, interventions and usual care delivery used as controls, which may have reduced the potential to detect an effect.

The last paper in the thesis discusses general methodological considerations for persistence research and provides a framework for assessing current research to help put some of the disparate estimates of persistence in context. These methodological considerations may also help guide research in the area of interventions to improve persistence.

6.2 Strengths of Studies Conducted

6.2.1 Studies of Dabigatran Persistence in Atrial Fibrillation

Prospective studies provide the opportunity to explore reasons for discontinuation, rarely reported from retrospective evaluations. The studies conducted in chapters 2 and 3 directly surveyed discontinuation reasons and hence increase our understanding of the reasons why patients may discontinue a NOAC. Assessing if patients started another OAC following discontinuation was also a strength of the current research. This has greater clinical utility as appropriate management may necessitate switching to alternative OAC medications and this does not necessarily imply negative outcomes.

In addition, the requirement for consecutive enrollment and participation of large numbers of patients from diverse care settings and geographical regions provide greater confidence in the representativeness of patients included. Persistence estimates from

patients enrolled from clinical practice settings provide greater clinical relevance compared to more controlled settings of clinical trials where patients are randomly assigned to interventions, and followed according to standard visit intervals.

Measures to improve data integrity and quality were implemented through routine database checks and periodic site monitoring to verify accuracy of extracted data and to ensure complete reporting of outcomes. This is advantageous when compared to retrospective studies, which are prone to missing data and for which additional quality initiatives are typically not undertaken.

Selection of start and stop dates as a persistence outcome measure has greater precision than prescription refill data and defining discontinuation as failure to restart medication within 30 days was purposefully selected to exclude temporary discontinuations which can occur in almost a quarter of patients[10]. The appropriateness of this outcome definition is further supported by an analysis of a large retrospective cohort study of commercial insurance claims data in over 60,000 patients. This analysis demonstrated that risk of thromboembolic or bleeding events was not higher in patients who discontinued treatment for 1 week to 1 month relative to those who discontinued for <1 week, even for those at highest risk for stroke[11].

6.2.2 Systematic Review of Supplemental Education in Patients on Anticoagulation

This was an important management question, prioritized by an expert guideline panel who provided input for the systematic review to optimize clinical relevance, including expert consensus on the most important outcomes for reporting. The methods for the

systematic review reported in chapter 4 followed the Cochrane methodology[12] with reporting according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[13]. Efforts to minimize bias were undertaken in the review process through use of a comprehensive search including all languages and multiple databases, and duplicate, independent screening of studies by two reviewers. Authors were contacted to obtain additional data including unpublished results where only abstracts were available. Data extraction and analysis conducted by one researcher were checked by a second researcher.

6.3 Limitations of Studies Conducted

6.3.1 Studies of Dabigatran Persistence in Atrial Fibrillation

As data reported in chapters 2 and 3 were collected as part of an observational registry, the behavior of both treating physicians and patients could be modified by virtue of awareness that data would be reviewed and monitored ("Hawthorne effect"[14]). Despite the direction to approach consecutive, eligible patients, patients were required to provide consent and these may generally reflect more motivated patients who may be more likely to persist with treatment than a general AF population.

One of the main limitations is that specific information on the "other" reasons for discontinuation (comprising more than half of the reasons) remained unexplored and entreats further exploration of these reasons. Therefore, while the reasons reported for discontinuation in these studies are of some benefit, detailed and descriptive information to formulate stronger hypothesis to deliver interventions was clearly missing. The reasons for non-persistence are likely complex, multifactorial and require more comprehensive

assessment than was undertaken in this registry. For example, use of an open text field to obtain detailed information on 'other reasons' for discontinuation and allowing investigators to choose more than one option for discontinuation would have provided richer insight.

The determinants of non-persistence identified primarily non-modifiable factors such as patient comorbidities, AF disease characteristics and co-medications. However, the 'other reasons not specified' may have provided identification of potentially modifiable determinants such as patient beliefs, knowledge or intentions[6]. For example, improving patient knowledge on the consequences of discontinuing anticoagulation may be effective as it has been demonstrated that over half of patients report having low or no stroke knowledge[15]. While it is reasonable to target interventions to groups of patients who are known to have higher risk for discontinuation, further understanding of the underlying reasons why they discontinue could be pivotal for developing effective interventions[6]. Furthermore, although start/stop dates are more precise surrogate markers for drug intake compared to prescription refill dates, they are still not a guarantee that medication is actually taken. As stop dates for medication were obtained by patient report, recall bias or intentional, inaccurate reporting of doses started or stopped may also have negatively influenced precision.

Incidence rates for outcomes after dabigatran discontinuation had relatively high levels of random error as evidenced by the wide confidence intervals, and there remains the potential for unmeasured confounding. Patients who discontinued could have been more

prone to experience an outcome event that was associated with, but not the causal result of discontinuing their OAC.

As the second phase of this registry was designed to assess safety and effectiveness of the first NOAC available on the market, data are only available for patients initiating dabigatran. Having prospectively obtained persistence information on the later available NOACs (ideally in direct comparison with VKA) will inform not only whether certain NOACs have evidence of better persistence, but if the reasons for discontinuation or switching vary by NOAC. Retrospective evaluations of electronic health records suggest there are differences in persistence between NOACs but prospective evaluations will better inform clinicians, to select the best OAC for patients based on clinical attributes and discontinuation patterns[16].

6.3.2 Systematic Review of Supplemental Education in Patients on Anticoagulation

There were limitations in assessing the impact of supplemental education on outcomes and these were mainly related to serious risk of bias and imprecision due to the small number of observed events. While larger studies with longer follow-up may partially address this issue, another significant weakness which may have resulted in failure to show effect may be due to the heterogeneity of content, delivery, timing and intensity of educational interventions.

In addition, the heterogeneity of ‘usual’ care with respect to patient education was an important limitation and these challenges and methodological biases should be addressed in future primary studies to facilitate robust synthesis of results. Researchers in this area

should be strongly encouraged to explicitly select and describe the content and delivery of their interventions and to employ appropriate and sensitive tools to evaluate if interventions are successful based on models of applied behaviour change[17]. Research suggests that interventions with the best chance for success are developed within a theoretical framework to describe the behavioural change techniques designed to result in specific changes[18].

Finally, all included studies targeted patients on VKA and further evidence is needed specifically for NOACs, to determine if (and which) interventions may be beneficial.

6.4 Ethical Considerations

The data collected for chapters 2 and 3 were obtained from an observational study. Although there were no interventions associated with the study, and patients were prescribed medications according to usual care, an informed consent detailing the purpose of the registry, and data to be collected at each visit was provided and signed by each patient. It was clearly outlined in the protocol that patients should be prescribed (or not prescribed) oral anticoagulants based on treating physician discretion. Furthermore, no medical procedures outside of their usual care were required by the protocol. There were no medical risks, nor any direct benefits to be gained from participating in the study. Patients were not provided medication free of charge (reducing inducements to participate), and all personal data were anonymized to protect patient privacy. No personal identifying information such as names, or contact information were entered into the database. Patients could withdraw from the study at any time.

A copy of the patient consent is included in the appendix of this chapter (Appendix 1). In chapters 2 and 3, there were no ethical concerns identified specifically pertaining to the hypothesis which aimed to describe and understand persistence to oral anticoagulation.

In chapter 4, there were no ethical concerns identified as there was no collection of primary data and the review was comprised of published data only. Similarly, in chapter 5, studies were summarized and methodology discussed but there were no direct ethical considerations for the data collected or the questions explored.

6.5 Implications for Policy Makers

In burdened health systems under significant cost containment pressures, resources to increase medication persistence and ultimately improve outcomes must be carefully considered and judiciously employed. This research suggests that health care resources, if allocated for such interventions, should be preferentially targeted in patients at high risk for discontinuation, and in the early period after treatment initiation. Well validated, cost effective and targeted interventions grounded in a clear theoretical framework may produce the most beneficial impact to improve patient OAC persistence.

6.6 Future Directions

Future research in the area of anticoagulation persistence is needed to increase understanding, with the ultimate aim to improve patient outcomes. A methodologically robust study (considering areas proposed in the framework presented in chapter 5), prospectively designed to directly compare the available OACs with respect to persistence outcomes would provide more definitive evidence of whether persistence varies by OAC treatment.

While a systematic review is currently in progress to evaluate real world OAC adherence more generally[19], the variability in methods may preclude synthesis of results. Conducting this study will increase confidence in the comparative persistence rates between available anticoagulants using the same outcome measure, in the same settings.

Furthermore, a prospective observational study examining patients with similar clinical profiles, prescribed different anticoagulants can provide further insight into reasons for discontinuation, which will likely not be available from the results of the systematic review in progress.

We require more comprehensive and detailed understanding of the reasons why patients or their physicians decide to discontinue anticoagulation. While the studies conducted in this thesis helped to identify groups who are at higher risk for discontinuation and thus may need more attention, knowing with greater detail the underlying reasons that are amenable to intervention will be key to developing effective interventions.

The objective should be to identify key determinants of non-persistence and to develop interventions to target the modifiable factors and tailor them to the high-risk groups[6]. Targeting high-risk groups may be key, as it has been shown that including non-adherent patients in adherence intervention studies is the single best predictor of effectiveness of such interventions[7].

Furthermore, the factors associated with discontinuation require further validation to examine potential for confounding by other factors and increase overall confidence of the association. For example by examining if the probability of persistence increases as a

function of increasing stroke risk, or by examining gradients of symptom burden to understand the association with persistence.

Further Considerations for Future Studies: Selecting newly diagnosed AF patients would promote balanced exposure between treatment groups and reduce bias for differentially selecting patients in one group who may be more likely to be persistent by virtue of prolonged exposure. The study should aim to enroll patients from clinical practice settings, prospectively recording baseline patient characteristics and controlling for any differences between groups in the analyses conducted.

Furthermore, it would be informative to understand whether the patient or physician decides to discontinue so these should be assessed in the detailed reasons for discontinuation or switch to an alternative OAC.

6.7 Conclusion

Long-term anticoagulation is a critical requirement to ensure best outcomes in AF patients with established stroke risk. The issue of non-persistence is a significant concern as many patients fail to persist with anticoagulation early in the treatment course. Although there is some evidence of improved persistence with the more contemporary NOACs over VKA, further research is needed to understand variability of persistence rates across OACs and comprehensive reasons for discontinuation of OAC.

With improved understanding of the reasons for discontinuation, better targeted interventions can be developed and tailored to the highest risk patients, or those who are non-persistent. Supplementary patient education may be part of such interventions, but it

does not appear to be effective on its own. For maximal impact, these interventions should be delivered in the early period after treatment initiation.

Our knowledge of OAC persistence in atrial fibrillation has improved but future studies with careful consideration of study methods and design will help to address the currently remaining gaps in our knowledge.

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APPENDICES

Appendix 1: PATIENT INFORMATION AND INFORMED CONSENT FORM – PHASE II

PATIENT INFORMATION

Registry Title:	**The GLORIA-AF Registry Program** (**G**lobal Registry Program on **L**ong-Term **O**ral Anti-thrombotic T**R**eatment **I**n P**A**tients with **A**trial **F**ibrillation (Phase II/III)
Registry #:	1160.129
Sponsor:	Boehringer Ingelheim International GmbH
Centre No.:	_____
Patient No.:	_____
Registry Doctor:	_____
Registry Coordinator:	_____
Telephone:	_____/_____

This Patient is participating in Phase II

Dear Patient,

Your attending physician has asked you to participate in the above mentioned observational study (in the following: "GLORIA-AF") because you have been diagnosed with atrial fibrillation.

The purpose of this Patient Information is to give you information about GLORIA-AF. If you decide to participate in GLORIA-AF, you will be asked to sign the attached Informed Consent Form. This information describes the purpose, procedures, risks and benefits of GLORIA-AF to help you decide if you want to participate.

Take your time, read this form carefully, and ask the registry doctor or staff any questions you may have. The registry staff will describe GLORIA-AF to you and take you through this Patient Information/Informed Consent Form. You can take the Patient Information/Informed Consent Form home and discuss it with family and friends or your doctor.

You should take part in GLORIA-AF only if you want to do so, participation is voluntary. You may refuse to take part or withdraw from GLORIA-AF at any time, without giving a reason and without any penalty or loss of benefits to which you are otherwise entitled and without any effect on your future medical care. Should any changes in the design or conduct of GLORIA-AF be made that may affect your decision to continue to participate, you will be informed and your consent will be sought.

If there is anything you do not understand, please ask your attending physician for further explanation.

Purpose of GLORIA-AF

The purpose of GLORIA-AF is to investigate the patient characteristics which influence the choice of antithrombotic (blood thinner) treatment for the prevention of stroke in patients who have non-valvular atrial fibrillation (AF) (in other words, AF which is not due to a heart valve problem) and are at risk for stroke. The study will also collect data on certain outcome events such as strokes, heart attacks, and bleeding episodes, in a "real-world" setting. "Real-world" setting means that the data come from patients who are being treated for AF in a normal medical practice situation, rather than in a controlled clinical trial. Additional goals of this observational study are to better understand subgroups of patients with different risk profiles affecting the safety and effectiveness of an antithrombotic drug called dabigatran etexilate; to investigate how well patients take their antithrombotic medication according to the dosing directions and whether they stay on their medication; and to collect real-world data on treatment related to AF, and potential side effects of antithrombotic treatments. It is hoped that the information to be collected will give valuable information on the current treatment practice to prevent stroke in patients with atrial fibrillation around the world.

Phase II and III: The program starts with Phase II and then when certain criteria are met, the investigator/clinic will switch to Phase III, and begin enrolling patients into Phase III. It is estimated that GLORIA-AF will collect information on up to 16,000 patients (age 18 or older) in Phase II, and up to 32,000 patients (also age 18 or older) in Phase III, from as many as 2200 physicians all over the world. The total duration of the combined Phase II and III programs is estimated to be approximately eight years. A patient can only be enrolled into one of the two phases (not both), and only into the currently ongoing phase. Phase II and III only differ in the data that are collected in the follow up visits.

If you chose to participate in GLORIA-AF you would be part of Phase II of the study program. Your participation will last for either one visit or for approximately two years, depending upon what treatment your doctor has prescribed for your AF. If you are prescribed dabigatran etexilate, your participation will last approximately two years. If you are not prescribed dabigatran etexilate, your participation will last for only one visit (the Baseline Visit), and will end at the conclusion of the Baseline Visit. Even if your treatment regimen would change over time or the number of patients enrolled would change, your participation will not be impacted.

Baseline and Follow-up Visits: If you agree to participate in GLORIA-AF the different parameters mentioned below will be collected at your Baseline Visit. The Baseline Visit is defined as the time point of the physical visit with your physician when you are enrolled into GLORIA-AF. If you have been prescribed dabigatran etexilate for your AF, you will also be asked to participate in four (4) additional Follow-up Visits, during which additional information will be asked. These Follow-up Visits will occur at approximately three (3) months, six (6) months, one (1) year, and two (2) years after the Baseline Visit.

Visit Windows for Follow-up Visits: Each of the Follow-up Visits has a "visit window" of plus or minus one (1) month (for the 3-month and 6-month visits), and plus or minus two (2) months (for

the one-year and two-year visits). If, for any of the Follow-up Visits, your normal medical care does not result in a visit within the visit window, you will be asked and expected to come to the study center to complete the visit within the visit window.

No influence to Usual Care: Participating in GLORIA-AF will not influence the usual care that you receive from your physician. In other words, the care you receive while participating in GLORIA-AF will be exactly the same as the care you would receive if you were not participating in this research program. No medical procedures outside of your usual medical care will be conducted. GLORIA-AF only collects data on the medical treatment your doctor is already conducting. To consent to GLORIA-AF means that you are accepting your data to be entered into the GLORIA-AF Registry Program Database.

Data to be collected

Should you agree to participate in GLORIA-AF, information about your background, your past and current health, previous and current illnesses, your disease (AF) and the treatment will be collected by the registry doctor or members of the registry staff.

Data collected during the GLORIA-AF Baseline Visit include:

- demographic information (including date of birth, gender, height, weight, and race/ethnicity)
- vital signs (blood pressure and heart rate from most recent information available)
- serum creatinine, which is a measure of kidney function (if this test was done during your usual care)
- atrial fibrillation disease information (for example, date of diagnosis, atrial fibrillation confirmatory tests, type of AF, previous interventions for atrial fibrillation)
- treatments related to atrial fibrillation
- personal medical history
- selected medications taken on a continuous basis (within the past month), including prescription medications, over the counter drugs, dietary supplements, and herbal preparations in case of discontinuation from GLORIA-AF: reason for discontinuation

Data collected during the GLORIA-AF Follow-Up Visits include:

- concomitant diseases (current and any change)
- antithrombotic treatment (current, and change, start and stop dates), including information on missed doses, and if you have remained on the medication; reasons for interruptions or discontinuation of therapy
- other drugs you may be taking and any changes
- serum creatinine, which is a measure of kidney function (if this test was done during your usual care)
- treatments related to atrial fibrillation
- outcome events such as stroke, heart attack, or bleeding episodes
- Adverse events, including all serious adverse events, and certain non-serious adverse events
- Vital status (only at last follow-up visit). This means we need to know if you are alive.

Your registry doctor or members of the registry staff may need to contact hospitals, clinics, labs, and other physicians who may have medical records or information which is needed as part of this observational study. In addition, if you are unable to come to the clinic for visits due to health issues or any other reason, you grant permission for the investigator or study staff to contact you, a family member or designated contact-person by phone or other means (e.g. e-mail) for information. This may include questions regarding missing or apparently incorrect information, or to obtain additional information about events such as hospitalizations, injuries, illnesses, outcome events, or other adverse events. Your vital status (that is, if you are alive) may also be determined from public records or from other sources such as employers, friends, and acquaintances.

All data collected by your physician will be reviewed and evaluated purely for the purposes of GLORIA-AF. The results may be used for scientific reasons including research, publications or presentations at congresses.

Eligibility

Patients who have recently (within the past three (3) months) been diagnosed with atrial fibrillation, have taken warfarin for less than sixty (60) days, and who meet other entrance criteria specified in the protocol are eligible to participate in GLORIA-AF.

Risks and Benefits

There are no expected medical risks related to your participation in GLORIA-AF. The most important non-medical risk involved in an information-gathering observational study is the unintended disclosure of your medical data. GLORIA-AF will conform to all applicable privacy and confidentiality laws to minimize this risk.

There are no direct medical benefits to you from participation in GLORIA-AF. The collection of data could potentially benefit patients and physicians as the data collected will improve the knowledge on atrial fibrillation and its treatment.

Organization and Funding of GLORIA-AF

The Sponsor, Boehringer Ingelheim, a research-based pharmaceutical company, is organising and funding GLORIA-AF. Outcome Sciences, Inc., (“Outcome”), a contract research organization (CRO), will help organize and manage the study on behalf of Boehringer Ingelheim. Other CROs may also be involved in helping to manage GLORIA-AF within the various participating countries.

Compensation

There will be no financial compensation to you for your participation in GLORIA-AF. The Sponsor will compensate the hospital, institution, or investigator for the work carried out in connection with GLORIA-AF.

Costs

As this is an observational study and no additional medical procedures are required over and above those which would be a part of your normal medical care, coverage for the medical services will not be managed differently during participation in this program than if you were not part of

GLORIA-AF. However, if you are a patient who will be attending Follow-up Visits, there could be some additional costs to you associated with a Follow-up Visit (such as transportation expenses) if your normal medical care does not result in a visit within the designated visit window (see above under "Purpose of GLORIA-AF"), and you are asked to come in to the clinic for a visit within the visit window.

Confidentiality and Information on Data Protection (Adapt this section according to your local requirements)

The data for GLORIA-AF will be collected and recorded by the registry doctor or members of the registry staff on paper and/or on electronic storage media and then entered into a secure web-based system. All data will be encrypted upon transfer from your treatment site via the Internet and will be stored in a secure and protected electronic database of Outcome, the **GLORIA-AF Registry Program Database,** located in the United States. The data will also be transferred to a secure and protected data storage system located at the Sponsor company (Boehringer Ingelheim). For scientific evaluation purposes, the data will be processed electronically and combined with data from other participants in GLORIA-AF.

As described above, in connection with GLORIA-AF, personal data, in particular data about your health, will be recorded, saved and evaluated. These personal data will be pseudonymized, i.e. coded so that a patient identification number is assigned to your data. Your name, initials, address, or phone number are never entered into the database. Please note that you are never personally identified in any analysis, report, or publication produced by the Sponsor, Outcome, or any third party working with the Sponsor. Your registry doctor keeps a record of your patient identification number so that you can always be contacted by him or her if there was a medical need, and to allow for audits or monitoring of your medical records as sometimes required as part of GLORIA-AF.

In order to ensure that GLORIA-AF is being conducted properly and that the data are being transferred correctly, the data collected and your patient's notes may be inspected by authorized representatives of the Sponsor who are obliged to observe confidentiality. To this end you release your doctor from his/her obligation to observe doctor-patient confidentiality. Health and regulatory authorities, registry personnel representing the Sponsor, Outcome, other CROs working for the sponsor, or ethics committees may be granted direct access to your medical records to verify the registry procedures or the accuracy of the data. The information will be treated confidentially and reviewed with the permission of your treating doctor.

Registry records may be provided to health and regulatory authorities worldwide and they may be sent abroad for processing by either the Sponsor's or Outcome's personnel or third parties. Recipients of these records may be located in a country, including the Unites States, which does not have a level of information protection equal to the country in which you are treated.
If you choose to stop your participation in GLORIA-AF, your registry doctor may ask you to perform a last Follow-up Visit. If you agree to such visit the data collected during the last Follow-up Visit will also be entered into the GLORIA-AF Registry Program Database.
If you withdraw your consent to participate in the study, your participation in the study will end at that point, (unless you have agreed to a last follow-up visit, in which case your participation in the study will end at the conclusion of the follow-up visit). No new information about you will be

collected after the conclusion of your participation in the study, with the possible exception of vital status, as described below. Because a main purpose of this study is to obtain safety-related data on patients with AF, we will retain your data already collected up to the conclusion of your participation in the study, and this data will be used and analyzed for the study. If you withdraw your consent to participate in the study, you will be asked if you will allow the investigator to enquire about your vital status (whether you are alive) when the study ends at the study center. You may agree to this by signing the special section at the end of this form at the time of your consent withdrawal.

Review of GLORIA-AF (Adapt according to local requirements)

GLORIA-AF has been reviewed and given a favourable opinion by the Ethics Committee.

Further information and Contact details (Adapt according to local requirements)

If you have any questions or concerns regarding your participation in GLORIA-AF and your rights as a participant, or if at any time you feel you have experienced a GLORIA-AF-related problem, please contact the Registry Doctor or Registry Coordinator named on the first page of this Patient Information.

INFORMED CONSENT FORM – PHASE II

Registry Title: **GLORIA- AF Registry Program**
(Global Registry Program on **L**ong-Term **O**ral Anti-thrombotic T**R**eatment **I**n P**A**tients with **A**trial **F**ibrillation; Phase II/III)
(in the following: "GLORIA-AF")

Registry #: 1160.129

Sponsor: Boehringer Ingelheim International GmbH

Centre No.: _____

Patient No.: _____

Registry Doctor: _____

Registry Coordinator: _____

Telephone: **_____/_____**

I have been briefed in detail and comprehensibly by the doctor,

Dr _____, or a designated research staff person,

in a personal conversation about the purpose of GLORIA-AF and the nature and significance of the data to be collected. My questions about GLORIA-AF and my participation in it have been answered clearly and in detail. I was given sufficient time to consider the information before I made my decision to participate. I have read and understood the Patient Information and this Informed Consent Form. By signing this consent form I will not give up any of my legal rights.

I understand that participation is voluntarily and that my care will not be affected should I decide not to participate in this observational study. I further understand that I may withdraw my consent at any time, without stating my reasons and without putting myself at any disadvantage.

I agree to take part in GLORIA-AF.

☐ yes ☐ no

Data Protection Declaration

I herewith agree that, in the course of GLORIA-AF, my personal data, in particular, details about my health, will be collected, recorded on paper and on electronic storage media and processed as described in the above Patient Information and might be passed on to competent health or regulatory authorities.

☐ yes ☐ no

I also give my consent that authorized persons from the Sponsor, central CRO (Outcome), CRO (Insert CROs involved in GLORIA–AF in your country), competent health or regulatory authorities and ethics committees may inspect these data (for example to ensure quality of GLORIA-AF).

☐ yes ☐ no

I herewith agree that the investigator or study staff may contact a family member or designated contact-person by phone or other means (e.g. e-mail) for information (e.g missing or apparently incorrect information, additional information on hospitalizations, injuries, illnesses, outcome events) if I am not able to come to the clinic for visits due to health issues, or any other reason.

☐ yes ☐ no

Only after I have signed the consent will the investigator enter any information of my medical status into GLORIA-AF.

I have received a signed and dated copy of this Informed Consent Form.

_____

Printed Name of Participant

_____ _____

Signature of Participant Place, Date

I attest that the participant named above had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to participate in the observational study GLORIA-AF. A copy of the Patient Information and the Informed Consent Form have been given to the patient.

_____

Printed Name of Person Explaining Consent

_____ _____

Stamp and/or Signature of Person Explaining Consent Place, Date

I attest that I or my representative discussed GLORIA-AF with the participant named above.

_____ _____

Stamp and/or Signature of Person Explaining Consent Place, Date

TO BE FILLED OUT ONLY IF THE PATIENT WITHDRAWS CONSENT TO PARTICIPATE IN GLORIA-AF

VITAL STATUS WAIVER

In case of a withdrawal in my consent in the participation of GLORIA-AF,

I give my consent for vital status information to be obtained by contacting me, a family member, or designated contact-person by phone or other means (e.g. e-mail). My vital status may also be determined from public records or from other sources such as employers, friends, and acquaintances.

☐ yes ☐ no

_____

Printed Name of Participant

_____ _____

Signature of Participant Place, Date