Université de Montréal

Les prédicteurs de saignements majeurs parmi des utilisateurs d'anticoagulants oraux ayant une fibrillation auriculaire

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Les prédicteurs de saignements majeurs parmi des utilisateurs d'anticoagulants oraux ayant une fibrillation auriculaire

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Résumé

Introduction: Il y a peu de données publiées sur les prédicteurs de saignement majeur (MB) dans une population d'utilisateurs d'anticoagulants oraux (OAC) qui inclue les OACs à action directe chez des patients ayant un diagnostic de fibrillation auriculaire (AF) en situation réelle.

Objectif: Développer un modèle de prédiction de MB et de ses sous-types pour une population de nouveaux utilisateurs de OAC ayant un diagnostic de AF en situation réelle.

Méthode : À l'aide de la base de données d'hospitalisation Med-Écho et des bases de données administratives de la RAMQ, nous avons identifié des patients ayant un diagnostic primaire ou secondaire de AF suite à une hospitalisation qui ont eu leur congé hospitalier de janvier 2011 à décembre 2017. Nous avons ensuite identifié ceux qui étaient des nouveaux utilisateurs de OAC et catégorisé ceux-ci selon le OAC utilisé ainsi que sa dose. L'entrée dans la cohorte était la première dispensation de OAC durant la période d'étude alors qu'un nouvel utilisateur a été défini par l'absence de dispensation de OAC un an avant cette date. Nous avons évalué l'incidence de MB, des saignements gastrointestinaux (GIB), extracrânien non-gastrointestinaux (NGIB) et intracrâniens (ICH) dans l'année de suivi. Nous avons utilisé la régression logistique-LASSO et logistique-LASSO adaptative pour la sélection des prédicteurs potentiels de MB dont l'âge, le sexe, les comorbidités (jusqu'à 3 ans avant l'entrée dans la cohorte) et l'utilisation concomitante de médicaments (jusqu'à 2 semaines avant l'entrée dans la cohorte). La discrimination et la calibration ont été évaluées afin de sélectionner le meilleur modèle. Des analyses de sous-groupe ont été effectuées pour le GIB et NGIB ainsi que les sous-catégories de OAC.

Résultats. Notre cohorte comprenait 36,381 nouveaux utilisateurs de OAC entre 70 et 86 ans. Les prédicteurs importants, dont l'âge, l'historique de MB et l'insuffisance hépatique, avaient des rapports de cotes de 1.37 à 1.64 pour le modèle global. Celui-ci avait une statistique c de 0.63 (95% CI 0.60-0.65), était calibré et performaient similairement pour le GIB et le NGIB. À l'exception de quelques prédicteurs importants, dont l'âge et l'historique de MB, la plupart des prédicteurs sélectionnées du GIB étaient distincts de ceux du NGIB dans la cohorte totale. Les prédicteurs de MB avaient des tendances similaires pour les DOACs et la warfarine.

Conclusion. Les prédicteurs de MB et de leurs sous-types étaient similaires parmi les utilisateurs de DOAC et de warfarine. Les prédicteurs sélectionnées par nos modèles et leur potentiel discriminatif concordaient avec la littérature publiée.

Mots-clés : Anticoagulant oral, fibrillation auriculaire, prédiction, saignement, pharmacoépidémiologie

Abstract

Background: The real-world predictors of major bleeding (MB) and its subtypes has not been well-studied in a population of oral anticoagulant (OAC) users diagnosed with atrial fibrillation (AF) that includes direct oral anticoagulant (DOAC) users.

Objectives: To derive prediction models for MB and its most prevalent subtypes from a dataset of new users of all approved OACs with AF.

Methods: We identified patients who were hospitalized and discharged in the community from January 2011 to December 2017 with a primary and secondary diagnosis of AF using the Med-Echo hospitalization database and the RAMQ administrative databases. From this subset, we identified new users of OACs, after which we categorized patients according to OAC type and dose. Cohort entry was defined as the first claim of OAC in the study period, while new users were defined by the absence of any OAC claim one year before cohort entry. We identified incident MB, gastrointestinal (GIB), non-GI extracranial bleeding (NGIB) and intracranial hemorrhage (ICH) within 1 year of follow-up. We used logistic-LASSO and logistic-adaptive LASSO regressions to identify MB predictors in this population from the following candidate predictors: age, sex, comorbidities (within 3 years before cohort entry), concomitant medication (within 2 weeks before cohort entry). Discrimination and calibration were assessed so that the best model could be selected. Subgroup analyses were performed for MB subtypes and OAC types.

Results: Our cohort consisted of 36,381 oral anticoagulant new users aged 70-86 years old. The important MB predictors were age, prior MB and liver disease with ORs ranging from 1.37-1.64 for the model derived from the full cohort. It had a c-statistic of 0.63 (95% CI 0.60-0.65) with adequate calibration and similar c-statistics for GIB and NGIB. Except for a few important predictors, such as age and prior MB, most selected GIB predictors were distinct

from those of NGIB in the full cohort. Lastly, MB predictors had similar trends for warfarin and DOACs.

Conclusions: MB and MB subtype predictors were similar among DOAC and warfarin users. The predictors selected by our models and their discriminative potential are concordant with published data.

Key words: Oral anticoagulant, atrial fibrillation, prediction, bleeding, pharmacoepidemiology

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Listes des sigles et abbréviations

Sigles ou abbréviations	Signification
ABS score	Anticoagulation-specific Bleeding Score
ABC score	Age – Biomarker - Clinical history score
ARISTOTLE trial	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial
ATRIA score	Anticoagulation Risk Factors in Atrial Fibrillation score
ASA	Acetylsalicylic acid
CHAD2-VASC2 score	Congestive heart failure/left ventricular ejection fraction ≤40%, hypertension, age≥75 years, diabetes mellitus, stroke/transient ischemic attack/thromboembolism history, vascular disease, age between 65–74 years, female sex) score
CHADS2 score	Congestive heart failure, hypertension, age≥75 years, diabetes mellitus, stroke/transient ischemic attack history score
HAS-BLED score	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile INR, Elderly/age≥65 years, drugs/alcohol use),
$HEMORR_2$ HAGES score	Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke
ORBIT-AF score	Outcomes Registry for Better Informed Treatment – Atrial Fibrillation
RE-LY trial	Randomized Evaluation of Long-Term Anticoagulation Therapy (dabigatran) trial
ROCKET-AF trial	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation trial
TRIPOD	Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis

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Introduction

Atrial fibrillation is the most diagnosed cardiac arrhythmia. It has a worldwide prevalence of 191.3 (182.1-200.1) per 100,000 people in 2013 (the equivalent of 10 million people), a North American prevalence between 700 and 775 per 100,000 people in 2010 and a U.S. incidence of approximately 350 cases per 100,000 person-years in 2007, all of which are growing numbers due to the aging population [4-7]. Moreover, in 2010, its prevalence in women (373 per 100,000) was significantly inferior to that of men (596 events per 100,000). This trend was most apparent in countries like the US, Brazil and Denmark [8].

In addition to its pervasiveness, atrial fibrillation is associated with a five-fold increase in ischemic stroke of which the cases are more severe relative to patients without atrial fibrillation [9, 10]. Similarly, there is an increased risk of thirty-day all-cause mortality in atrial fibrillation-associated stroke relative to stroke that is not associated with atrial fibrillation (Hazard ratio [HR] 1.84 95% confidence interval [CI] 1.04-3.27). Other embolic events such as venous thromboembolism (deep vein thrombosis in the legs or pulmonary embolism) and systemic embolic events (embolism to the aorta, renal, mesenteric, pelvic regions as well as extremities) were found to be more likely in atrial fibrillation with a relative risk of 1.71 (95% CI 1.32-2.22) for venous thromboembolism, 4.0 (95% CI 3.5-4.6) for systemic embolism in men and 5.7 (95% CI 5.1-6.3) for systemic embolism in women [11-13].

Given that they are each major risk factors for ischemic stroke, systemic thromboembolism, heart failure, myocardial infarct and all-cause mortality, atrial fibrillation places a significant burden on health care and is a major public health concern, thereby requiring a very involved treatment regimen [4, 5]. The risk of atrial fibrillation-exacerbated outcomes such as stroke, can be significantly reduced using antithrombotic agents. These antithrombotic agents can be subdivided in two categories: antiplatelet agents (most commonly, acetylsalicylic acid [ASA]) and anticoagulants. The optimal use of these drugs is defined by treatment guidelines that are regularly updated to implement novel research findings [14]. These guidelines recommend prophylactic oral anticoagulation with oral vitamin K antagonists or direct oral anticoagulants upon atrial fibrillation diagnosis in patients at moderate or high risk of stroke. This clinical decision is driven by the CHA_2DS_2-VASc (congestive heart failure, hypertension, age between 65-74 years, diabetes mellitus, stroke/transient ischemic attack/thromboembolism history,

vascular disease, age≥65 years, female sex) stroke risk score or its variants (i.e. the $CHADS_2$ score) [14-16]. In the Canadian and US guidelines, oral anticoagulant use is recommended if the patient has a CHA_2DS_2-VASc of 2 or greater ($CHADS_2$ score of 1 or greater), while no antithrombotic agents are recommended for score values inferior to 2 with some exceptions [17]. In the presence of vascular disease (coronary, peripheral or aortic artery disease) and the absence of all other stroke risk factors ($CHADS_2<1$), ASA monotherapy or no therapy will be prescribed. Dual antiplatelet and oral anticoagulant therapy is also recommended short-term among patients who underwent a percutaneous coronary intervention and have concomitant acute coronary syndrome or patients that have coronary or peripheral vascular disease at high risk of stroke [18, 19]. Of note, the most recent European guidelines contradict the Canadian and US guidelines with regards to the risk-benefit trade-off of any antithrombotic therapy in an atrial fibrillation patient population at low risk of stroke [20]. Currently, the two oral anticoagulant categories indicated for stroke and thromboembolism prevention in patients with atrial fibrillation are warfarin and the direct oral anticoagulants. Although all antithrombotic agents reduce stroke risk, they also increase the risk of major bleeding, both of which need to be considered in the management of atrial fibrillation.

For the greater part of the last 50 years, warfarin has presented greater effectiveness in stroke and mortality risk reduction relative to other therapeutic alternatives, such as ASA. However, since the advent of direct oral anticoagulants, warfarin was no longer the sole treatment choice for atrial fibrillation patients, nor the ideal one. According to a meta-analysis of randomized clinical trials**,** direct oral anticoagulants were not only associated with a greater reduction in stroke or systemic embolism (OR=0.76, 95% CI 0.68-0.84) relative to warfarin, but, also, a lower risk of major bleeding, the most common adverse event associated with oral anticoagulation, relative to warfarin (OR=0.85, 95% CI 0.74-0.97) [21]. Conversely, observational study findings suggest a similar reduction in stroke risk between warfarin and direct oral anticoagulant users, but there are varying conclusions with regards to major bleeding and its subtypes [22]. Just as is the case for stroke, the risk of major bleeding can be exacerbated by the presence of patient characteristics, which needed to be accounted for in the management of anticoagulation in patients with atrial fibrillation.

Currently, the monitoring of major bleeding is guided by the HAS-BLED, a clinical score used to flag at-risk patients [23]. Although the HAS-BLED cannot be used alone to inform the discontinuation of anticoagulation, it has been an indispensable tool to ensure that anticoagulated patients at high-risk of major bleeding receive proper follow-up [24]. With the exceptions of the 2015 Canadian Cardiovascular Society, 2018 Cardiac Society of Australia and New Zealand and 2019 AHA/ACC/HRS guidelines, the HAS-BLED is the explicitly recommended major bleeding risk score worldwide [17]. However, despite its utility, the score was derived from warfarin user data, exclusively, and potentially does not take into account the predictors of major bleeding that are associated with the use of direct oral anticoagulants [25]. Since then, major bleeding scores like the ORBIT-AF and ABS have been derived from more recent oral anticoagulant user populations. However, while the ORBIT-AF left out rivaroxaban and apixaban user data from its derivation cohort, the ABS score used validated codes to define its candidate predictors and did not specify a candidate predictor look-back period (e.g. it is unclear how far back bleeding history or antiplatelet use was assessed) which limits the applicability of the tool. Moreover, although the ABS score included warfarin, dabigatran, rivaroxaban and apixaban in its derivation and validation cohorts (2007 to 2015), it represented a population in which the uptake of direct oral anticoagulants in US healthcare was still ongoing. For instance, apixaban use was only shown to increase significantly and exceed the other direct oral anticoagulants in 2016 in the US and real-world prescription practices have changed since the latest oral anticoagulant approval [26]. Thus, their model may not perform as well in a current OAC user population, thereby highlighting the importance of deriving prediction models from current populations, especially, when newly approved drugs are involved. Finally, there exist no prediction models for any major bleeding subtypes, which include intracranial hemorrhage, gastrointestinal bleeding and non-gastrointestinal extracranial bleeding, that were derived from current oral anticoagulant user data. For these reasons, we aim to establish a model to predict major bleeding and its common subtypes as well as provide insights on their potential risk factors for all oral anticoagulant users.

Current state of the knowledge

Oral anticoagulation among patients with atrial fibrillation at high stroke risk: their practical advantages and disadvantages

Since 1954, the vitamin K antagonist, warfarin, has been the most long-standing therapy for stroke prevention among individuals with atrial fibrillation. It minimizes the long-term risk of thromboembolism and stroke more significantly than other antithrombotic drugs such as ASA [27, 28]. However, as is the case for all antithrombotic therapies, warfarin use is also associated with a high risk of bleeding, of which the most fatal is intracranial hemorrhage and the most common is gastrointestinal bleeding. The rate of major bleeding (defined by the International Society of Thrombosis and Hemostasis as a clinically overt bleed leading to a decrease of at least 2 g/dL in hemoglobin, to a transfusion of at least 2 units of red blood cells, or to death) stands high at 7.2 per 100 person-years among warfarin users [29, 30]. Moreover, the use of warfarin is also associated with a high number of drug-drug and drug-food interactions leading to unpredictable drug responses. Consequently, while the associated dietary restrictions are difficult to maintain, necessary concomitant medication use may occasionally need to be restricted [31].

Warfarin also requires many practical considerations that constrain its use in a clinical setting. Its narrow therapeutic window as well as the high inter- and intra-individual variability in drug responses among its users requires very tedious therapeutic management that negatively impacts self-reported quality of life and causes anxiety to patients [32]. Specifically, to ensure safe warfarin dosing, the international normalized ratio, an index of coagulation speed that needs to be followed up on at least weekly, must be maintained between 2 and 3 [33, 34]. Conversely, it is worth noting that, despite these difficulties in therapeutic management, there exist extensive monitoring options and reversal strategies adapted to warfarin users. Additionally, although inconvenient, the routine monitoring brings with it a relatively high adherence [35]. Finally, with the exception of a few sub-populations, warfarin use was also more cost-effective than other treatment options available at the time, although the resources involved in therapeutic management somewhat offsets this benefit [35, 36]. Despite having significantly improved over time, these management strategies are still built around the unpredictability of patient responses to warfarin, which is a consequence of the high variability of warfarin dosing and INR, thus welcoming the search for alternative therapeutic strategies.

In 2010, the first direct oral anticoagulant, dabigatran (Pradaxa®; 110 mg and 150 mg), was approved on the US and Canadian markets for thromboprophylaxis in non-valvular atrial fibrillation patients, followed by rivaroxaban (Xarelto®; 15 mg and 20 mg), apixaban (Eliquis®;

2.5 mg and 5 mg) and edoxaban (Lixiana®; 30 mg and 60 mg). These medications constituted promising putative treatment alternatives due to their wider therapeutic window (shorter half-life and therapeutic effect onset) and their more manageable monitoring requirements relative to warfarin [37]. However, just like their predecessor, the direct oral anticoagulants' most common side-effect constitutes major bleeding. Until 2019, the unavailability of approved reversal agents specific to each of the direct oral anticoagulants also constrained their use.

According to meta-analyses of observational studies, as a class, direct oral anticoagulant effectiveness with respect to stroke risk reduction and safety with respect to major bleeding risk was, for the most part, equivalent to warfarin's with very little differences between each individual direct oral anticoagulant [21, 38]. Conversely, when considering major bleeding subtypes, direct oral anticoagulants were associated with a greater risk of gastrointestinal bleeding and a lower risk of intracranial hemorrhage relative to warfarin. Of note, apixaban was the only direct oral anticoagulant to consistently present a lower risk of major bleeding and its subtypes relative to warfarin, dabigatran and rivaroxaban. However, for each direct oral anticoagulant, there was significant heterogeneity with regards to at least one of the major bleeding outcomes [21, 22, 38].

Thus, to determine whether direct oral anticoagulant are the preferred choice for a given patients over warfarin, clinical decision-making needs to weigh in their advantages (a greater risk reduction of all-cause-mortality, a similar risk reduction of ischemic stroke and a lower risk of intracranial hemorrhage) and limitations (a greater risk of gastrointestinal bleeding and a higher risk of major bleeding in patients with severe renal impairment) to choose the optimal treatment tailored to the needs of individual patients [21, 38]. Likewise, to ensure patient safety, the risk-benefit profile of each oral anticoagulant needs to be carefully assessed while taking into account factors associated with a predisposition to bleeding. These factors are largely determined by the pharmacokinetic and pharmacodynamic properties of each oral anticoagulant.

The implications of the pharmacokinetics and pharmacodynamics oral anticoagulants

The theoretical benefits of direct oral anticoagulants can be explained, in large part, by their favorable pharmacokinetic and pharmacodynamic properties.

Both direct oral anticoagulants and warfarin target the coagulation cascade, a protein pathway whose function is preventing blood loss in injured blood vessels, specifically, the maintenance of hemostasis. During blood vessel injury, a properly balanced and sequenced activation and inhibition of the cascade leads to the formation of platelet plugs stabilized by a protein called fibrinogen at the site of injury exclusively until the tissue is healed [39, 40]. Dysregulated hemostasis can lead to either uncontrolled clotting or bleeding. Rapid and short-term healing via platelet aggregation at a site of injury (primary hemostasis) is regulated by the intrinsic pathway which includes factors I (fibrinogen), II (prothrombin), IX, X, XI, and XII. Long-term healing via the stabilization of the platelet aggregate with activated fibrin filaments is regulated by the intrinsic pathway in addition to the extrinsic pathway. It includes factors I, II, VII, and X [39]. Other supportive processes are necessary to the proper functioning of the coagulation cascade. For instance, following the production of inactive coagulation factors in the liver, Vitamin K regulates their post-translational activation, a necessary precursor to the coagulation cascade [40].

From a pharmacodynamic standpoint, while warfarin indirectly targets the coagulation pathway via Vitamin K antagonism, direct oral anticoagulants all target the coagulation pathway directly. Dabigatran inhibits thrombin directly while rivaroxaban, apixaban and edoxaban target factor Xa. Both targeting pathways decrease the formation of fibrin, thrombin and platelet aggregation. Consequently, they all decrease thrombus formation. Factor Xa inhibitors target factor Xa, thereby inhibiting both the extrinsic and intrinsic coagulation cascade. Similarly to dabigatran, these drugs induce a decrease in clot formation by limiting thrombin formation and platelet activation [41]. Please refer to figure 1 for a graphical representation of the effect of each oral anticoagulant on the pathway.

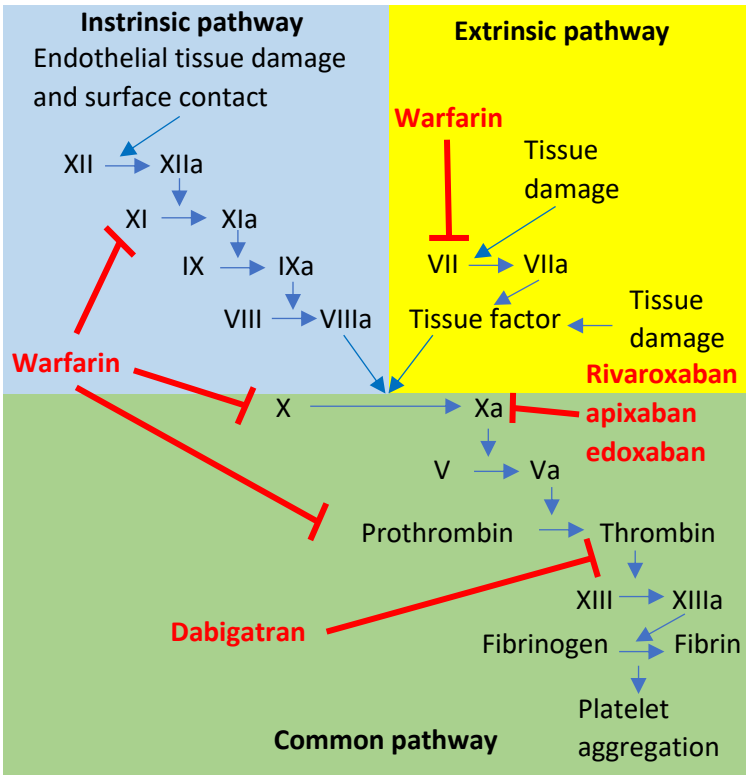

Figure 1. A graphical representation of the coagulation pathway and the targets of each oral anticoagulant. Adapted from [1].

From a pharmacodynamic standpoint, while the oral bioavailability (the fraction of the drug reaching systemic circulation) of warfarin is close to 100%, it is primarily metabolized in the liver, has a half-life of 32 hours or 42 hours, depending on its enantiomer, and has an onset of action ranging between 36 and 72 hours. Meanwhile, the direct oral anticoagulants have oral bioavailabilities ranging between 58.3% and 80% apart from dabigatran which is bioavailable at around 6-7%. Collectively, direct oral anticoagulants have half-lives from 5 to 15 hours and an onset of action between 0.5 and 4 hours. Finally, dabigatran and rivaroxaban have the highest percentage of renal clearance (75 to 80% of the drugs), while apixaban and edoxaban have the lowest (25 to 35%) [3, 34]. Being the direct oral anticoagulant that relies the most on renal excretion, dabigatran is the only dialyzable direct oral anticoagulant [42].

Finally, dabigatran, apixaban and edoxaban are primarily metabolized via P-glycoprotein transporters, while rivaroxaban is metabolized by CYP3A4. The concomitant use of drugs that modulate P-glycoprotein transporters, such as verapamil, dronedarone, and amiodarone may be problematic. The same goes for CYP3A4 modulators, such as erythromycin, ketoconazole, and

amiodarone [3]. Meanwhile, warfarin displays substantially more drug-drug and drug food interactions being impacted by modulators of CYP3A4, CYP1A2, CYP2C9, CYP2D6 and CYP2J [2].

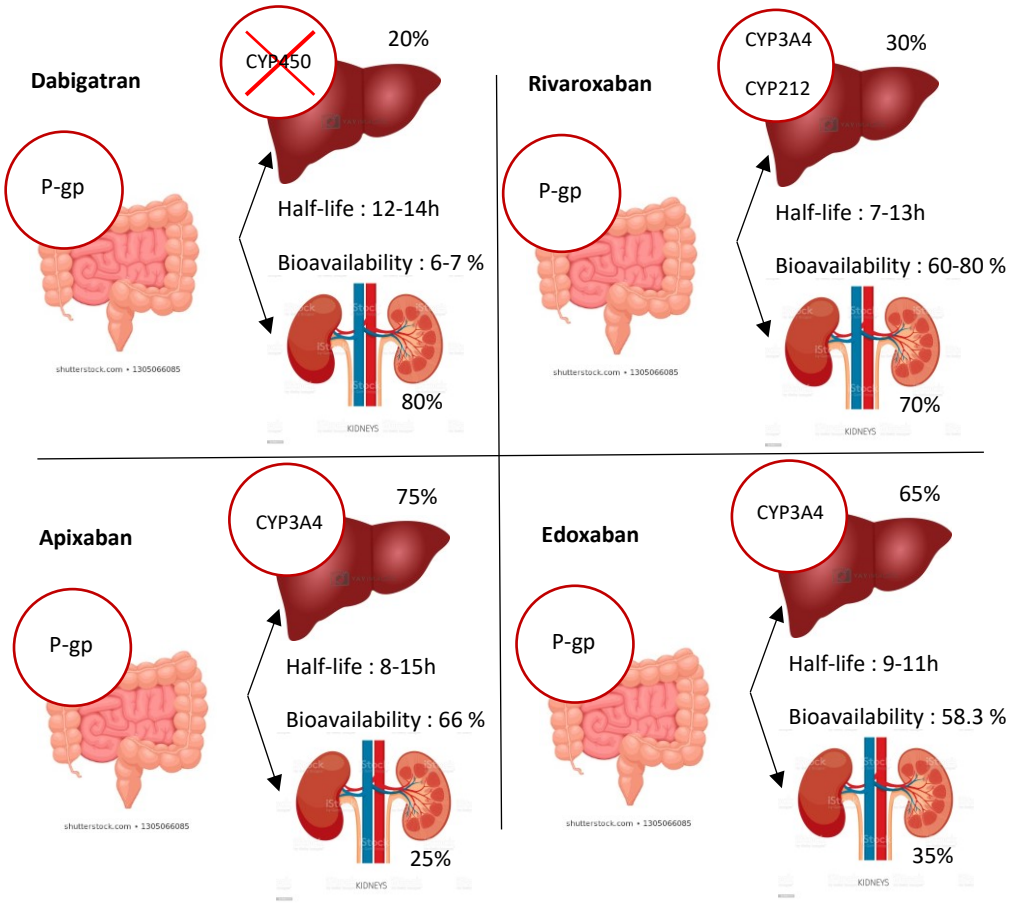

Figure 2. A graphical summary of oral anticoagulant pharmacokinetics. Adapted from [2, 3] using stock footage.

The rapid onset of direct oral anticoagulants reduces the required duration of use of anticoagulant alternatives such as low molecular-weight heparin (LMWH) in acute stages of atrial fibrillation (the "initiation" stage of treatment) in which warfarin's slow onset keeps it from being an effective therapeutic option. Their rapid clearance also minimizes the need for reversal agents although they are still necessary [35]. Their fewer drug-drug and drug-food interactions also contribute to more predictable therapeutic responses in terms of both effectiveness and safety [2].

Conversely, there are still pharmacokinetic disadvantages in that the reliance of direct oral anticoagulants on renal excretion limits their use in the growing number of patients suffering

from severe renal failure. Moreover, the comparatively higher predisposition to gastrointestinal bleeding observed in direct oral anticoagulant-treated patients is thought to be primarily due to the fecal excretion of their active agents [35].

Lastly, unlike dabigatran, rivaroxaban and edoxaban, the drug concentration of apixaban does not seem to be associated with the most significant clinical outcomes, namely ischemic stroke and major bleeding [43-46]. Consequently, the superior risk-benefit profile of apixaban may be attributable to a lower interindividual variability in drug responses due to its more stable pharmacokinetic properties.

The pharmacokinetic advantages and limitations of each oral anticoagulant underlie their respective effectiveness and safety profiles. For warfarin, despite having the best oral bioavailability out of the oral anticoagulants and being safer for patients with renal impairment, it has a slow onset, a very long-half life, many drug-drug interactions and, most notably, a narrow therapeutic window. Meanwhile, although direct oral anticoagulants have a rapid onset, shorter half-lives and a wider therapeutic window along with fewer drug-drug and drug-food interactions, they rely heavily on renal excretion and have lower oral bioavailabilities than warfarin. These advantages and disadvantages provided fairly complete explanations of the randomized clinical trial findings of each oral anticoagulant, but real-world data is needed to validate them.

A timeline of randomized clinical trials for oral anticoagulation in atrial fibrillation

Warfarin randomized clinical trials and meta-analyses

The first pivotal randomized clinical trials pointing towards the effectiveness of warfarin for stroke prophylaxis in atrial fibrillation patients took place in 1990s. When compared to placebo, all warfarin users presented lower risk of cerebral infarction, a term analogous to ischemic stroke, with a risk reduction 0.79 (95% CI 0.52-0.90). In a subgroup of patients older than 75 years old, the results remained unchanged with warfarin presenting a risk reduction of 0.79 ($p<0.05$). However, to its detriment, the mortality rate was similar in both groups ($p<0.05$) and

warfarin use displayed slightly more major bleeding (mainly, gastrointestinal), but the rates were too low for hypothesis testing to be possible [47]. A later meta-analysis of randomized clinical trials comparing warfarin to placebo in atrial fibrillation patients confirmed these findings by demonstrating that warfarin had superior effectiveness in the reduction of stroke and systemic embolism (OR~0.2 95% CI 0.1-0.3) and no statistically significant difference in major bleeding across six trials that took place in the US, Europe and Canada [48].

Meanwhile, the most recent and commonly referred to meta-analysis of randomized clinical trials comparing warfarin to antiplatelet use concluded a significant reduction in stroke risk for warfarin users relative to ASA users (risk reduction 39% CI 22%-52%). Conversely, it also increased the risk of major intracranial hemorrhage by 128% [49]. The last randomized clinical trials comparing warfarin to antiplatelet agents took place in the late 2000s and are still referred to in the most recent atrial fibrillation management guidelines [20]. For one, the ASPIRE-W trial concluded that ASA and clopidogrel dual treatment was less effective in reducing stroke (relative risk [RR] 1.44 95% CI 1.18-1.76) and presented a higher rate of any bleeding (RR 1.21 95% CI 1.08-1.35) than patients taking warfarin with no difference in major bleeding (RR 1.30 95% CI 0.94-1.79) [50]. Subsequently, in the BAFTA trial, warfarin use presented significant risk reduction (RR 0.48 95% CI 0.28-0.80) relative to ASA in patients aged over 75 years [51]. With the exception of the placebo-controlled trials, the patients from the antiplatelet-controlled trials were considered at moderate or high risk of stroke.

Thus, it is important to note that patients at moderate as well as high risk of stroke ($CHADS_2$>1) and low risk of stroke ($CHADS_2$<1) are different populations. In current North American guidelines, ASA is only recommended in low risk patients and under specific conditions (the presence of coronary or peripheral vascular disease), while warfarin was indisputably recommended over ASA for high risk patients [14, 19]. Rather than basing the decision to recommend ASA or no antithrombotic agents for patients at low stroke risk on clinical trial findings, it was most likely based primarily on clinical judgement.

Direct oral anticoagulants randomized clinical trials and meta-analyses

As of 2010, four pivotal randomized clinical trials led to the approval of the direct oral anticoagulants for the same indication in patient with non-valvular atrial fibrillation (RE-LY for

dabigatran, ROCKET-AF for rivaroxaban, ARISTOTLE for apixaban, and ENGAGE-AF for edoxaban). Of note, the non-valvular atrial fibrillation definitions were not uniformly defined across trials with the RE-LY trial only excluding patients with severe heart valve disorder and the ENGAGE-AF trial excluding moderate-severe mitral stenosis cases, while the ARISTOTLE trial defined the exclusions more broadly and the ROCKET-AF trial defined theirs via electrocardiography. Nonetheless, they each concluded that each direct oral anticoagulant presented a non-inferior efficacy in the reduction of the rates of stroke, systemic thromboembolism, myocardial infarct, and all-cause mortality relative to warfarin (with the exception of ARISTOTLE, which evaluated superiority), but varying results in terms of their safety with regards to major bleeding.

Taken as a whole, the effectiveness of direct oral anticoagulants is variable, but tended to be non-inferior to warfarin's. While there was no statistically significant difference in the relative risk of ischemic stroke/systemic embolism as well as myocardial infarct between dabigatran 110 mg and warfarin, at 150 mg, dabigatran presented non-inferior (HR 0.66 95% CI 0.53-0.82) and higher (HR 1.38 95% CI 1.00-1.91) risk of stroke/systemic embolism and myocardial infarct, respectively [52]. Meanwhile, the per-protocol cohort of rivaroxaban users presented non-inferiority in the risk of stroke and systemic embolism (HR 0.79 95% CI 0.66-0.96) with no difference in myocardial infarct [53]. The ARISTOTLE trial presented the same conclusions as rivaroxaban users with regards to stroke/systemic embolism and myocardial infarct [54]. Moreover, apixaban (HR 0.90 95% CI 0.81-1.00) and edoxaban (HR=0.90 95% CI 0.83-0.97) were the only direct oral anticoagulants with lower rates of all-cause mortality [55]. Please refer to table 1 for a summary of the important effectiveness outcomes.

Pertaining to oral anticoagulant safety, these studies identified incidences of major bleeding of 2.71% per year for dabigatran 110 mg, 3.11% per year for dabigatran 150 mg, 3.6% per year for rivaroxaban (all doses) and 2.13% per year for apixaban (all doses) according to the RE-LY, ROCKET-AF and ARISTOTLE trials, respectively. Intracranial hemorrhage incidence rates were significantly lower with incidence rates of 0.31% per year, 0.4% per year, 0.5% per year, 0.33% per year, for each drug, respectively, whereas major gastrointestinal bleeding displayed more variability with incidence rates of 1.12% per year, 1.51% per year, 3.2% per year, 0.76% per year, respectively [21, 53, 56-58].

According to randomized clinical trial findings, although dabigatran 110 mg and apixaban displayed a lower risk of major bleeding relative to warfarin with HRs of 0.69 (95% CI 0.60-0.80) and 0.80 (95% CI 0.69-0.93), respectively, dabigatran 150 mg and rivaroxaban displayed no significant difference relative to warfarin. Additionally, dabigatran, rivaroxaban, and apixaban displayed a lower risk of intracranial hemorrhage relative to warfarin with HRs of 0.31 (95% CI 0.20-0.47), 0.40 (95% CI 0.27-0.60), 0.67 (95% CI 0.47-0.93), 0.42 (95% CI 0.30-0.58), respectively. Dabigatran 150 mg and rivaroxaban displayed greater gastrointestinal bleeding risk than warfarin whereas dabigatran 110 mg and apixaban displayed no statistically significant difference with HRs of 1.50 (95% CI 1.20-1.89), 1.46 (95% CI 1.20-1.79), 1.11 (95% CI 0.87-1.42), and 0.88 (95% CI 0.68-1.14), respectively. Finally, the relative risk of non-gastrointestinal extracranial bleeding has not been evaluated in any of the clinical trials [21, 53, 56, 57]. Please refer to table 1 for a summary of the important safety outcomes.

	Dabigatran vs warfarin (RE-LY)	Rivaroxaban vs warfarin (ROCKET-AF)	Apixaban vs warfarin (ARISTOTLE)	Edoxaban vs warfarin (ENGAGE-AF)
Efficacy HR (95% CI)	110 mg : All stroke: 0.92 (0.74-1.13) Stroke/systemic embolism: 0.91 (0.74-1.11) All-cause mortality 0.91 (0.80-1.03) 150 mg : All Stroke: 0.64 (0.51-0.81) Stroke/systemic embolism: 0.66 (0.53-0.82) All-cause mortality: 0.88 (0.77-1.00)	All Stroke: 0.85 (0.70-1.03) Stroke/systemic embolism: 0.79 (0.66-0.96) All-cause mortality: 0.85 (0.70, 1.02)	All stroke: 0.79 (0.65-0.95) Stroke/systemic embolism: 0.79 (0.66-0.95) All-cause mortality: 0.89 (0.80-1.00)	30 mg: All stroke: 1.13 (0.91-1.31) Systemic embolism: 1.24 (0.72-2.15) All-cause mortality: 0.87 (0.79-0.96) 60 mg: All stroke: 0.88 (0.75-1.03) Systemic embolism: 0.65 (0.34-1.24) All-cause mortality: 0.92 (0.83-1.01)
Safety HR (95% CI)	110 mg Major bleeding: 0.80 (0.69-0.93) Intracranial hemorrhage: 0.31 (0.20-0.47) Gastrointestinal bleeding: 1.10 (0.86-1.41) 150 mg Major bleeding: 0.93 (0.81-1.07) Intracranial hemorrhage: 0.40 (0.27-0.60) Gastrointestinal bleeding: 1.50 (1.19-1.89)	Major bleeding: 1.04 (0.90-1.20) Intracranial hemorrhage: 0.67 (0.47-0.93) Gastrointestinal bleeding: NA	Major bleeding: 0.69 (0.60-0.80) Intracranial hemorrhage: 0.42 (0.30-0.58) Gastrointestinal bleeding: 0.89 (0.70-1.15)	30 mg: Major bleeding: 0.47 (0.41-0.55) Intracranial hemorrhage: 0.30 (0.21-0.43) Gastrointestinal bleeding: 0.67 (0.53-0.83) 60 mg: Major bleeding: 0.80 (0.71-0.91) Intracranial hemorrhage: 0.47 (0.34-0.63) Gastrointestinal bleeding: 1.23 (1.02-1.50)

Table 1. Summary of direct oral anticoagulant efficacy and safety outcomes in randomized clinical trials.

*Only the most comparable endpoints were selected in this table.

Randomized clinical trial meta-analyses suggest that, when direct oral anticoagulant clinical trial findings are pooled together, they display greater effectiveness to warfarin in terms of stroke/systemic embolism (HR=0.76 95% CI 0.68-0.84), all-cause-mortality (HR=0.89 95% CI 0.84-0.95) and vascular mortality (HR=0.86 95% CI 0.79-0.94), but not myocardial infarct (HR=0.94 95% CI 0.83-1.08). Pooled clinical trial findings also demonstrated a lower risk of major bleeding relative to warfarin (OR=0.85, 95% CI 0.74-0.97), a lower risk of intracranial hemorrhage (OR=0.48, 95% CI 0.40-0.57) and a higher risk of gastrointestinal bleeding (OR=1.26, 95% CI 1.06-1.48) relative to warfarin [21].

There are inherent differences between real-world and randomized clinical trial findings. Namely, clinical trials estimate efficacy, possess significantly more exclusion criteria than real-world studies due to their interventional nature and are therefore subjected to more stringent ethical criteria. For this reason, in the direct oral anticoagulant randomized clinical trials, many patients at a much higher bleeding risk than the eligible patients were excluded from the study. Furthermore, clinical trial direct oral anticoagulant users with atrial fibrillation were both younger and healthier (a lower rate of stroke and fewer co-morbidities) than real-world direct oral anticoagulant users with atrial fibrillation [59, 60]. Moreover, even if direct oral anticoagulant early discontinuation ranged between 21% and 25.3%, the controlled environment of a randomized clinical trial involves significantly better adherence relative to real-world oral anticoagulant users and prevents contraindicated oral anticoagulant use [31, 59, 61]. For these reasons, findings from these randomized clinical trials cannot be extrapolated to a real-world setting. Thus, using observational studies to evaluate real-world effectiveness and safety is essential to confirm clinical trial findings as well as to evaluate the impact of real-world practices.

Oral anticoagulant real-world findings

Most recent findings on the comparative effectiveness and real-world safety of oral anticoagulants

Warfarin observational studies

Before direct oral anticoagulants were made available, the use of warfarin had to be well-researched given how extensively it was (and still is) used. However, there were only a few observational studies comparing the risk of clinical outcomes associated with warfarin use relative to that of warfarin-era treatment alternatives and placebo. A US observational study evaluated warfarin use and effectiveness to non-use in warfarin-eligible patients with non-valvular atrial fibrillation between 2000 and 2002. The study suggested that warfarin users showed a greater effectiveness in reducing ischemic stroke (HR 0.78 95% CI 0.65-0.93) and thromboembolism (HR 0.66 95% CI 0.59-0.75) relative to warfarin-eligible patients who were not yet using oral anticoagulants, with no significant increase in hemorrhage ($p<0.05$) [62]. A similar study that followed warfarin-naïve patients from 2009 to 2011 similarly concluded a lower risk of all-cause mortality (HR 0.72 99% CI 0.63-0.84) and ischemic stroke (HR 0.63 99% CI 0.48-0.83) relative to non-users, but no difference regarding intracranial hemorrhage (HR 1.37 99% CI 0.61-3.06) [63]. However, to our knowledge, no real-world studies directly compared warfarin's safety and effectiveness to antiplatelet agents.

Recent direct oral anticoagulant observational studies

Since the approval of direct oral anticoagulants, upwards of 26 observational studies comparing their use to warfarin or to each other emitted varying conclusions regarding comparative effectiveness and real-world safety [38, 59, 64]. Given the changing trends in oral anticoagulant use and the characteristics of their users, it is important to identify recent observational studies to truly understand and monitor their effectiveness and real-world safety. It is also important to keep in mind that these studies are thus, unlikely, to be representative of all direct oral anticoagulant observational studies.

A recent US cohort study found that direct oral anticoagulant users with nonvalvular atrial fibrillation had a lower risk of ischemic stroke (HR 0.88 95% CI 0.79-0.98), hemorrhagic stroke (HR 0.65 CI 0.46-0.92), systemic embolism (HR 0.53 95% CI 0.43-0.65) relative to warfarin

users and a lower risk of bleeding. These pooled findings echoed many observational studies preceding it regarding the comparative effectiveness and safety of direct oral anticoagulants relative to warfarin [65]. However, adherence may have been overestimated and discontinuation rates, underestimated. Moreover, the authors also pointed a potential for confounding by a contraindication associated with patients with renal impairment.

The recently published NAXOS observational study showed that apixaban had a lower risk of gastrointestinal bleeding (HR=0.44 95% CI 0.40-0.50), intracranial bleeding (HR=0.42 95% CI 0.37-0.48) and non-gastrointestinal extracranial bleeding (0.43 95% CI 0.39-0.47) relative to vitamin K antagonist users with nonvalvular atrial fibrillation. It also showed approximately double the effectiveness relative to vitamin K antagonist use in terms of reduction of stroke and systemic embolism as well as all-cause mortality. Relative to rivaroxaban, the risk of major bleeding was lower, but the effectiveness was similar in terms of both outcomes. Finally, the effectiveness and real-world safety of apixaban was most comparable to dabigatran in which the only differences were a lower risk of gastrointestinal bleeding (HR=0.60 95% CI 0.48-0.76) and a higher risk of intracranial bleeding in apixaban users (HR=1.72 95% CI 1.20-2.48) [66]. The study may have been susceptible to selection bias due to the possible omission of non-severe AF patients and residual confounding from unmeasured variables.

Like the NAXOS study, an US observational study made comparisons between the direct oral anticoagulants with nonvalvular atrial fibrillation that were approved at the time and presented optimistic results for apixaban. Apixaban presented a lower risk of stroke and systemic embolism as well as major bleeding relative to dabigatran and rivaroxaban. Meanwhile, dabigatran showed comparable effectiveness and a lower risk of major bleeding relative to rivaroxaban [67]. However, the authors reported potential biases from not being able to ascertain over-the-counter medication use, nor oral anticoagulant adherence as well as the use of non-validated diagnostic codes for certain covariates and certain cohort selection steps.

Depending on the study, there is a tendency that, as real-world research on oral anticoagulants progresses over time, the perceived superiority of the risk-benefit profile of direct oral anticoagulants, while still present, is less significant as it was initially thought to be. This might have been due to the fact that real-world direct oral anticoagulant users were typically younger and healthier relative to warfarin users in observational studies preceding 2017 on account of

channeling bias as well as a potential indication bias due to differential severity of illnesses across treatment groups, thereby precluding the value of a new user study design [68]. The exception to the rule is apixaban, which has consistently superseded the risk-benefit profile of the other oral anticoagulants. However, as exemplified by the studies presented in this section, the heterogeneity of oral anticoagulant user populations makes it difficult to emit any conclusions on the basis of individual observational studies. Moreover, selection bias due to selection of previous oral anticoagulant users, informative censorship bias, confounding by indication, time-varying confounding, residual confounding and disproportionate non-adherence rates between treatment groups were commonly reported in observational studies [22, 64]. Most observational studies are also susceptible to misclassification bias as a consequence of using non-validated diagnosic coding and estimating medication use with dispensation data.

Meta-analyses of oral anticoagulant observational studies

Unlike randomized clinical trial populations, the heterogeneity of real-world patient populations, differing conclusions were emitted with regards to both effectiveness and real-world safety outcomes with widely varying relative risk measurements. This variability highlights the importance of pooling their findings, identifying which outcomes present more stable associations across studies and attempting to understand any pervasive biases (or risk thereof). Thus, observational study meta-analyses were required to adequately summarize the existing real-world findings. Of note, observational studies at high risk of bias should be excluded from such pooled analyses, while findings from significantly different populations should not be pooled together. Over 25 meta-analyses were performed in our population of interest or specific subgroups, with 4 main studies focusing on a general population of oral anticoagulant users with atrial fibrillation and 4 focusing on an older such population [22, 38, 59, 64, 69-72]. However, meta-analyses evaluating more recent observational studies display an older and frailer population of direct oral anticoagulant users relative to less recent ones [38, 59, 64]. This is most likely due to an under-prescribing of direct oral anticoagulants in older and frailer atrial fibrillation patients in the years immediately following the approval of direct oral anticoagulants (i.e. channeling bias). Because of the changing trends in oral anticoagulation prescription, it is important to continuously update our pooled findings about oral anticoagulants and consider only the meta-analyses that include the most recent studies for real-world insights about oral

anticoagulation in atrial fibrillation, while avoiding poor quality studies with potential conclusion-altering biases. Of note, is that only one of these meta-analyses singled out non-valvular atrial fibrillation over atrial fibrillation as a whole in their search terms [59]. That being said, virtually none of the observational studies selected by the meta-analyses did not single out non-valvular atrial fibrillation patient populations [38, 59, 64].

In terms of effectiveness, a meta-analysis of observational studies concluded that dabigatran, rivaroxaban and apixaban did not display statistically significant differences in the relative risks of a composite risk of stroke and systemic embolism [38]. In terms of real-world safety, dabigatran displayed no difference in major bleeding risk relative to warfarin with a lower risk of intracranial hemorrhage (HR=0.42 95% CI 0.37-0.49), a greater risk of gastrointestinal bleeding (HR=1.2 95% CI 1.06-1.36) and lower risk of all-cause mortality (HR=0.63 95% CI 0.52-0.76). For rivaroxaban, the relative risk of intracranial hemorrhage is lower (HR=0.64 95% CI 0.47-0.86), whereas the relative risk of gastrointestinal bleeding is greater (HR=1.24 95% CI 1.08-1.41) and the relative risk of major bleeding and death, non-significant [38]. Finally, apixaban displays a lower relative risk for all safety outcomes with HRs of 0.45 (0.31-0.63), 0.63 (0.42-0.95), 0.55 (0.48-0.63) and 0.65 (0.56-0.75) for intracranial hemorrhage, gastrointestinal bleeding, major bleeding and all-cause mortality, respectively [38]. These results were mostly confirmed by a meta-analysis of propensity score-matched observational studies of direct oral anticoagulant use among atrial fibrillation patients. Although they have found that pooled direct oral anticoagulants has a lower risk of ischemic stroke and systemic embolism (HR=0.88 95% CI 0.83-0.94), there was no difference in risk of major bleeding and a lower risk of mortality (HR=0.71 95% CI 0.58-0.87) [59]. Conversely, a recent comparative review found that observational study findings confirmed randomized clinical trials by suggesting that direct oral anticoagulants are as effective in mitigating stroke risk as warfarin and a lower risk of major bleeding [73]. Despite consistent findings about the superior real-world safety of direct oral anticoagulants relative to warfarin regarding intracranial hemorrhage, there is a current lack of consensus on the impact of direct oral anticoagulants on gastrointestinal bleeding although the literature suggests a dose-associated increase in the risk of this outcome relative to warfarin [38, 59, 64, 73].

	Dabigatran vs warfarin	Rivaroxaban vs warfarin	Apixaban vs warfarin
Effectiveness HR (95% CI)	Ischemic Stroke: 0.96 (0.80-1.16) Any stroke/systemic embolism: 0.93 (0.77-1.14) All-cause mortality: 0.63 (0.72-0.76)	Ischemic stroke: 0.89 (0.76-1.04) Any stroke/systemic embolism: 0.87 (0.71-1.07) All-cause mortality: 0.67 (0.35-1.30)	Ischemic stroke: 0.95 (0.75-1.19) Any stroke/systemic embolism: 0.67 (0.46-0.98) All-cause mortality: 0.65 (0.56-0.75)
Safety HR (95% CI)	Major bleeding: 0.83 (0.65-1.05) Intracranial hemorrhage: 0.42 (0.37-0.49) Gastrointestinal bleeding: 1.20 (1.06-1.36)	Major bleeding: 1.00 (0.92-1.08) Intracranial hemorrhage: 0.64 (0.47-0.86) Gastrointestinal bleeding: 1.24 (1.08-1.21)	Major bleeding: 0.55 (0.48-0.63) Intracranial hemorrhage: 0.45 (0.31-0.63) Gastrointestinal bleeding: 0.63 (0.42-0.95)

Table 2. Summary of direct oral anticoagulant effectiveness and real-world safety outcomes in observational study meta-analyses. [38]

*Edoxaban findings were not presented due to lack of relevance to the ensuing study.

Observational studies pertaining to oral anticoagulant users with atrial fibrillation presented statistically significant heterogeneity in various efficacy and safety outcomes [38, 59, 64]. Specifically, each direct oral anticoagulant showed significant heterogeneity in one or more of all efficacy and safety outcomes, stroke, all-cause mortality, major bleeding, intracranial hemorrhage and gastrointestinal bleeding [38]. In these meta-analyses, heterogeneity was reported to be due to dosage (given that observational studies with different distributions of prescribed direct oral anticoagulant dosages often pooled them together without controlling for them), safety outcome definition, oral anticoagulant-experienced vs naïve population, adherence, persistence, time-within-therapeutic range for vitamin K antagonist users, adherence to prescription recommendations by prescribing physicians and length of study follow-up [38, 59, 64, 72]. Although more difficult to control for, populational differences may have played into the significant heterogeneity as well [74]. It will be important to consider all of these variables when designing further observational studies. In particular, the lack of consistency in real-world safety findings for different oral anticoagulant user populations makes it particularly important to find effective ways to monitor them.

Major bleeding risk factors

There is a wide range of factors associated with bleeding. Bleeding can be a direct result of uncontrolled pharmacological action (i.e. drugs whose capsules have corrosive properties such as tartaric acid in dabigatran), underlying conditions (i.e. ulcers), or physical injury. However, bleeding risk can also be exacerbated by a variety of factors including age, underlying conditions (e.g. conditions that weaken the wall of blood vessels, weakened kidney and liver function) and drug use (i.e. drugs that impact that inhibit the coagulation pathway) [60, 75]. To properly monitor this outcome, it is important to identify their most important risk factors.

Age

Older patients are more likely to have a slower metabolism (including poorer renal function), lower body mass index, multiple comorbidities, polypharmacy and a high risk of falling. For these reasons, age was considered to be a bleeding risk factor of important clinical significance before and after direct oral anticoagulant approval as evidenced by both observational and randomized clinical trial findings. A systematic review of bleeding risk factors among anticoagulated atrial fibrillation patients identified age as a borderline significant (1 observational study) and independent (3 observational studies; defined by the study as a significant association to major bleeding after control for multiple clinically plausible risk factors) major bleeding risk factor. While one study reported an aOR of 6.6 (95% CI 1.2-37) for the risk of major bleeding in patients older than 75 years relative to those younger, another identified an aOR of 2.45 ($p=0.006$; no available CIs). Two other studies found no significant association with bleeding when evaluating age as a continuous variable or comparing patients over 75 years to those between 60 and 69 [76]. Randomized clinical trial findings suggested that dabigatran 110 mg displayed a greater incidence of major bleeding relative to warfarin (1.89% versus 3.04%; $p<0.001$; no available CIs) at age<75, but not ≥75, while dabigatran 150 mg displayed greater incidence at both age groups [52]. Rivaroxaban users did not display a significant difference in major bleeding risk relative to warfarin users, but the major bleeding risk in the entire ROCKET-atrial fibrillation cohort increased with age 65-74 and age ≥75 relative to age<65 (157). Finally, every 10-year increase in age resulted in an increase in major bleeding risk (HR=1.36 95%1.23-1.51) within the ARISTOTLE cohort [77]. Thus, although the risk varies somewhat depending on the definition of increased age, there is strong evidence that

older age constitutes a significant major bleeding risk factor among both warfarin and direct oral anticoagulant users.

Sex

A systematic review of bleeding risk factors among warfarin users with atrial fibrillation identified a marginal gender-difference in bleeding risk among the 10 relevant studies. Both favored female gender with ORs of 1.40 and 3.19 (p=0.05) [76]. Meanwhile, comparatively less studies have been completed among direct oral anticoagulant user. One Canadian population-based study stated that female dabigatran users were at higher risk of bleeding than male users [78]. While sex was not independently associated with major bleeding among clinical trial rivaroxaban users, male apixaban and warfarin users with atrial fibrillation were shown to display a lower major bleeding risk relative to female users (HR=0.74 95% CI 0.63-0.87) [77, 79]. Among oral anticoagulant users, female sex seems to exacerbate major bleeding risk, but this claim needs to be further validated given the paucity of observational studies evaluating sex-differences among direct oral anticoagulant users (i.e. a single study per direct oral anticoagulant).

Comorbidities

The effectiveness and safety of all oral anticoagulants depends on many different organ systems. While drug absorption, metabolism and excretion depend on the GI lining, the liver and the kidneys, the proper functioning of the coagulation pathway relies on the cardiovascular system and the liver. Thus, renal, hepatic, cardiovascular, pulmonary and metabolic comorbidities were shown to significantly influence major bleeding risk.

As a rule of thumb, the higher the degree of renal impairment, the higher the bleeding risk associated with direct oral anticoagulant use relative to warfarin and the less advantages they have over warfarin [80, 81]. This is attributable to the much greater percentage of direct oral anticoagulant renal metabolism compared to warfarin's. Despite this, warfarin users with severe CKD still spent less time with an international normalized ratio in the target (safe) range ($p<0.05$) compared with patients with no, mild, or moderate CKD (p=0.05). Thus, warfarin users with severe CKD had around twice the risk of major bleeding of patients with no, mild, or moderate CKD (HR=2.4 95% CI 1.1-5.3) [82]. In a meta-analysis of observational studies, real-world dabigatran and rivaroxaban users displayed no difference in major bleeding relative to

warfarin among patients with moderate renal impairment and atrial fibrillation. No studies encompassing atrial fibrillation patients were reported for apixaban users in this meta-analysis [81, 83]. However, in the meta-analysis, among patients with moderate renal impairment (defined by an eGFR anywhere between 25 and 60 mL/min depending on the study), apixaban and edoxaban both displayed a lower major bleeding risk relative to warfarin with HRs of 0.50 (0.38-0.66) and 0.76 (0.58-0.98) , respectively [83]. Furthermore, severely impaired dabigatran and rivaroxaban users on dialysis displayed a greater major bleeding risk relative to warfarin (respectively, HR=1.76 95% CI 1.44-2.15 and HR=1.45 95% 1.09-1.93) with no difference among apixaban-users [81, 83]. The reliability of the apixaban findings in patients with severe renal failure was called into question since the study was underpowered.

Given that warfarin relies purely on liver metabolism, hepatic disease has significant impact on quality of anticoagulation control. The complex relationship between the liver and the coagulation pathway stemming from the secretion endogenous procoagulants and anticoagulants further exacerbates the constraints placed on the effectiveness of anticoagulation by this condition. This ultimately leads to a higher predisposition to both bleeding and thrombosis. Bleeding predisposition occurs due to reduced platelet-blood vessel interaction, reduced thrombin generation and increased fibrinolysis [84]. Given that liver cirrhosis patients have a greater likelihood of both thrombosis and hemorrhage through systemic effects of the medication, it is important to consider the impact of chronic liver impairment on the safety of direct oral anticoagulant use [85]. However, clinical guidelines for the prescription of direct oral anticoagulants for atrial fibrillation patients concomitantly suffering from chronic liver disease are not as well informed as those with renal conditions. Ultimately, they recommend the use of direct oral anticoagulants for mild and moderate cases of liver disease, but not for severe cases [86]. A systematic review of liver disease among direct oral anticoagulant users has reported that most observational studies were founded on very limited data with sample sizes ranging from 36 to 69 patients, thus calling into question their findings, while no prospective clinical trials were conducted in this population in any population of oral anticoagulant users [86, 87]. Moreover, a recent observational suggested a lower bleeding prevalence among direct oral anticoagulant users relative to warfarin users (4% vs 28%), while an observational study found that liver cirrhosis predisposed to intracranial hemorrhage (HR=1.20, $p<0.05$) in a population of warfarin and ASA users as well as non-users [88, 89]. For most of these studies, the authors suggested

that it was inadvisable to emit firm conclusions from the study findings on account of the limited data.

Some metabolic conditions have been found to exacerbate the real-world risk of major bleeding among oral anticoagulant users. A systematic review identified no observational studies in which diabetes mellitus was identified as an independent risk factor among warfarin users, while randomized clinical trial findings suggests the opposite [76]. Among dabigatran and warfarin users, clinical trial findings suggest an increased risk of major bleeding among diabetic patients (HR=1.44 95% CI 1.27-1.63) [90]. Conversely, the relative risk of major bleeding in rivaroxaban versus warfarin regarding was not exacerbated by the presence of type 2 diabetes (HRs of 1.00 and 1.12 for patients with and without diabetes, respectively, $p>0.05$) [91]. These findings were confirmed in observational studies in which the incidence of major bleeding was greater in diabetic rivaroxaban users relative to the non-diabetic ones. Ultimately, apixaban displayed similar findings [76]. Similarly, according to clinical trial findings, apixaban users with normal BMI observed that major bleeding risk reduction those with higher BMI with similar findings. Female edoxaban users also displayed a significantly higher risk of major bleeding as BMI increased [92]. While supplementing the lack of data on the effect of weight on bleeding risk informing treatment recommendation, in a meta-analysis of direct oral anticoagulant randomized clinical trials and observational studies, obesity is a major bleeding risk factor that is supported by conflicting evidence [92]. Pooled observational study data showed no difference in bleeding risk between overweight, obese and healthy weight individuals, while randomized clinical trials paradoxically suggested that obesity has a protective effect (0.84, 95% CI 0.72-0.98) as opposed to being overweight (NS) relative to normal weight individuals [93, 94]. Hyperlipidemia, a factor highly correlated to obesity, has also been explored as a risk factor for gastrointestinal bleeding and was shown to not influence the risk [95]. On the other hand, BMIs below the healthy range seem to be at an increased risk of bleeding for direct oral anticoagulants altogether, but the bleeding risk within this subpopulation has not been explored for individual direct oral anticoagulants, thereby needing to be explored further to account for this knowledge gap [96].

Many cardiovascular co-morbidities have been shown to exacerbate the risk of bleeding. In a review of warfarin-associated bleeding risk factors, hypertension and blood pressure were identified as weak risk factors (defined by a univariate association to at least one bleeding

outcome) in two separate studies [76]. The prevalence of hypertension was higher in warfarin users with bleeding relative to those without [76]. Conversely, among randomized clinical trial warfarin users, higher quartiles of blood pressure were not associated with an increased risk of bleeding [97]. Although warfarin users with the most severe heart failure have been shown to display a fourfold increase in major bleeding risk than users with less severe heart failure, the impact of heart failure on bleeding among anticoagulated patients requires further evaluation [98]. History of myocardial infarct and ischemic heart disease, which encompasses chronic heart failure, coronary artery disease and peripheral vascular disease were associated with an increased prevalence of bleeding in real-world warfarin users with atrial fibrillation [76]. Lastly, a history of cerebrovascular disease, a history of bleeding (mostly, gastrointestinal bleeding) and anemia were reported to predispose warfarin users to major bleeding in a review [30]. Meanwhile, a systematic review identified history of bleeding as well as stroke and VTE history as independent bleeding risk factors in two separate studies [76].

Thus, putting aside major bleeding prediction studies, there are varying levels of evidence regarding the independent association between each co-morbidity and major bleeding, but most require further research to further these claims.

Medication use

Broadly, concomitant medication use can impact oral anticoagulant function synergistically or antagonistically and consequently act as major bleeding risk factors. This synergistic or antagonistic action can be a product of pharmacodynamics (i.e. more than one drug acting on the coagulation pathway) or, more commonly, pharmacokinetics, through which other drugs can modulate the absorption, distribution, metabolism and excretion of oral anticoagulants.

A meta-analysis of 10 clinical trials found that concomitant warfarin and ASA use was highly predictive of bleeding (OR=2.5 95% CI, 1.7-3.7), compared to warfarin monotherapy [30, 34]. An observational study corroborated these findings in direct oral anticoagulant users showing an increase in major adverse cardiac events (defined by the presence of ischemic stroke, systemic embolism or acute coronary syndrome, HR=2.12, 95% CI 1.85-2.43) and bleeding (HR=1.31, 95% CI 1.17-1.46) in patients taking ASA and direct oral anticoagulants relative to patients solely taking direct oral anticoagulants [99]. Moreover, concomitant warfarin and NSAID use showed a 15% elevation in international normalized ratio (used as a surrogate major bleeding

marker in this study) relative to warfarin alone. A multivariate analysis identified a high warfarin maintenance dose, concomitant use of medications with recorded interactions with warfarin, the use of the NSAID, meloxicam, and a low baseline international normalized ratio value as bleeding risk factors in an outpatient population of warfarin users [100]. Similarly, two randomized clinical trial post-hoc analyses showed that the concomitant use of dabigatran or apixaban and NSAIDs displayed higher risks of major bleeding (HR=1.68 95% CI 1.40 to 2.02 and HR=1.61 95% CI 1.11-2.33, respectively) [101].

Other medications may theoretically exacerbate the risk of bleeding but have yet to display empirical clinical evidence for it. These include diuretics (loop and thiazide) which may be important to explore as they would influence renal function, thereby potentially influencing direct oral anticoagulant pharmacokinetics, although the timeline of this effect is unclear [102]. Angiotensin receptor blockers (ACEI/ARBs), antiarrhythmics and statins may increase the risk of bleeding systemically by modulating blood flow or by inhibiting CYP450 enzymes responsible for the breakdown of direct oral anticoagulants [103, 104]. Conversely, proton pump inhibitors and H2 Receptor antagonists are protective against gastrointestinal bleeding [105, 106], whereas rate-control therapies (digoxin, beta-blockers and calcium-channel blockers) and statins present lower risks of direct oral anticoagulant-associated major bleeding [2]. Among warfarin users, the concomitant use of selective serotonin reuptake inhibitors and warfarin showed a greater major bleeding risk relative to the use of warfarin, alone (OR=2.6 95% CI 1.01-6.40) [107]. Similarly, serotonin-modulating antidepressants are known to interact with direct oral anticoagulants by impacting their metabolism, thereby increasing the overall risk of bleeding [104]. However, the concomitant selective-serotonin reuptake inhibitors and rivaroxaban use was not shown to significantly impact on bleeding displayed in a randomized clinical trial meta-analysis [108].

Polypharmacy is a common occurrence in elderly patients. While most of these patients do not fully understand the possible side-effects of the medications prescribed to them, this practice often leads to poor health outcomes. A systematic review of warfarin users before 2007 identified that the presence of polypharmacy (defined as either more than 3 medication or concomitant antiplatelet use) predisposed to bleeding in four separate studies [76]. Conversely, in the absence of concomitant antiplatelet or antibiotics, the use of NSAIDs or any other

medication was not shown to be associated with bleeding in one of the studies included in the systematic review [109]. When deprescription is not a possibility, the way to protect these vulnerable populations is to ensure that there be a comprehensive understanding of the drugs predisposing to major bleeding and that this information be concisely communicated to medical professionals.

Without considering prediction models, some major bleeding risk factors have been better studied than others in a population of oral anticoagulant users. The most important demographic variable was old age with OR values exceeding 2.0 for age>75 relative to <75 years old [76]. Meanwhile, the most important co-morbidities included severe CKD (HR=2.4 95% CI 1.1-5.3) and diabetes (HR=1.44 95% CI 1.27-1.63) [79, 90]. Although hypertension and cardiovascular comorbidities are important risk factors, they are better studied in the context of prediction models. Lastly, the most important concomitant medication-associated risk factors are ASA and SSRIs with ORs exceeding 2.5.

Management of major bleeding risk factors in clinical practice

As described earlier, the great inter-individual variability in bleeding rates can be explained by various important pharmacokinetic and pharmacodynamic features that outline patient response to specific direct oral anticoagulant treatments. The identification of important major bleeding risk factors is crucial since it will help individualize anticoagulation to specific patient profiles. More importantly, it will inform how closely, and frequently specific anticoagulated patients should be monitored when one or multiple major bleeding risk factors are present. These practices would significantly improve oral anticoagulant safety, adherence and patient quality of life. Since direct oral anticoagulants have several indications, it is important to identify these risk factors in an atrial fibrillation patient population as this population may have different clinical features and a distinct treatment regimen impacting their risk of bleeding relative to other patient populations receiving direct oral anticoagulants for a different indication.

Some of the ways in which these risk factors are concretely incorporated into care practices are through prescription guidelines, decisional algorithms and other decision-making tools. The current Quebec guidelines of thromboprophylactic anticoagulation in patients diagnosed with atrial fibrillation outlined by the "*Institut national d'excellence en santé et en service sociaux*" and Canadian guidelines focus on age, sex, renal function, hepatic function, body weight, recent

history of stroke and TIA, concomitant hypertension, heart failure, diabetes, P glycoprotein inhibitor use, surgical history, and the $CHAD_2$-$VASc_2$ score as factors that should be accounted for anticoagulant prescription with certain minor discrepancies and differences in cut-off values for individual factors [14, 15, 23]. However, the most practical way that risk factors are implemented into care practices is via the use of major bleeding risk scores to classify at-risk patients. Moreover, although nonmodifiable risk factors have great prognostic value, the monitoring of modifiable risk factors is often emphasized in clinical practice**.** A prospective cohort study derived from a registry of rivaroxaban users concluded that the presence of one modifiable risk factor such as uncontrolled hypertension (which can be controlled) or alcohol abuse (which can be treated) double the risk of bleeding as opposed to non-modifiable risk factors such as age (which cannot be changed) which did so to a significantly lesser extent [110]. For this reason, clinical scores that incorporate modifiable risk factors are given more weight than those that do not.

The most common major bleeding prediction models

HAS-BLED

The most widely used score, the HAS-BLED has been created using candidate predictors (variables to be evaluated as predictors prior to any analyses) identified by a literature review of bleeding risk factors associated with the use of warfarin or antiplatelet agents. In the analyses from which the score was derived, a stepwise logistic regression was used to determine the predictors that would be incorporated in the score and the values to be attributed to each point estimate. The score incorporated uncontrolled hypertension (systolic blood pressure > 160 mm Hg; OR=0.60, 95% CI 0.21-1.72), abnormal kidney function (dialysis or Cr >2.26 mg/dL; OR=2.86, 95% CI 1.33-6.18), abnormal liver function (cirrhosis or bilirubin levels a greater than twice the normal level with standard liver function testing greater than three times the normal value; not included in the regression), prior stroke (OR=0.94, 95% CI 0.32-2.86), prior major bleeding (OR=7.51, 95% CI 3.00-18.78), labile international normalized ratio (time in therapeutic range < 60%; not included in the regression), age > 65 years (OR= 2.66, 95% CI 1.33-5.32), antiplatelet use (0.81, 95% CI, 0.43-1.51) and alcohol abuse (more than 8 drinks per week; OR=0). Although they were forced in the final logistic regression model and were used in

the final score, there was no significant association between hypertension, stroke, antiplatelet use or alcohol abuse and the risk of bleeding. Thus, in addition to solely being derived from a population of warfarin and antiplatelet users as well as antithrombotic agent non-users, the HAS-BLED relied heavily on literature review and clinical judgement in the selection of predictors for its final model at the expense of using effective prediction methods [25]. On the other hand, one of the most notable advantages of the selection of predictors for the HAS-BLED was the emphasis placed on modifiable risk factors. Thus, in addition to being used to ensure proper monitoring of patients at higher major bleeding risk, the HAS-BLED score can be used as a tool to incentivize patients to address conditions that may predispose them to major bleeding (i.e. discontinuing antiplatelet use or controlling hypertension) and clinicians to recommend these changes to significantly decrease the risk of bleeding. However, it should be noted that, although these factors are modifiable, they may not reflect a true causal relationship due to the constraints associated with the type of modelling used to derive the score. Therefore, the decrease in risk that may be predictive and not causal (i.e. an artifact of confounding). This point will be further discussed in the methods section.

After the advent of the HAS-BLED, there have been attempts to derive models from more recent population of oral anticoagulant users to better predict major bleeding. Table 3 identifies the main major bleeding risk scores established after the HAS-BLED, while emphasizing differences and similarities of the predictors used in each existing score as well as the analyses used to derive them.

	HAS-BLED	**ATRIA**	**HEMMORR2-HAGES**	**ORBIT**	**ABC**	**ABS**
Outcome definition	Major bleeding (any location) in year of follow-up	Major bleeding (any location) in year of follow-up	Major bleeding (any location) in year of follow-up	Major bleeding (any location) in 2 years of follow-up	Major bleeding (any location) in year of follow-up	Major bleeding (any location) in year of follow-up
Prediction method	Logistic regression	Cox proportional hazards regression	Narrative review	Cox proportional hazards regression	Bootstrapped cox proportional hazards regression	Bootstrapped cox proportional hazards regression
Age (definition, RR value)	**Age>64:** OR=2.66 (1.33-5.32)	**Age>74:** HR=1.99	**Age>74:** NA	**Age>74:** HR= 1.38 (1.17-1.61)	**Age (continuous):** HR~1.4 95% CI 1.2-1.6	**Age (continuous):** HR=1.02 (1.02,1.03)
Sex (definition, RR value)	NA	NA	NA	NA	NA	**Male:** HR=0.95 (0.89,1.02)

Co-morbidities (definition, RR value and 95% Confidence intervals)	**Hypertension:** OR=0.60 (0.21-1.72) **Renal disease:** OR=2.86 (1.33-6.18) **Liver disease:** NE** **Prior stroke:** OR=0.94 (0.32-2.86) **Prior major bleeding:** OR=7.51 (3.00-18.78) **Labile INR:** NE**	**Hypertension:** HR=1.38 **Severe renal disease:** HR=2.53 **Prior bleeding (excluding non-gastrointestinal extracranial bleeding):** HR=1.56 **Anemia:** HR=3.27	**Hypertension:** NA **Hepatic or renal disease:** NA **Prior stroke:** NA **Prior major bleeding:** NA **Anemia:** NA **Reduced platelet count:** NA **Cancer history:** NA **Excessive fall risk:** NA **Genetic predisposition:** NA	**Renal disease:** HR=1.44 (1.21-1.72) **Prior major bleeding:** HR=1.73 (1.34-2.23) **Anemia:** HR= 2.07 (1.74-2.47)	**Prior bleeding** NA **Troponin T concentration** HR~1.4 95% CI 1.2-1.6 **GDF-15 concentration** HR~1.2 95% CI 1.1-1.3 **Hematocrit** HR~1.3 95% CI 1.1-1.6	**Renal disease:** HR=1.35 (1.24-1.46) **Prior stroke:** HR=1.15 (1.07-1.23) **Prior bleeding:** HR=1.27 (1.18-1.36) **Anemia:** HR=1.38 (1.29-1.48) **COPD** HR=1.21 (1.13-1.30) **CAD:** HR=1.11 (1.03-1.19) **Heart failure:** HR=1.24 (1.16-1.33) **Diabetes:** HR=1.24 (1.16-1.32) **Cancer history** HR=1.19 (1.10-1.28)
Medication use (definition, RR value)	**ASA: clopidogrel or NSAID use:** OR=0.81 (0.43-1.51)	NA		**Antiplatelet agent use:** HR=1.51 (1.30-1.75)	NA	**Antiplatelet agent use:** HR=1.25 (1.16-1.35) **Antiarrhythmic** HR=0.75 (0.66-0.85) **Diuretics:** HR=1.17 (1.10-1.26)
Lifestyle factors (RR value)	**Alcohol abuse:** OR=0		**Alcohol abuse:** NA			
Reference	Pisters et al., 2010 Lip et al. 2011	Singer et al., 2011	Gage et al., 2006	O'brien et al., 2015	Hijazi et al., 2016	J'Neka et al., 2018

Table 3. Major bleeding predictors in anticoagulant users with atrial fibrillation from existing risk scores.

*NA means that the value was not evaluated.

ATRIA and HEMORR$_2$ HAGES

Like for the HAS-BLED, the candidate predictors used to derive the ATRIA (Anticoagulation Risk Factors in Atrial Fibrillation) and HEMORR$_2$ HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke) were also created using pre-direct oral anticoagulant era bleeding risk factors [111, 112]. As its name suggests, the HEMORR$_2$ HAGES incorporates hepatic or renal disease (Cr >2.5 mg/dL or end-stage renal failure; cirrhosis or end-stage liver failure), alcohol abuse (ICD-9 codes : 291.0-2, 303.x, 305.0x, 571.0-3, 535.3), malignancy history (ICD-9 codes: 141-172, 174-208), age greater than 75, reduced platelet count or function (ASA use, thrombocytopenia or hemophilia; patient charts),

prior major bleeding (patient charts), hypertension (401.0, 402.0x, 403.0x, 404.0x, 405.0x), anemia (Hgb <13 g/dL for men and <12 g/dL for women), genetic factors (CYP2C9 mutations), high risk of falling defined by the presence of dementia or a risk of falling (according to patient charts), and prior strokes (ICD-9 codes: 434-436) [111]. The score was created from three pre-existing bleeding risk stratification schemes identified by literature review without using any prediction method [111]. Meanwhile, the ATRIA incorporated anemia (HR=3.27), severe renal disease (dialysis or GFR <30 mL/min; HR=2.53), age greater than 75 (HR=1.99), prior bleed (HR=1.56) and hypertension history (HR=1.38) [112]. The predictors were selected using bootstrapped cox regressions from a set of candidate predictors from 6 bleeding risk scores identified by literature review [112]. Despite its limitations, the ATRIA score has the advantage of being the most parsimoniousness one to date.

ORBIT-AF

Despite a few commonalities, there are clear distinctions between direct oral anticoagulant and warfarin-associated risk factors attributable to the pharmacokinetic and pharmacodynamic differences. The three previous scores did not account for bleeding risk factors relevant to direct oral anticoagulant users. For this reason, the ORBIT-AF score has been developed while accounting for both warfarin and dabigatran users from the RE-LY clinical trial. The score incorporates age > 75 years old (HR=1.38 95% CI 1.17-1.61), prior bleeding (HR=1.73 95% CI 1.34-2.23), anemia (HR=2.07 95% CI 1.74-2.47), GFR <60 mL/min/1.73 m2 (HR=1.44 95% CI 1.21-1.72) and antiplatelet agent use (HR=1.51 95% CI 1.30-1.75). The predictors were identified from a list of candidate predictors from the original ORBIT-AF registry. A Cox regression with a backward selection was used and the five values with the greatest chi-squared values were selected for the score [113].

ABS

Ultimately, the ABS (anticoagulation-specific bleeding score) has been recently developed using data from all currently available oral anticoagulants indicated for atrial fibrillation. From the 35 candidate predictors used in the 4 aforementioned scores and identified in a literature review, 13 demographic and clinical variables that were selected using bootstrapped Cox regressions to create the ABS score. The variables included age (continuous; HR=1.02 95% CI 1.02-1.03), kidney disease (HR=1.35 95% CI 1.24-1.46), COPD (HR=1.21 95% CI 1.13-1.30), prior

bleeding event (HR=1.27 95% CI 1.18-1.36), anemia (1.38 95% CI 1.29-1.48), heart failure (1.24 95% CI 1.16-1.33), antiplatelet therapy (1.25 95% CI 1.16-1.35), diuretics (1.17 95% CI 1.10-1.26), diabetes mellitus (1.24 95% CI 1.16-1.32), cancer history (1.19 95% CI 1.10-1.28), antiarrhythmic agents (0.75 95% CI 0.66-0.85), ischemic stroke (1.15 95% CI 1.07-1.23), CAD (1.11 95% CI 1.03-1.19), male sex (0.95 95% CI 0.89-1.02), dabigatran (0.74 95% CI 0.66-0.83; ref. warfarin), rivaroxaban (1.01 95% CI 0.90-1.15; ref. warfarin) and apixaban (0.59 95% CI 0.45-0.78; ref. warfarin). Contrary to the previous score, the ABS has left its score in the form of the survival model from which it was derived, thus making the tool less user-friendly that its predecessors [114]. One advantage of this study is that it identifies major bleeding risk factors relevant to warfarin users and all direct oral anticoagulant users indicated for atrial fibrillation.

ABC

The ABC score (age, biomarkers, clinical) is a biomarker-based score that has been derived from the ARISTOTLE clinical trial cohort. It incorporates age (HR~1.4 95% CI 1.2-1.6), 3 biomarkers (growth differentiating factor-15, GDF-15, [HR~1.4 95% CI 1.2-1.6]), a marker of oxidative stress cardiac troponin, a marker of myocardial injury [HR~1.4 95% CI 1.2-1.6] and blood concentration of haemoglobin [HR~1.2 95% CI 1.1-1.3]) and prior bleeding via clinical chart review (HR~1.3 95% CI 1.1-1.6). These variables were selected from a bootstrapped Cox proportional hazard regression. They used the five predictors with the greatest HR values in a final model that was fit with 19 candidate predictors. The candidate predictors originated from the ABC stroke risk score and a post-hoc analysis from the ARISTOTLE trial [115].

Although prediction models are not designed for causal inference, the consistent selection of specific major bleeding predictors across different models can be a useful indicator of risk factors that are important to consider clinically. For instance, age (albeit defined differently across models) is consistently selected with HR values ranging from 1.02 to 1.99. Hypertension, on the other hand, was not selected for all models, but still consistently used in many of the risk scores. Renal disease (moderate or severe) and prior bleeding, on the other hand, were consistent major bleeding predictors with HRs exceeding 1.35 and 1.27, respectively. Lastly, antiplatelet use was incorporated in the risk scores with relative consistency with HR values exceeding 1.25. Despite the limitations in the analyses used to derive the HAS-BLED, it seems that it is still the

model that incorporates the most important (consistently selected) predictors relative to the other risk scores.

The performances of the most common major bleeding prediction models

HAS-BLED

Within its derivation cohort, which constituted users of all the oral antithrombotic agents available at the time of the study, the HAS-BLED performed moderately well in predicting major bleeding with a c-statistic of 0.72 (95% CI 0.65-0.79). In the warfarin group alone, the HAS-BLED performed similarly with a c-statistic of 0.69 (95% CI 0.59-0.80) [25]. The HAS-BLED was then formally validated in a cohort of rivaroxaban users with a similar performance (c-statistic=0.68, p=0.07) [116]. A recent meta-analysis of the HAS-BLED identified a pooled c-statistic of 0.65 (95% CI 0.61-0.69) based on 7 studies. The same meta-analysis showed that the HAS-BLED underpredicted major bleeding risk among patients at moderate and high risk of the outcome [117]. However, the moderate risk subgroup displayed significant heterogeneity.

Most of the other scores were compared to the HAS-BLED in a full population of oral anticoagulant users or a subgroup of this population in their corresponding derivation studies. Albeit less frequent, they have also been tested for their ability to detect MB in separate independent studies. Table 4 compares the derivation and validation cohort characteristics and performances of the HAS-BLED to that of the scores that followed it.

	HAS-BLED	**ATRIA**	**HEMMOR2HAGES**	**ORBIT**	**ABC**	**ABS**
Derivation cohort characteristics	Warfarin, antiplatelet and non-OAC users	Warfarin users	Warfarin and ASA users	Warfarin, dabigatran and antiplatelet users	Clinical trial warfarin, and apixaban users (ARISTOTLE cohort)	Warfarin and DOAC users
Validation cohort population	**Validation 1:** 7 warfarin user cohorts (from a meta-analysis) **Validation 2:** Clinical trial rivaroxaban users	**Validation:** 3 warfarin user cohorts (from a meta-analysis)	**Validation:** 5 warfarin user cohorts (from a meta-analysis)	**Validation 1:** Clinical trial warfarin and rivaroxaban users **Validation 2:** Clinical trial warfarin users	Clinical trial warfarin, and dabigatran users (RE-LY cohort)	Warfarin, DOAC and antiplatelet users

Model performance metric	**Derivation:** C-statistic **Validation 1:** C-statistic NRI (relative to ATRIA and HEMM.), IDI (relative to ATRIA and HEMM.) **Validation 2:** C-statistic	**Derivation:** C-statistic **Validation:** C-statistic, NRI (relative to HAS-BLED), IDI (relative to HAS-BLED)	**Derivation:** Bootstrapped c-statistic **Validation:** C-statistic, NRI (relative to HAS-BLED)	**Derivation:** C-statistic **Validation 1:** C-statistic **Validation 2:** C-statistic	**Derivation:** Bootstrapped c-statistic **Validation:** Bootstrapped c-statistic	**Derivation:** C-statistic **Validation:** C-statistic
Model performance with major bleeding	**Derivation :** 0.72 ($p<0.05$) **Validation 1 :** 0.65 (0.61-0.69) NRI : conflicting findings IDI: $p<0.05$ in favor of HAS-BLED **Validation 2 :** 0.65 ($p>0.05$; NS)	**Derivation:** 0.69 ($p<0.05$) **Validation 1:** 0.63 (0.56-0.72) NRI/IDI: $p<0.05$ in favor of HAS-BLED	**Derivation:** 0.67 ($p<0.05$) **Validation:** 0.63 (0.61-0.66) NRI: conflicting findings	**Derivation:** 0.67 (0.64, 0.69) **Validation 1:** 0.62 (0.60, 0.64) **Validation 2:** 0.61 (0.51-0.70)	**Derivation:** 0.68 (0.66-0.70) **Validation:** 0.71 (0.68-0.73)	**Derivation:** 0.68 (0.67-0.69) **Validation:** 0.68 (0.67-0.69)
Model performance major bleeding subtypes	**Validation (intracranial hemorrhage) :** 0.58 (0.54-0.61)	**Validation (intracranial hemorrhage):** NS	**Validation (intracranial hemorrhage):** NS	**Derivation (intracranial hemorrhage):** 0.69 (0.63, 0.74)	**Validation (intracranial hemorrhage):** 0.66 (0.62-0.69)	NA
Calibration*	Inadequate	Adequate	NA	Adequate	Adequate	Adequate
References	Pisters et al., 2010 Zhu et al., 2015 Gorman et al., 2016 Hijazi et al., 2016	Singer et al., 2011 Zhu et al., 2015 Apostolakis, 2012	Gage et al., 2006 Zhu et al., 2015 Apostolakis, 2012	O'brien et al., 2015 Senoo et al, 2016	Hijazi et al., 2016	J'Neka et al., 2018

Table 4. Studies evaluating the performance of existing major bleeding risk scores.

*Adequate calibration implies a non-statistically significant Hosmer-Lemeshow test or no statistically significant difference from baseline in a calibration plot. **NA means that the value was not evaluated.

ATRIA and HEMORR$_2$ HAGES

In its original study, the HEMORR$_2$ HAGES had an adequate discrimination of major bleeding in different patient populations of antithrombotic agent users with a c-statistics of 0.67 ($p<0.05$) among warfarin users, 0.72 ($p=0.05$) among ASA users and 0.66 ($p<0.05$) among non-antithrombotic agent users. Calibration was originally not assessed [111]. The score was validated in five separate study in a meta-analysis of studies in which the HAS-BLED was compared to other scores. It displayed a pooled c-statistic of 0.63 95% CI 0.56-0.72 [117]. Of note, each of the five studies used cohorts of warfarin users and, to our knowledge, the

$HEMORR_2$ HAGES was never validated as a standalone (without being compared to other scores).

Shortly after, the ATRIA score was derived from a cohort of warfarin users. It performed on a similar scale than the HAS-BLED with c-statistics of 0.69 (95% CI 0.66-0.71) and 0.74 (95% CI 0.72-0.76) for the 3 category and continuous versions of the score, respectively. The score was also deemed well-calibrated [112]. Subsequently, a real-world study comparing the HAS-BLED's performance to that of the ATRIA suggested that the ATRIA score performed on a similar scale as it did in its derivation cohort (c-statistic=0.68 95% CI 0.65-0.71), but not as well when it was dichotomized as greater than or less than 5 (c-statistic=0.59 95% CI 0.55-0.62) [118]. Once more, the calibration of neither models was assessed.

ORBIT-AF

In its derivation cohort of randomized clinical trial dabigatran and warfarin users, the continuous model had a c-statistic of 0.69 (95% CI 0.67, 0.72), but performed less well in the validation cohort of randomized clinical trial rivaroxaban and warfarin users (c-statistic 0.63 95% CI 0.61, 0.65). The categorical score displayed similar results with c-statistics of 0.67 (0.64, 0.69) and 0.62 (0.60, 0.64) in its derivation and validation cohorts, respectively. However, the ORBIT-AF was shown to overpredict major bleeding risk among patients with moderate major bleeding risk [113]. A study aimed at externally validating the ORBIT and HAS-BLED scores in a real-world Asian population found that the score performed similarly to its original study with a c-statistic of 0.64 95% CI 0.59-0.70 and generally adequate calibration with a mild overprediction of risk among patients at moderate major bleeding risk [119].

ABS

The ABS had the same discrimination values in its derivation and validation cohorts with a c-statistic of 0.68 (95% CI 0.67, 0.69). It performed more poorly in a subpopulation of older patients (>75 years old) with c-statistic of 0.63 (95% CI 0.61-0.64) and 0.63 (95% CI 0.62-0.65) in the derivation and validation cohort, respectively. This subgroup analyses were performed since a categorical definition of age was not included in the model. The model was adequately calibrated in the full derivation and validation cohort as well as the older patient subgroup [119]. However, the score has yet to be validated in another study.

ABC

The ABC score performed equally well in its full derivation and validation cohorts (from the ARISTOTLE and RE-LY trials respectively) with c-statistics of 0.68 (0.66-0.70) and 0.71 (95% CI 0.68-0.73), respectively [115]. In subpopulations of non-bleeders, warfarin users, direct oral anticoagulant users as well as antiplatelet or NSAID users, the score performed similarly to the full cohort with c-statistics of 0.68 (0.65-0.70), 0.68 (0.65-0.70), 0.68 (0.65-0.71) and 0.69 (0.66-0.72). A second validation study among patients from the RE-LY trial reached a similar conclusion with the score displaying a c-statistic of 0.70 ($p<0.05$) and adequate calibration [120].

Comparative performances

All original studies for major bleeding score indicated superior performance to previous scores. Therefore, a few external studies have been conducted to compare the performances of different scores using the HAS-BLED as benchmark given its widespread clinical use. A meta-analysis found little difference in discrimination between the HAS-BLED (c-statistic=0.65 95% CI 0.61-0.69 across 7 studies), the $HEMORR_2HAGES$ (c-statistic=0.63 95% CI 0.6-0.66 across 5 studies) and ATRIA (c-statistic=0.63 95% CI 0.56-0.72 across 3 studies) [121]. However, the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) values, metrics suggested to better represent the comparative performance of two models relative to the c-statistic, were also assessed. Assuming the existence of meaningful risk categories (a pre-determined cut-off value within the models being compared), the NRI calculates how many individuals will be classified in each risk category for the two compared scores and compares these classifications to the real event rates. The IDI does so for every possible risk category cutoff value [121, 122]. Out of three studies, two identified a statistically significant NRI in favor of the HAS-BLED when comparing to the ATRIA (+31.0% and +19.6%, $p<0.05$ for both studies) and $HEMORR_2HAGES$ (+26.0%, $p<0.05$ for one of the studies) [117]. Likewise, a single study identified a statistically significant IDI (+10.0%, $p<0.05$) in favor of the HAS-BLED [117].

Subsequently, a study seeking to validate the superiority of the ORBIT-AF score to the HAS-BLED found no statistically significant differences in discrimination with c-statistics of 0.63 (95% CI 0.56-0.71) and 0.70 (95% CI 0.62-0.77), respectively [123]. A Spanish retrospective hospital-based study found little difference in discrimination between the HAS-BLED, (c-

statistic=0.62 95% CI 0.59-0.65), the ATRIA, (c-statistic=0.61 95% CI 0.58-0.64) and ORBIT (c-statistic=0.59 95%CI 0.56-0.62) (182). Ultimately, a comparative meta-analysis of the HAS-BLED and ORBIT found that, across 7 studies, the HAS-BLED had similar discrimination relative to the ORBIT (c-statistics=0.63 95% CI 0.60-0.66 and 0.65 95% CI 0.60-0.69, respectively). However, unlike the HAS-BLED, the ORBIT seemed to underpredict bleeding across all major bleeding risk strata [124].

Ultimately, in a real-world atrial fibrillation patient population, the HAS-BLED outperformed the ABC score while both scores performed sub-optimally (c-statistics of 0.583 versus 0.518, respectively; $p<0.05$) [125]. Conversely, among patients from the ENGAGE-AF trial, the ABC outperformed the HAS-BLED in detecting major bleeding (c-statistics of 0.69, 95% CI, 0.66-0.71 versus 0.62, 95% CI, 0.60-0.64, respectively; $P<0.001$) [126]. Finally, the ABS score, being the most recent score, only outperformed the other scores in an internal validation and requires further external validation.

Taken altogether, these studies suggest that the HAS-BLED performs better or similarly to the other existing scores across different populations of oral anticoagulant users, while the ABS score showed the most promise in predicting major bleeding in a current population of direct oral anticoagulant and warfarin users in a single study. However, scores were not always compared using adequate prediction model comparison metrics (the NRI and IDI) [127]. Moreover, although major bleeding is the outcome of interest for most clinicians, it is still important to consider the risk factors of major bleeding subtypes. Intracranial hemorrhage, gastrointestinal bleeding and non-GI extracranial bleeds may differ in etiology, incidence, their impact on patient quality of life and post-bleed oral anticoagulant adherence.

Major bleeding subtype prediction models

While the identification of intracranial hemorrhage risk factors is very important due to their high associated fatality rate, other MB subtypes are also highly pertinent on account of their frequency. The identification of gastrointestinal bleeding risk factors and emphasizing them in prescription guidelines would help make practices, such as endoscopy, more routine. This would not only help mitigate the safety risks associated with oral anticoagulant use, but, as mentioned in earlier sections, also lessen the impact of these adverse events on patient quality of life and

lessen the impact on drug effectiveness by improving adherence. While the predictors of GIB are poorly researched in post-warfarin era oral anticoagulant user populations, non-GI extracranial bleeding such as hematuria and genitourinary bleeding have not been evaluated at all in this population. The predictors of major bleeding subtypes identified by the most comprehensive models specifically designed to detect them are summarized in Table 5.

	Qbleed UGIB		**QBleed ICH**		**Lauffenburger et al.**
Outcome definition	Upper GIB (GI ulcer, melena, haematemesis, laceration, varices, haemorrhagic gastritis, and unspecified GIB) within 5 years		Subarachnoid, intracerebral, subdural, extradural, or unspecified bleeding within 5 years		Upper, lower and unspecified GIB within the study period
Prediction method	Cox proportional hazard regression with backward selection		Cox proportional hazard regression with backward selection		Cox proportional hazard regression
Sociodemographic variables	Age/10^-1: evaluated, but not reported Ethnicity Townsend material deprivation score *Models are stratified by sex		Age/10^-1: evaluated, but not reported Ethnicity Townsend material deprivation score *Models are stratified by sex		**Age<55:** Ref **Age 55-64:** 1.54 (0.89-2.68) **Age 65-74:** 2.72 (1.59-4.65) **Age>75:** 4.52 (2.68-7.64) *US region also evaluated
Sex (definition)	NA		NA		**Male sex :** 0.78 (0.64-0.95)
Co-morbidities (definition; HRs)	**Women** **Previous bleed** 2.26 (2.10 to 2.43) **Esophageal varices** 3.35 (2.58 to 4.33) **Chronic liver disease or pancreatitis** 2.81 (2.44 to 3.23) **Atrial fibrillation** 1.24 (1.11 to 1.39) **Venous thromboembolism** 1.16 (1.04 to 1.30) **Congestive heart failure** 1.41 (1.25 to 1.59) **Treated hypertension** 1.06 (1.01 to 1.12) **Cancer** 1.22 (1.13 to 1.31) **Anemia** 1.68 (1.52 to 1.85)	**Men** **Previous bleed** 2.11 (1.98 to 2.26) **Esophageal varices** 2.07 (1.59 to 2.68) **Chronic liver disease or pancreatitis** 3.08 (2.75 to 3.45) **Atrial fibrillation** 1.21 (1.07 to 1.36) **Venous thromboembolism** 1.12 (0.98 to 1.28) **Congestive heart failure** 1.46 (1.30 to 1.64) **Treated hypertension** 1.11 (1.05 to 1.16) **Cancer** 1.39 (1.29 to 1.50) **Anemia** 1.79 (1.64 to 1.96)	**Women** **Previous bleed** 1.33 (1.23 to 1.44) **Esophageal varices** 3.22 (2.07 to 5.01) **Chronic liver disease or pancreatitis** 1.92 (1.50 to 2.46) **Atrial fibrillation** 1.17 (1.01 to 1.35) **Treated hypertension** 1.06 (1.00 to 1.14) **Anemia** 1.62 (1.41 to 1.88)	**Men** **Previous bleed** 1.32 (1.23 to 1.42) **Esophageal varices** 1.72 (1.01 to 2.91) **Chronic liver disease or pancreatitis** 2.21 (1.79 to 2.73) **Atrial fibrillation** 1.36 (1.18 to 1.57) **Treated hypertension** 1.18 (1.09 to 1.26) **Anemia** 1.61 (1.41 to 1.83)	**Hypertension** 1.07 (0.85-1.35) **Renal disease** 1.67 (1.24-2.25) **Prior stroke** 0.96 (0.71-1.30) **Prior bleeding** 1.32 (1.01-1.72) **Anemia** 1.25 (0.97-1.62) **Venous thromboembolism** 1.14 (0.72-1.80) **Peripheral vascular dis.** 1.28 (0.94-1.73) **Coronary artery dis.** 1.37 (1.10-1.69) **Heart failure:** 1.24 (1.16-1.33) **Hyperlipidemia:** 0.88 (0.72-1.07) **Diabetes:** 1.21 (0.98-1.48) **Peptic ulcer disease** 1.59 (0.59-4.28) **H. Pylori infection** 4.75 (1.93-11.68)

Lifestyle factors (definition; HRs)	**Smoking status (cigarettes/day)** Non-smoker: Ref Former smoker: 1.09 (1.04 to 1.14) Light smoker (1-9): 1.31 (1.23 to 1.40) Moderate smoker (10-20): 1.30 (1.19 to 1.43) Heavy smoker (>=20): 1.56 (1.39 to 1.74) **Alcohol intake (units/day)** None: Ref Trivial (<1): 0.87 (0.83 to 0.92) Light (1-2): 0.79 (0.74 to 0.85) Moderate (3-6): 0.99 (0.92 to 1.07) Heavy (7-9): 1.85 (1.47 to 2.32) Very heavy (>9): 2.85 (2.27 to 3.59)	**Smoking status (cigarettes/day)** Non-smoker: Ref Former smoker: 1.12 (1.07 to 1.18) Light smoker (1-9): 1.40 (1.33 to 1.49) Moderate smoker (10-20): 1.39 (1.28 to 1.52) Heavy smoker (>=20): 1.62 (1.48 to 1.76) **Alcohol intake (units/day)** None: Ref Trivial (<1): 0.82 (0.78 to 0.86) Light (1-2): 0.82 (0.77 to 0.87) Moderate (3-6): 0.89 (0.85 to 0.95) Heavy (7-9): 1.35 (1.21 to 1.50) Very heavy (>9): 1.79 (1.57 to 2.04)	**Smoking status (cigarettes/day)** Non-smoker: Ref Former smoker: 1.12 (1.04 to 1.21) Light smoker (1-9): 1.80 (1.63 to 1.99) Moderate smoker (10-20): 2.12 (1.86 to 2.43) Heavy smoker (>=20): 2.37 (2.01 to 2.81) **Alcohol intake (units/day)** None: Ref Trivial (<1): 0.96 (0.89 to 1.03) Light (1-2): 1.03 (0.92 to 1.16) Moderate (3-6): 1.05 (0.93 to 1.18) Heavy (7-9): 2.13 (1.49 to 3.03) Very heavy (>9): 2.62 (1.73 to 3.97)	**Smoking status (cigarettes/day)** Non-smoker: Ref Former smoker: 1.04 (0.97 to 1.12) Light smoker (1-9): 1.44 (1.31 to 1.58) Moderate smoker (10-20): 1.72 (1.50 to 1.97) Heavy smoker (>=20): 1.72 (1.47 to 2.00) **Alcohol intake (units/day)** None: Ref Trivial (<1): 0.84 (0.77 to 0.92) Light (1-2): 0.85 (0.77 to 0.93) Moderate (3-6): 0.97 (0.88 to 1.06) Heavy (7-9): 1.58 (1.34 to 1.86) Very heavy (>9): 1.48 (1.14 to 1.92)	
Medication use (definition; HRs)	**Anticoagulant (warfarin or DOAC)** 3.89 (2.75 to 5.49) **Antiplatelet drug** 1.26 (1.19 to 1.33) **NSAIDs** 1.16 (1.11 to 1.21) **Corticosteroid** 1.26 (1.18 to 1.34) **Antidepressant** 1.57 (1.51 to 1.64) **Phenytoin or carbamazepine** 1.40 (1.18 to 1.65)	**Anticoagulant (warfarin or DOAC)** 4.43 (3.32 to 5.92) **Antiplatelet drug** 1.21 (1.15 to 1.28) **NSAIDs** 1.09 (1.05 to 1.14) **Corticosteroid** 1.26 (1.17 to 1.36) **Antidepressant** 1.69 (1.60 to 1.78) **Phenytoin or carbamazepine** 1.30 (1.10 to 1.55)	**Anticoagulant (warfarin or DOAC)** 3.62 (1.25 to 10.49) **Antiplatelet drug** 1.31 (1.22 to 1.41) **Antidepressant** 1.31 (1.22 to 1.40) **Phenytoin or carbamazepine** 2.20 (1.79 to 2.70)	**Anticoagulant (warfarin or DOAC)** 3.99 (1.86 to 8.55) **Antiplatelet drug** 1.27 (1.17 to 1.36) **Antidepressant** 1.38 (1.27 to 1.50) **Phenytoin or carbamazepine** 2.03 (1.64 to 2.53)	**Antiplatelet agent use:** 1.49 (1.19-1.88) **Antiarrhythmic** 1.10 (0.89-1.37) **Digoxin:** 1.33 (1.05-1.68) **β-blocker:** 0.97 (0.78-1.19) **Calcium channel blocker:** 0.97 (0.80-1.18) **ACE inhibitors or angiotensin receptor blockers:** 1.23 (0.99-1.51) **Statins:** 1.08 (0.87-1.34) **Corticosteroid:** 1.17 (0.95-1.45) **NSAID:** 1.04 (0.82-1.31) **GI protective agent:** 1.02 (0.78-1.35) **High dabigatran dose:** 1.14 (0.86-1.53)
Reference	Hippisley-Cox and Coupland, 2014		Hippisley-Cox and Coupland, 2014		Lauffenburger et al.,2015

Table 5. Major bleeding subtype predictors in the most relevant existing models.

*NA means that the value was not evaluated.

HAS-BLED

Although it is the most commonly used major bleeding risk score, the HAS-BLED's ability to predict intracranial hemorrhage is poorly researched. One real-world study found that, among warfarin users with atrial fibrillation, the score had a c-statistic of 0.527 (0.513-0.541) [126]. The HAS-BLED performed somewhat better in a cohort of Danish real-world warfarin, ASA, warfarin-ASA and non-users of either medication (c-statistic~0.6) [128].

As the most frequent bleeding outcome impacting anticoagulated patients, an understanding of the mechanisms that lead to anticoagulant-associated gastrointestinal bleeding is essential to better characterize their risk factors. The proposed pathogenesis of gastrointestinal bleeding dictates that it can stem from systemic effects or topical effects triggered by incomplete drug absorption in the upper GI tract, the direct corrosive effect from certain components in the dabigatran pill formulation and the inhibition of mucosal healing [60]. Although these factors are not accounted for by the HAS-BLED, it has been shown to detect gastrointestinal bleeding fairly well with a c-statistic of 0.74 (95%CI, 0.71-0.76) in a Spanish-based hospital study [129]. However, a real-world study comparing its performance to the ABC score suggested the contrary with the HAS-BLED displaying a c-statistic of 0.596 [125]. An additional limitation of using the HAS-BLED to predict this outcome is that it has been shown to underpredict gastrointestinal bleeding in subpopulation with risk factors specific to gastrointestinal bleeding that are unaccounted for by the HAS-BLED such as H. Pylori infection [130]. Generally, with the exception of a few underpowered studies, the HAS-BLED's discrimination with respect to gastrointestinal bleeding has been understudied and requires validation. With only a single study suggesting that the ORBIT-AF can detect risk of small bowel bleeding, the association between the ATRIA, ORBIT-AF and HEMORR$_2$HAGES scores and gastrointestinal bleeding is even more dubious.

ATRIA and HEMORR$_2$ HAGES

The HEMORR$_2$ HAGES detected slightly better than random (c-statistic=0.525, 95% CI 0.510-0.539), while the ATRIA could not effectively predict intracranial hemorrhage in a cohort of warfarin users with atrial fibrillation [126]. Similarly to the HAS-BLED, the

HEMORR$_2$HAGES displayed moderate discrimination (c-statistic~0.6) within a cohort of Danish warfarin, ASA, warfarin-ASA users and non-users of either medication [128]. Neither score has been tested for its ability to predict gastrointestinal bleeding or non-gastrointestinal extracranial bleeding.

ORBIT-AF

The original ORBIT-AF study evaluated its ability to detect intracranial hemorrhage within the derivation cohort. Here, the ORBIT had a c-statistic of 0.69 95% CI 0.63-0.74 [113]. However, with the exception of one study suggesting that it performed no better than chance, there have been very few validation studies for this outcome [128]. The score has also not been tested for its ability to predict gastrointestinal bleeding or non-gastrointestinal extracranial bleeding.

ABC

In its derivation cohort, the ABC bleeding score predicted intracranial hemorrhage moderately well with a c-statistic of 0.66 (95% CI 0.62-0.69) [115]. In a real-world validation study of the ABC score's discriminatory potential, its c-statistic was inferior to that of the HAS-BLED for an intracranial hemorrhage-gastrointestinal bleeding composite outcome (0.593 and 0.527, respectively, $p<0.05$). Moreover, its statistically significant negative NRI relative to the HAS-BLED further supported the findings about the inferiority of the score to the HAS-BLED [125].

A single validation study among showed the ABC score predicted gastrointestinal bleeding no better than random with a c-statistic of 0.519 [125]. However, it has been tested for its ability to predict non-gastrointestinal extracranial bleeding.

QBleed

Few models were designed solely for the detection of major bleeding subtypes as opposed to major bleeding. The Qbleed prediction models for the 5-year risk of intracranial hemorrhage are some of the few major bleeding (or major bleeding subtype) models for which the discriminatory potential exceeded a c-statistic of 0.70 (the proposed cut-off value for good prediction models) [131]. Two separate models were generated derived from British oral anticoagulant non-users and users for each sex using Cox proportional hazard models and backward selection. These methods selected the Townsend material deprivation score (5 unit increases), ethnicity (relative to Caucasian), smoking status (relative to non-smokers), magnitude of alcohol intake (relative to

non-drinkers), any previous bleeding (timeline undefined), esophageal varices, liver disease/pancreatitis, atrial fibrillation, treated hypertension, most recent platelet count, anticoagulant use, antiplatelet use, antidepressant use and anticonvulsant use. The female and male sex models had c-statistics of 0.847 (95% CI 0.838 to 0.856) and 0.812 (95% CI 0.80 to 0.824), respectively. The performances of the models were confirmed in a subsequent validation study of UK scoring tools for different health outcomes in which the Qbleed for intracranial hemorrhage had c-statistics ranging between 0.79 and 0.85 depending on the validation cohort and sex [132]. Nonetheless, given that the prediction models mostly involved patients who have not used any anticoagulant (~99%), contains very little direct oral anticoagulant users (>0.05%) and did not it focus on an patients with atrial fibrillation, it is unlikely that they can adequately predict intracranial hemorrhage in our population of interest.

One of the most comprehensive models for detecting the 5-year risk of upper gastrointestinal bleeding were the Qbleed models. Just like with the intracranial hemorrhage QBleed models, two separate models were generated derived from a British patient population for each sex using Cox proportional hazard models. The method selected the same variables as the intracranial hemorrhage QBleed with the addition of venous thromboembolism, congestive heart failure and cancer. The female and male sex models had c-statistics of 0.766 (95% CI 0.758-0.775) and 0.747 (95% CI 0.738-0.756), respectively [131]. Validation study findings showed that the models performed similarly in other cohorts of British patients with c-statistics ranging between 0.747 and 0.775 [132].

Lauffenburger et al. gastrointestinal bleeding prediction model

Female sex (HR=1.28, 95% CI 1.05-1.56), age over 75 age between 65 and 75 and age between 55 and 65 (relative to 55 and under; HR=4.52, 95% CI 2.68-7.64, HR=2.72, 95% CI 1.59-4.65, HR=1.54, 95% CI 0.89-2.68, respectively), renal impairment (HR=1.67, 95% CI 1.24-2.25), heart failure (HR=1.25, 95% CI 1.01-1.56), coronary artery disease (HR=95% CI 1.37 95% CI 1.10-1.69), a history of bleeding, alcohol abuse (HR=2.57, 95% CI 1.52-4.35), prior Helicobacter Pylori infection (HR=4.75, 95% CI 1.93-11.68), concomitant antiplatelet use (HR=1.49, 95% CI 1.19-1.88) and digoxin use (HR=1.33, 95% CI 1.05-1.68) were identified as the most gastrointestinal bleeding important predictors in a U.S. cohort of dabigatran-users [95].

However, this study's caveats are that the prediction method that was used to derive the model was not robust. Moreover, neither model performance, nor calibration was assessed.

Female sex (HR=1.28, 95% CI 1.05-1.56), age over 75 age between 65 and 75 and age between 55 and 65 (relative to 55 and under; HR=4.52, 95% CI 2.68-7.64, HR=2.72, 95% CI 1.59-4.65, HR=1.54, 95% CI 0.89-2.68, respectively), renal impairment (HR=1.67, 95% CI 1.24-2.25), heart failure (HR=1.25, 95% CI 1.01-1.56), coronary artery disease (HR=95% CI 1.37 95% CI 1.10-1.69), a history of bleeding, alcohol abuse (HR=2.57, 95% CI 1.52-4.35), prior Helicobacter Pilori infection (HR=4.75, 95% CI 1.93-11.68), concomitant antiplatelet use (HR=1.49, 95% CI 1.19-1.88) and digoxin use (HR=1.33, 95% CI 1.05-1.68) were identified as the most gastrointestinal bleeding important predictors in a U.S. cohort of dabigatran-users [95]. However, this study's caveats are that the prediction method that was used to derive the model was not robust. Moreover, neither model performance, nor calibration was assessed.

Comparative performance

Among real-world warfarin users with atrial fibrillation, the HAS-BLED had a statistically significant NRI relative to the ATRIA (+0.060, 95% CI +0.026-+0.093) and ORBIT-AF (+0.048 95% CI +0.013-+0.082), but not the HEMORR$_2$HAGES (+0.030 95% CI -0.001-+0.060) [126]. Conversely, the HEMORR$_2$HAGES and HAS-BLED were not shown to display any difference among warfarin, ASA and warfarin-ASA users in a Danish cohort (185). In a Chinese population, the HAS-BLED outperformed the ATRIA (NRI=+0.324, 95% CI +0.321-+0.327), ORBIT-AF (NRI=+0.375 95% CI +0.373-+0.378) and HEMORR$_2$HAGES (NRI= +0.295 95% CI +0.292-+0.298) [133]. In its original study, the ABC-bleeding score outperformed the HAS-BLED, but not the ORBIT in detecting intracranial hemorrhage with c-statistics of 0.66 (95% CI 0.62-0.69), 0.58 (95% CI 0.54.0.61), and 0.60 (95% CI 0.56-0.64), respectively [115]. However, these findings have never been validated.

Most recent prediction models for major bleeding subtypes have not been compared to others, but it is important to understand the extent to which they perform well in the populations they are each, respectively, derived from. Table 6 describes the performance of these models and their associated derivation and validation populations.

	Qbleed UGIB	QBleed ICH	Lauffenburger et al.
Derivation cohort characteristics	Warfarin, DOAC or OAC non-user *DOAC users (>0.05% of derivation cohort)	Warfarin, DOAC or OAC non-user *DOAC users (>0.05% of derivation cohort)	Dabigatran new users
Validation cohort population	Warfarin, DOAC or OAC non-user *DOAC (>0.05% of derivation cohort, likely)	Warfarin, DOAC or OAC non-user *DOAC (>0.05% of derivation cohort, likely)	NA
Model performance	**Internal Validation** Women: c-statistic=0.77 (0.76-0.78) Men: c-statistic=0.75 (0.74-0.76) **External validation** Women: c-statistic=0.78 (0.77-0.78) Men: c-statistic= 0.76 (0.75-0.76)	**Internal validation** Women: c-statistic= 0.85 (0.84-0.86) Men: c-statistic=0.81 (0.80-0.82) **External validation** Women: c-statistic=0.81 (0.80-0.82) Men: c-statistic=0.79 (0.78-0.80)	NA
Calibration	Qualitatively adequate, but no formal quantitative evaluation	Qualitatively adequate, but no formal quantitative evaluation	NA
References	Hippisley-Cox and Coupland, 2014 Hippisley-Cox et al., 2014	Hippisley-Cox and Coupland, 2014 Hippisley-Cox et al., 2014	Lauffenburger et al., 2015

Table 6. Studies evaluating the performance of existing major bleeding subtype risk scores.

*Adequate calibration implies a non-statistically significant Hosmer-Lemeshow test or no statistically significant difference from baseline in a calibration plot. **NA means that the value was not evaluated.

Although, the intracranial hemorrhage QBleed models were never formally compared to the HAS-BLED or any other score and were only reported to outperform them on the basis of their c-statistics [54]. However, this will require further confirmation. Thus, the HAS-BLED is the only score validated to outperform other scores and models in detecting intracranial hemorrhage beyond their derivation studies in our population of interest. Yet, it only does so moderately well.

Unlike with intracranial hemorrhage, the HAS-BLED performed similarly to the ATRIA and ORBIT in detecting gastrointestinal bleeding (c-statistics of 0.74, 95% CI 0.71-0.76, 0.71, 95% CI 0.68-0.74, and 0.69 95% CI 0.66-0.72, respectively) [129]. Conversely, the HAS-BLED was shown to outperform the ABC score (c-statistics of 0.596 and 0.519, respectively; $p<0.05$) in a validation study for the latter [125]. Meanwhile, the upper gastrointestinal bleeding QBleed was never formally compared to the HAS-BLED or any other score but seemed to outperform them all. However, it is important to consider that it has yet to be tested in our population of interest and unlikely to have a comparable discriminatory potential since it was not fully derived from our population of interest. Lastly, in addition only encompassing half of anticoagulant-associated gastrointestinal bleeding, upper gastrointestinal bleeding are proposed to be mechanistically different from them and thus associated with significantly different risk factors [60].

Although there is little evidence, the HAS-BLED seems to be the best available validated tool to detect intracranial hemorrhage in our population of interest. However, the predictors of gastrointestinal bleeding within this population are poorly studied. Moreover, to our knowledge, there isn't a single prediction model for non-GI extracranial bleeding.

Bleeding risk scores in clinical practice: a lack of consensus

The first major post-warfarin era consensus on the recommended use of the HAS-BLED was established in 2012. Both the European Society of Cardiology and the Canadian Cardiovascular Society recommended to use the score to identify patients at high risk of major bleeding (HAS-BLED $\geq$ 3) that would need closer follow-up. Meanwhile, just as is the case now, the HEMORR$_2$HAGES and ATRIA were not recommended due to their generally inferior prediction power relative to the HAS-BLED [134]. More recently, a study by the European Heart Rhythm Society reported many disparities between practices and monitoring guidelines in 2018, with 60% of clinicians using the HAS-BLED, 26.8% using the society's 2016 bleeding risk factors guidelines table, 13.3% using clinical judgment and none using the ABC score [135]. In 2019, an update of atrial fibrillation guidelines from the American College of Cardiology, American Heart Association, and Heart Rhythm Society recommended the HAS-BLED to monitor bleeding risk with no further details about other tools [19]. Conversely, a 2020 summary of American recommendations for atrial fibrillation management stipulated that the American College of Cardiology, American Heart Association, and Heart Rhythm Society questioned the clinical value of the HAS-BLED rather preferring direct comparisons of stroke and bleeding risks. Conversely, the American Academy of Family Physicians, the American College of Physicians and American College of Chest Physicians favored the use of the HAS-BLED in the estimation of bleeding risk [136]. Although the estimation and management of major bleeding risk lacks consensus, the atrial fibrillation guidelines from each of these groups consistently recommend using the CHA$_2$DS$_2$-VASc ($\geq$ 2) or one of its variants to drive the decision to prescribe anticoagulation, rather than considering major bleeding risk [18, 19, 135, 136].

The main knowledge gaps and their implications

Oral anticoagulant safety depends highly on the frequency of major bleeding monitoring in patients at high risk of this outcome. Adequate major bleeding monitoring hinges on the available knowledge on major bleeding risk factors in the most current population of oral anticoagulant users with atrial fibrillation. The advent of direct oral anticoagulants introduced the need to update our understanding of major bleeding risk factors and to potentially introduce new monitoring tools. Although some new tools are available and have been shown to test well in subpopulations of oral anticoagulant users, they still require improvement. For instance, Quebec and Canadian oral anticoagulant prescription guidelines, as outlined by the "*Dialogue avec votre patient*" and "*Guide d'usage optimal - fibrillation auriculaire chez l'adulte"* Quebec clinical diagnosis tools as well as the "Canadian Cardiovascular Society's Atrial Fibrillation Guidelines" contain gaps in information with regards to certain risk factors. For one, there is insufficient data on the impact of severe renal impairment (CrCl<30ml/min) among edoxaban and dabigatran users [14, 15, 23, 137]. Moreover, the HAS-BLED, recommended by most atrial fibrillation guidelines, lacks external validation in large North American and European populations of specific oral anticoagulant users (i.e. dabigatran and apixaban users) as well as real-world direct oral anticoagulant users with atrial fibrillation, has performed sub-optimally (c-statistic<0.70) in current validation studies, and has been shown to underperform in predicting major bleeding subtypes. Thus, there is a need for newer scores derived from up-to-date oral anticoagulant user data [117]. Lastly, the lack of prediction models for intracranial hemorrhage, gastrointestinal bleeding and, most notably, non-gastrointestinal extracranial bleeding, among direct oral anticoagulant and warfarin users with atrial fibrillation makes it difficult to accurately monitor major bleeding and major bleeding subtypes to actively engage in their prevention.

Research objectives

The overarching goal of this study is to develop predictive models for major bleeding and for the most prevalent major bleeding subtypes (gastrointestinal bleeding and non-GI extracranial bleeding) based on data of patients with atrial fibrillation taking any type of oral anticoagulant. Thus, our primary objective is to establish a model to predict major bleeding in a population of all oral anticoagulant users with atrial fibrillation. Our secondary objective is to identify important predictors of the most prevalent major bleeding subtypes (gastrointestinal bleeding and non-gastrointestinal extracranial bleeding). Our tertiary objective is to compare the predictors of

major bleeding between warfarin and direct oral anticoagulant users as well as doing so with the major bleeding subtypes. Our final objective is to evaluate the discriminatory potential of the major bleeding model fit to all oral anticoagulant users for gastrointestinal bleeding and non-gastrointestinal extracranial bleeding.

Methods

Data source

The Régie de l'Assurance Maladie du Québec (RAMQ) possesses three databases. The first contains basic demographic data such as age, sex and timeline of healthcare coverage. The second contains information on medical services rendered and their associated medical diagnoses, which are identified via International Classification of Diseases (9th Revision) or ICD-9 codes and their updated analogs, ICD-10 codes. The final database contains extensive data on inpatient drug prescription and claims. In 1990, a study evaluated the missingness and precision of important data, such as Quebec healthcare insurance number, the name of dispensed medications, their quantity and the date and duration of dispensation, in these databases. It found that these variables were only missing or out of range in 0-0.4% of records. Moreover, up to 83% of these dispensations were filled by the patient during which both patient and drug were correctly identified by their relevant identifiers [138, 139]. Effectively, the data for this study was compiled from a dataset of the RAMQ drug and medical services database linked to the "Maintenance et exploitation des données pour l'étude de la clientèle hospitalière" (Med-Echo) hospitalization database using encrypted patient healthcare insurance numbers [140]. Meanwhile, the Med-Echo database contains precise inpatient data on patients admitted for surgery in any Quebec hospital center and includes non-primary diagnoses associated with a hospitalization. Thus, the linkage of these two databases is crucial since it greatly improves the detectability of co-morbidities in pharmacoepidemiologic studies.

Study design

To evaluate our research questions, we conducted a cohort study using a cohort that was previously put together by Dr. Perreault. As the outcomes had occurred prior to the study period,

the study could be done more rapidly and was less costly than if another study design was used with the exception of a nested case-control study. However, since the outcomes of interest (major bleeding and its subtypes) were common and it is methodologically difficult to derive prediction models using case-control data, the benefits of a cohort study outweighed the latter [141]. Since the dataset had a vast range of variables to select from, we could choose a set of clinically pertinent candidate predictors that was sufficiently large to establish a model with adequate predictive power.

Selection criteria

Inclusion criteria

We first identified adult patients with a primary or secondary diagnosis of atrial fibrillation who had been hospitalized for all cause and discharged in the community between January 2010 and December 2017. We did so using atrial fibrillation ICD-9 and ICD-10 codes with median positive predictive values of 89% and 95.7% in two distinct validation studies [142, 143]. A systematic review of medical databases suggested that the ICD-9 codes had a 89% and 77% median positive predictive values for prevalent and incident atrial fibrillation, respectively [142]. Inpatient data from Med-Echo hospitalization records were crucial to calculate the HAS-BLED and CHA_2DS_2-VASc scores as well as to allow for the evaluation of important clinical candidate predictors.

Patients that were included in the cohort had to be covered by the RAMQ for one year prior to hospitalization and have a filled prescription of at least one of the following oral anticoagulants during the study period: dabigatran, rivaroxaban, apixaban or warfarin. Cohort entry (study index) was defined as the first filled oral anticoagulant prescription after hospitalization discharge. Since they also had to be new users of oral anticoagulants, we only included patients who did not have an oral anticoagulant claim within a year from cohort entry.

Exclusion criteria

We excluded patients with all other indications for oral anticoagulation to ensure all cohort patients are solely anticoagulated for stroke prophylaxis due to atrial fibrillation. Other indications included recent post-orthopedic surgery within 6 weeks before hospitalization and a primary or secondary diagnosis of venous thromboembolism during the hospitalization period.

We also excluded patients with oral anticoagulant contraindications (end-stage chronic renal disease or dialysis for a minimum of 3 months) within 3 years preceding hospitalization. Finally, we excluded those having undergone cardiac catherization, stenting, bypasses, cerebrovascular procedures or defibrillator implantation within 3 months prior to hospitalization and those having underwent valve replacement within 5 years prior to hospitalization. Please refer to the following flowchart for the details about the selection process and the population size associated with each selection step.

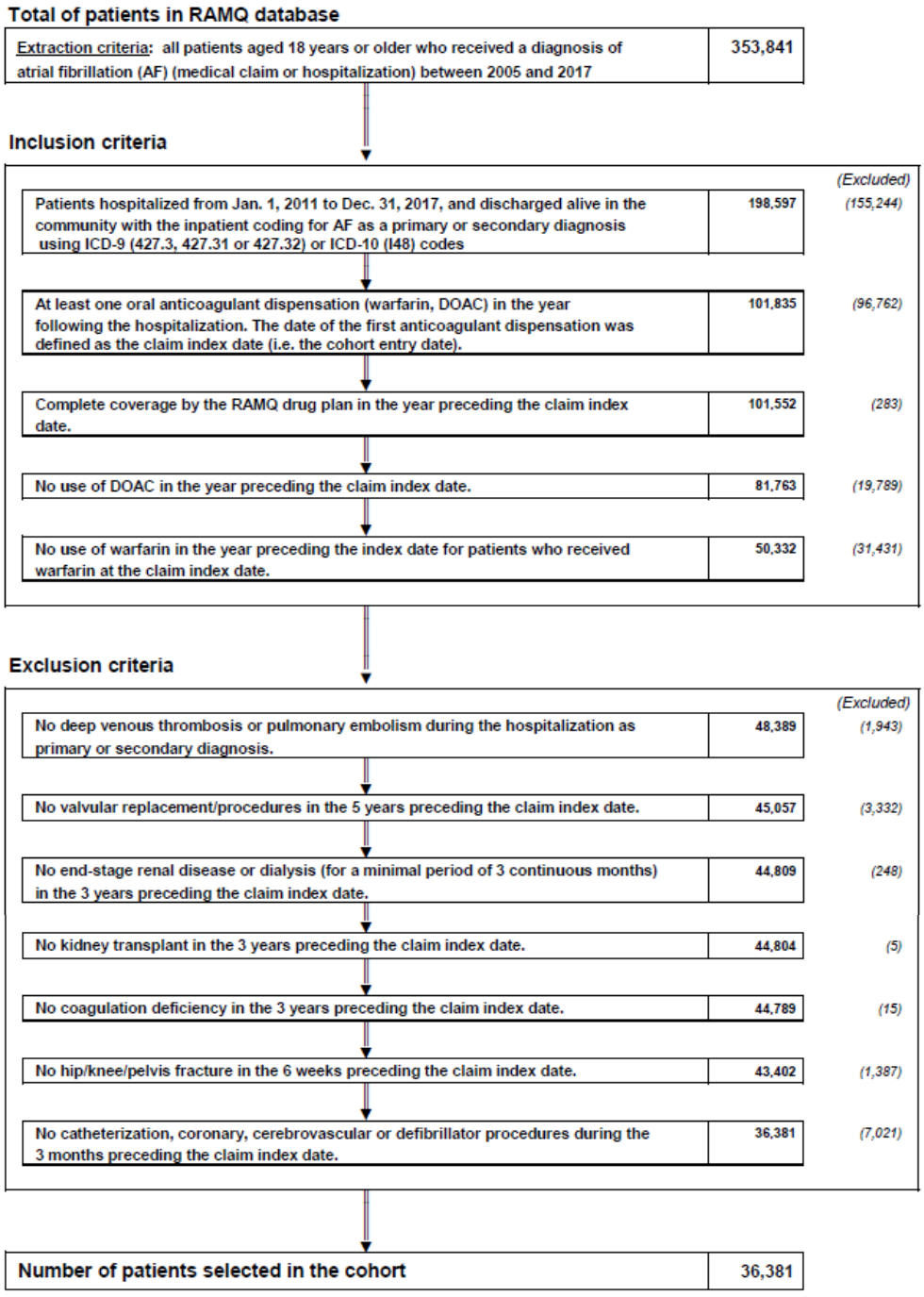

Figure 3. Population-based cohort definition flowchart.

*AF: atrial fibrillation; OAC: oral anticoagulant, DOAC: direct oral anticoagulant, RAMQ: Régie d'Assurance-Maladie du Quebec.

Study variables

Oral anticoagulant exposure

We defined oral anticoagulant exposure as the first claim filed for any oral anticoagulant after hospital discharge (i.e. the cohort entry date) with no oral anticoagulant claim one year prior to cohort entry (see Fig 4 for the study timeline). Patients were classified in accordance to the oral anticoagulant type they were using at cohort entry (warfarin or direct oral anticoagulants). Oral anticoagulant exposure will be evaluated as candidate predictor. The approved doses of direct oral anticoagulant use in Canada are 110 mg and 150 mg for dabigatran, 15 mg and 20 mg for rivaroxaban, and 2.5 mg and 5 mg for apixaban. Warfarin was not categorized in accordance to dose. Given that the database had very few users of edoxaban, they were not included in our cohort. By only selecting new users for our cohort as opposed to prevalent users, we could avoid missing early adverse events (e.g. warfarin-associated bleeding typically happens in the first 90 days) [30]. We could also establish a clearer temporal sequence between exposure and baseline or pre-exposure covariates [144]. Moreover, a prevalent user design would have led to a disproportionate selection of warfarin users and a survival bias given that patients who have been treated for a long time are more likely to be sicker.

Primary and secondary outcomes

The primary outcome of this study was major bleeding. These included major gastrointestinal bleeding, non-gastrointestinal extracranial bleeding and intracranial hemorrhage, which were defined using 6 observational studies [145-150]. The secondary outcomes were the aforementioned major bleeding subtypes. Both the primary and secondary outcomes were defined as the first of each respective bleeding outcome leading to a hospitalization, while the subsequent bleeds were not considered in our outcome definition. As such, if two or more bleeding events of the same type were to occur, competing risk is inconsequential as the only the first is considered. Similarly, if two or more bleeding events were to occur at separate locations during follow-up,

we do not suspect a competing risk due to the rarity of this scenario (24 or 2.4% of patients who bled).

They were defined with ICD-9 and ICD-10 codes from inpatient claims on account of their high accuracy (see appendix, table S1). The definition of major bleeding included ICD-9 and ICD-10 codes for traumatic hemorrhagic stroke, non-traumatic hemorrhagic stroke, upper gastrointestinal bleeding, lower gastrointestinal bleeding, hematuria, hemoptysis, vitreous bleeding, urogenital bleeding, hemarthrosis, hemopericardium, hemoperitoneal major bleeding, unspecified major bleeding, and post-bleed anemia. These codes were highly valid with positive predictive value ranging from 85% to 95% [151-154].

Patient follow-up started at cohort entry and ended at the earliest occurrence of one of the following events: a major bleeding event, the end of insurance coverage, death of any cause one year of follow-up in the absence of a bleeding outcome or the end of the study follow-up period (December 31st, 2018). As was the case in previous prediction studies, treatment discontinuation or switching did not act as censorship criteria [25, 113, 114]. Lastly, since follow-up started after the first oral anticoagulant claim, 85% of the first oral anticoagulant claims occurred within 2 weeks from hospital discharge and oral anticoagulant effect peaks at most within 96 hours (in the case of warfarin), a major bleeding event can feasibly happen rapidly after this claim and an immortal time bias is unlikely (Fig 4).

Covariates: baseline characteristics and candidate predictors

While baseline characteristics are meant to summarize important attributes of patients enrolled in the beginning of a study and preliminarily assess associations to our study outcomes, the selection of candidate predictors hinges on maximizing the predictive power of the ensuing model. In the case of our study, while the overlap between the two sets of variables was significant, it was an important distinction to make.

Our baseline characteristics were defined as follows. Sociodemographic variables (age, sex, and material and social deprivation indices) were defined at cohort entry. Material and social deprivation indices were measured using their respective Pampalon indices [155]. Associated co-morbidities were assessed up to three years prior to cohort entry [156, 157]. They consisted of stroke/transient ischemic attack, hypertension, dyslipidemia, cardiomyopathy, coronary artery disease, myocardial infarct, peripheral vascular disease, venous thromboembolism, chronic heart

failure, anemia, chronic kidney disease, chronic kidney disease (< 30 ml/min), acute renal failure, liver disease, diabetes mellitus, asthma and chronic obstructive pulmonary disease, history of major (not minor) bleeding, and prior Helicobacter Pylori infection. It is important to note that chronic renal failure (< 30 ml/min) was estimated using Med-Echo hospitalization data with positive and negative predictive values ranging from 94.5% to 97.7% and 91.1% to 94.2%, respectively [158]. Hypertension, diabetes (with or without), prior acute myocardial infarction, COPD, chronic (30-60 ml/min) and acute renal failure, peripheral vascular disease all had positive predictive values exceeding 80% [156]. The CHA_2DS_2-VASc score, a modified HAS-BLED excluding labile international normalized ratio, and the Charlson-Deyo comorbidity index, were assessed up to 3 years before cohort entry (see appendix, table S2) [128, 159]. Finally, we documented baseline concomitant medication use, which included antiplatelets, proton pump inhibitors, non-steroidal anti-inflammatory agents, digoxin, amiodarone, antidepressants, β-blockers, calcium channel blockers, inhibitors of renin-angiotensin system, diuretics, loop diuretics, and antidiabetics, within 2 weeks before cohort entry (see appendix, table S3).

The variables that were to be evaluated as predictors of any major bleeding or major bleeding subtypes were selected on the basis of availability in our dataset and clinical relevance. Clinical relevance was defined as inclusion in bleeding scores, significant differences in baseline measurements, or a strong association with major bleeding based on narrative review [76, 95, 110, 128]. These consisted of age >=75 vs <75 years old, sex, prior co-morbidities (stroke/transient ischemic attack, hypertension, dyslipidemia, cardiomyopathy, coronary artery disease, myocardial infarction, peripheral vascular disease, venous thromboembolism, chronic heart failure, chronic kidney disease, chronic kidney disease (< 30 ml /min), acute renal failure, liver disease, asthma and chronic obstructive pulmonary disease, history of major bleeding, and prior Helicobacter Pylori infection) and prior medication use (antiplatelets, proton pump inhibitors, non-steroidal anti-inflammatory agents, antidepressants, and antidiabetics), up to 2 weeks prior to cohort entry (Fig 4).

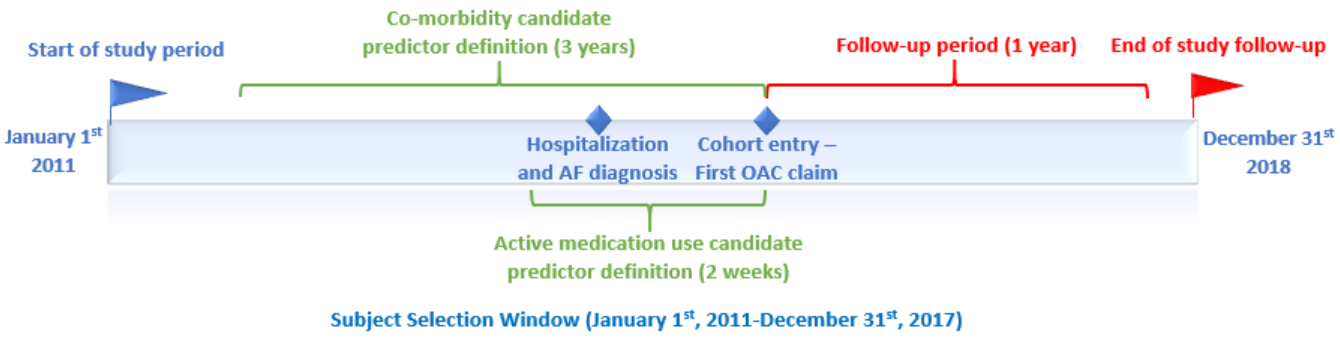

Figure 4. Study timeline.

*AF: atrial fibrillation; OAC: oral anticoagulant, RAMQ: Régie d'Assurance-Maladie du Quebec

Sample size

Since our cohort was previously established, it was only possible to determine the number of candidate predictors that it would be possible to evaluate in our models, rather than determining the sample size necessary to evaluate predetermined candidate predictors. As recommended by the TRIPOD guidelines for clinical prediction score derivation, the minimal sample size hinges on the total number of events, not the total number of patients [160]. While the 10 event per candidate predictor (EPP) is typically used in prediction studies, a review of the sample size requirements of penalty-based regression methods for the detection of rare outcomes suggested otherwise. In studies in which the outcomes are rare and there are noise predictors (predictors presenting possible redundant information), LASSO regression was shown to yield stable predictions (neither overfitted nor underfitted models) with an EPP of 5. Assuming a limit of 10, evaluating 28 candidate predictors would have required around 280 events which would have been sufficient to generate robust models for any bleeding outcome in our full cohort with events ranging from 438 to 1027. Assuming an EPP limit of 5, our study would have required a sample with at least 140 outcomes, in which case we had enough events to detect any major bleeding subtype in any treatment group (between 167 and 528 in our treatment groups). Another simple way of evaluating minimal sample size for a binary outcome is by making sure that the sample size is sufficient to estimate of the overall risk of the lest frequent outcome. With the exclusion of intracranial hemorrhage, we can consider the rarest outcome for which there is incidence data recorded in the literature to be major gastrointestinal bleeding. Thus, assuming a conservative

outcome proportion of 0.0082, a margin of error of 0.0021 and an alpha of 0.05, we would need at least 7099 patients to precisely detect major gastrointestinal bleeding in the smallest subgroup of oral anticoagulant users [161, 162]. Of note, no previous MB prediction studies provided any justification of their sample size.

	MB	GIB	NGIB	MB	GIB	NGIB	MB	GIB	NGIB
	All OAC			Warfarin			DOAC		
10 events per candidate predictor	280*	280*	280*	280	280	280	280	280	280
5 events per candidate predictor**	140*	140*	140*	140*	140*	140*	140*	140*	140*

Table 7. Sample size justification for the evaluation of 28 candidate predictors in each subgroup.

*The number of outcomes in these groups would be sufficient to yield robust prediction models.
**In a simulation study, it was found that under the assumption that outcomes are rare and that noise predictors (predictors presenting redundant information) are present, LASSO regression was shown to yield stable predictions (neither overfitted, nor underfitted models) with an events per candidate predictor ratio of 5.

Analyses

Cohort description

We generated descriptive data for warfarin, direct oral anticoagulant and all oral anticoagulant users with and without gastrointestinal bleeding, non-gastrointestinal extracranial bleeding and any major bleeding. We calculated percentages for categorical variables and means with standard deviations for the continuous ones. We did not include intracranial hemorrhage since there were too few events for the information to be meaningful.

Incidence rate of major bleeding

We generated Kaplan-Meier curves to graphically represent the cumulative incidence of each bleeding outcome (major bleeding, gastrointestinal bleeding, non-gastrointestinal extracranial bleeding and intracranial hemorrhage) within the first year after cohort entry for warfarin and each direct oral anticoagulant at both dosages available in Quebec. We used the log rank test to compare the unadjusted major bleeding, gastrointestinal bleeding, non-gastrointestinal extracranial bleeding and intracranial hemorrhage cumulative incidences of each direct oral anticoagulant treatment group to those of warfarin

users, as defined by the very first oral anticoagulant use during the study period. Finally, we determined the incidence rate of major bleeding, gastrointestinal bleeding, non-gastrointestinal extracranial bleeding and intracranial hemorrhage (events per 100 person-years) along with associated 95% CIs. Of note, all the incidence measurements only referred to the first of each respective bleeding outcomes.

Prediction modelling

Explanatory and predictive modelling are often confused in risk factor epidemiology. If a study defines a risk factor etiologically, then its overarching goal should be the identification of factors to modify or intervene on in a care setting. In prediction, risk factors are defined as predictors, which are used to identify individuals most at-risk of a specific outcome. Predictors are not necessarily a direct cause of an outcome as there are instances in which a causally-unrelated factor predicts an outcome better than a causally-related factor [163, 164]. In either case, the methods involved also vary [163]. Despite their differences, the effectiveness of both types of modelling relies on the concept of model fitting (the "proximity" of each datapoint to the model), while its usability (i.e. a more user-friendly model) relies on the concept of variable selection (the parsimoniousness of the final model).

The Least absolute shrinkage and selection operator (LASSO) is a method that has been designed to select the best set of predictors of an outcome from large datasets from high numbers of candidate predictors. It does so more robustly than other model fitting methods more commonly used in epidemiology [165]. It is a penalty-based method, meaning that it introduces a slight bias do the model to minimize the possibility of overfitting the model to the derivation data.

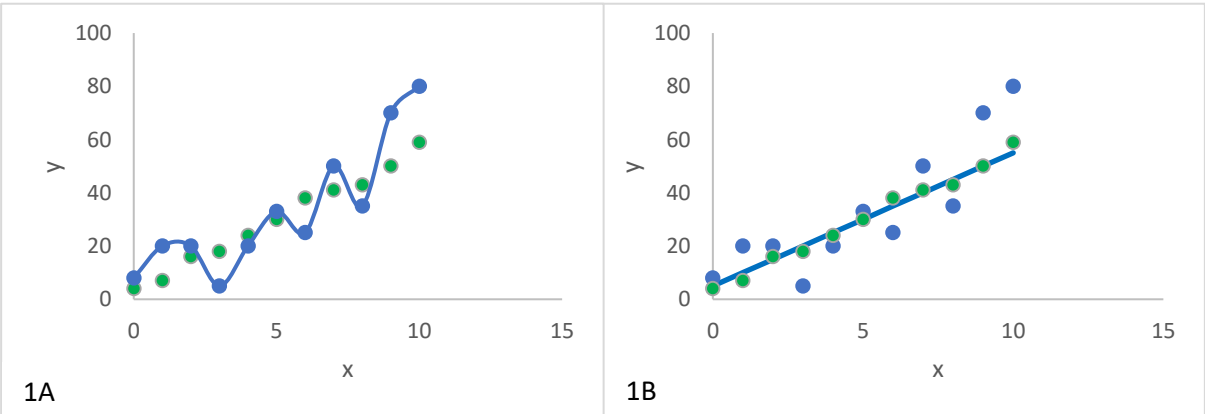

Figure 5. A graphical representation of overfitting and penalty-based modelling.

1A. An "overfit" model (blue curve) is one that is estimates the derivation data (blue dots) so well that it does not do so with the testing data (green dots). 1B. By using a model (blue line) that estimates the

derivation data (blue dots) slightly less well, we obtain a model that does so similarly well with the testing data (green dots).

LASSO uses an L1 penalty whose properties lead to both a reduction in the model coefficient values and cuts down the number of selected predictors resulting in a more interpretable (parsimonious) model. This property underlies the method's effectiveness in performing variable selection and adequate model fitting. LASSO assumes data sparsity (that the true model will have a small number of variables) and requires data completeness (no missing data) [165]. Adaptive LASSO (adaLASSO), a variant of the LASSO, attributes a larger penalty to smaller coefficients than larger coefficients. This property theoretically results in more consistent variable selection in a dataset with highly correlated variables and a more parsimonious model [165]. See figure 5 for the formulas associated with both methods.

For both methods, the robustness of the ensuing models is attributable to a method called cross-validation. The dataset in broken down into n equivalent groups (i.e. 10). A subset of the dataset is used to derive the model (ex. 9 groups) and the remainder is used to test how well the model fit to the derivation data is fitted to "non-derivation" or testing data. The process is repeated until all of n groups were used to test their corresponding subsets and the overall performance of the method used on each group is summarized using a sum of the 10 measurements of model fit (i.e. sum of squared residuals or likelihood). In our case, this process was repeated over one thousand distinct logistic-LASSO models with penalty different penalty values and the model with the best fit was selected. Due to the iterative testing process, the ensuing cross-validated models are significantly more robust. See figure 6 for a graphical representation of cross-validation.

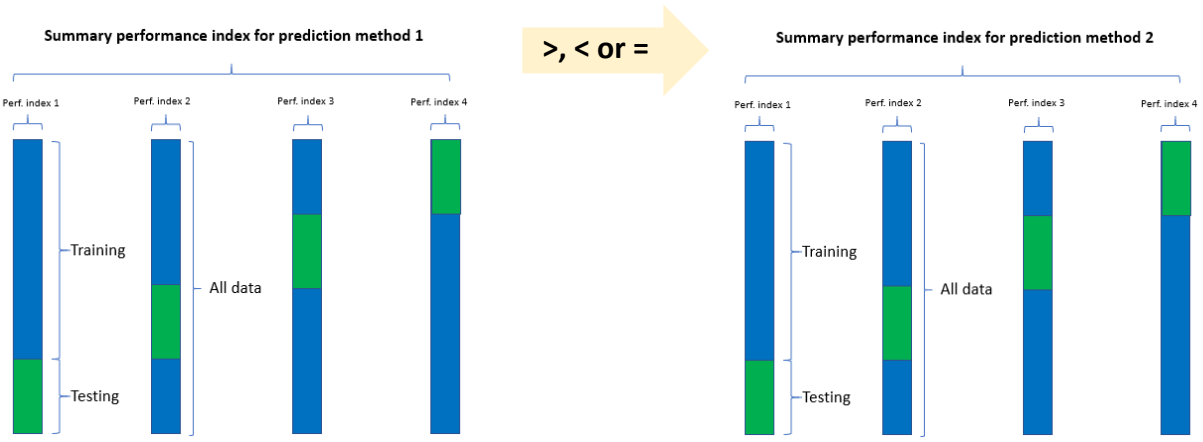

Figure 6. A graphical representation of cross-validation.

Cross-validation involves sequentially testing a given prediction method or model on different subsets of the full dataset (one full rectangle). A different subset (green section) of the full dataset (one large rectangle) is used to test the model that is derived from the training subset (blue section). Each testing subset will be associated with an index of predictive performance (likelihood, sum of squared residuals, prediction rate on dichotomous outcome, etc). Ultimately, the summary performance indices will be compared across the compared prediction methods or models to select the best one.

As these mathematical penalties can be incorporated into logistic regression, logistic-LASSO and logistic-adaLASSO was used [165]. For each outcome, odds ratios (ORs) were calculated for warfarin, direct oral anticoagulant and oral anticoagulant treatment groups using logistic-LASSO and logistic-adaLASSO regressions (R v3.6.2, package "glmnet"). The 95% confidence interval (CI) refers to a range of values that should contain the true value of a measurement 95% of the time. However, because they are difficult to interpret in penalty-based regression, 95% CIs were not presented for the OR estimates associated to each predictor. Moreover, confidence interval estimation for LASSO and adaLASSO regression have not yet been integrated to R for dichotomous outcomes.

To evaluate how well a model can classify patients who had major bleeding during follow-up and those that did not, a property called "discrimination", receiving operator curves were used. The associated cross-validated concordance (c-) statistics and their 95% CIs were reported (R v3.6.2, package cvAUC) [43]. Finally, the calibration of each model was quantitatively characterized using Hosmer-Lemeshow tests, a chi-squared test of mean squared differences of true and predicted outcome between quantiles of outcome measurements, and qualitatively characterized using calibration plots (R v3.6.2, packages "generalhoslem" and "PredictABEL") [122].

To meet our primary objective, the best model to predict major bleeding was identified. The "best" model was defined as having the best discrimination, adequate calibration and the most parsimoniousness within each oral anticoagulant subgroup (warfarin, direct oral anticoagulant and any oral anticoagulants). In accordance with our second objective, this process was repeated to build MB subtype models for each treatment group. For our third objective, it was determined whether the predictors of MB and their subtypes were similar across users of each oral anticoagulant category. Ultimately, the final major bleeding model's ability to detect the most prevalent major bleeding subtypes (gastrointestinal bleeding and non-gastrointestinal extracranial bleeding) was evaluated via discrimination and calibration testing using the previously discussed methods.

Finally, sensitivity analyses were added to evaluate the consequence of omitting patients who were lost to follow up (mostly due to death), non-adherent or adherent patients and patients who switched oral anticoagulant during follow-up on the performance of our global model. These omissions made little difference to discrimination and will be discussed in the study limitations.

Results

Déclaration des coauteurs d'un article

1. **Identification de l'étudiant et du programme**

   Jakub Qazi, 20140655

   M.Sc. Sciences Pharmaceutiques

   Médicaments et Santé des Populations

2. **Description de l'article**

Jakub Z. Qazi, BSc, Mireille E. Schnitzer, PhD, Robert Côté, MD, Marie-Josée Martel, PhD, Marc Dorais, MSc, and Sylvie Perreault, BPharm, PhD

Predicting Major Bleeding among Hospitalized Real-World Oral Anticoagulant Users with Atrial Fibrillation

L'article sera soumis au journal PlosOne.

3. **Déclaration de tous les coauteurs autres que l'étudiant**

À titre de coauteur de l'article identifié ci-dessus, je suis d'accord pour que *Jakub Qazi* inclut cet article dans son mémoire de maîtrise qui a pour titre *Les prédicteurs de saignements majeurs parmi des utilisateurs d'anticoagulants oraux souffrant de fibrillation auriculaire.*

Sylvie Perreault

Coauteur Signature Date

Mireille E. Schnitzer

Coauteur Signature Date

Robert Côté

Coauteur Signature Date

Marie-José Martel

Coauteur Signature Date

Marc Dorais

Coauteur Signature Date

Predicting major bleeding among hospitalized patients using oral anticoagulants for atrial fibrillation after discharge

Bleeding predictors in oral anticoagulant users

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Abstract

Aim: Real-world predictors of major bleeding (MB) have been well-studied among warfarin users, but not among all direct oral anticoagulant (DOAC) users diagnosed with atrial fibrillation (AF). Thus, our goal was to build a predictive model of MB for new users of all oral anticoagulants (OAC) with AF.

Methods: We identified patients hospitalized for any cause and discharged from 2011 to 2017 with a primary or secondary diagnosis of AF in Quebec's RAMQ and Med-Echo administrative databases. Cohort entry occurred at the first OAC claim. Patients were categorized according to OAC type. Outcomes were incident MB, gastrointestinal bleeding (GIB), non-GI extracranial bleeding (NGIB) and intracranial bleeding within 1 year of follow-up. Covariates included age, sex, co-morbidities (within 3 years before cohort entry) and medication use (within 2 weeks before cohort entry). We used logistic-LASSO and adaptive logistic-LASSO regressions to identify MB predictors among OAC users. Discrimination and calibration were assessed for each model and a global model was selected. Subgroup analyses were performed for MB subtypes and OAC types.

Results: Our cohort consisted of 14,741 warfarin, 3,722 dabigatran, 6,722 rivaroxaban and 11,196 apixaban users aged 70-86 years old. The important MB predictors were age, prior MB and liver disease with ORs ranging from 1.37-1.64. The final model had a c-statistic of 0.63 (95% CI 0.60-0.65) with adequate calibration. The GIB and NGIB models had similar c-statistics of 0.65 (95% CI 0.63-0.66) and 0.67 (95% CI 0.64-0.70), respectively.

Conclusions: MB and MB subtype predictors were similar among DOAC and warfarin users. The predictors selected by our models and their discriminative potential are concordant with published data. Thus, these models can be useful tools for future pharmacoepidemiologic studies involving older oral anticoagulant users with AF.
MESH key words: Anticoagulants, Atrial Fibrillation, Hemorrhage, Risk Factors, Pharmacoepidemiology

Key points

- The goal of this study was to derive robust predictive models for major bleeding (MB) and its subtypes from a real-world population of oral anticoagulant (OAC) users with atrial fibrillation.
- We derived predictive models for MB using data from a current OAC user population, and predictive models for key MB subtypes, such as gastrointestinal (GIB) and non-GI extracranial bleeding (NGIB).
- The most important predictors of MB that were selected by our models were age greater than 75, prior MB and liver disease. With some differences, these predictors were echoed by the GIB prediction model, but not the NGIB prediction model.
- The predictors of MB and GIB are similar between warfarin and direct oral anticoagulant users, while the opposite was true for NGIB.
- The performance of our models and the associated predictors are comparable to published MB predictive models, thus confirming their real-world relevance for future pharmacoepidemiologic studies involving older OAC users with AF.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide with increasing incidence due to the aging population [1-3]. It is associated with 5-fold and 3-fold increases in the risk of stroke and systemic embolism, respectively, with AF-associated stroke showing twice the risk of thirty-day all-cause mortality relative to non-AF associated stroke [4-6]. Before 2010, the vitamin K antagonist, warfarin, was the only medication used for stroke and systemic embolism prevention for AF patients at moderate and high risk of these outcomes [7-9]. However, warfarin is associated with a high risk of major bleeding (MB; 7.2 per 100 person-years), of which the most common type is gastrointestinal bleeding (GIB) and the most lethal type, intracranial hemorrhage (ICH) [9, 10]. In 2010, the first of the direct oral anticoagulants (DOAC) received approval from the US Food and Drug Administration for stroke prevention in patients diagnosed with atrial fibrillation (AF). In addition to circumventing the need for INR, the DOACs (dabigatran, rivaroxaban, apixaban and edoxaban) presented pharmacokinetic, pharmacodynamic and safety advantages over warfarin [9].

The four DOAC clinical trials for AF, namely RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE-AF, concluded non-inferior (or superior, in the case of ARISTOTLE) efficacy in reducing stroke, systemic embolism and all-cause mortality rates for each DOAC relative to warfarin and a lower risk of MB for all DOACs [11-16]. Given that randomized clinical trials (RCTs) do not account for real-world patient characteristics, pharmacoepidemiologic studies were required to complement and confirm RCT findings. According to meta-analyses of observational studies, DOAC effectiveness and safety with respect to MB risk was equivalent to warfarin's [17, 18]. Additionally, pooled DOAC analyses were associated with a greater GIB risk and lower ICH risk in patients over 75 years old [17, 18]. However, apixaban was the only DOAC with an associated lower risk of MB, GIB, and ICH relative to warfarin. It also had an associated lower risk of MB relative to the other DOACs [17, 19, 20]. Within each DOAC

subgroup, significant heterogeneity existed in at least one of the bleeding outcomes (MB, ICH or GIB) [17, 21, 22].

To ensure oral anticoagulant (OAC) safety, the risk-benefit profile needs to be carefully assessed while taking into account factors associated with a predisposition to bleeding [9]. The HAS-BLED, a scoring system used to identify patients at risk of bleeding, was developed based on warfarin user data and validated among rivaroxaban users [23, 24]. Since then, other MB prediction scores have been developed to improve bleeding prediction within this population. The HEMORR2AGES and ATRIA scores were derived from warfarin user data, while the ORBIT-AF also accounted for dabigatran user data. Ultimately, the ABS score was derived from DOAC and warfarin user data [9, 25-28]. However, given that the HAS-BLED is still the most commonly used score, a user-friendly MB prediction tool derived from a recent population of OAC users is essential.

Moreover, the HAS-BLED and other prediction models were developed to predict any MB, but it is also of interest to establish risk factors for specific MB subtypes, GIB, non-GI extracranial bleeding (NGIB) and ICH [9, 25-28]. The lack of prediction models for MB subtypes, and the lack of studies identifying MB subtype-specific predictors makes it difficult to accurately monitor MB and actively engage in their prevention [29, 30]. Specifically, we aimed to develop predictive models for MB and for the most prevalent MB subtypes (GIB and NGIB) based on data from real-world patients with AF taking any type of OAC. Therefore, our primary objective is to establish a model to predict MB in a population of all OAC users with AF. Our second objective is to identify important predictors of the most prevalent MB subtypes (GIB and NGIB). Our third objective is to compare the predictors of MB between warfarin and DOAC users as well as doing so with the MB subtypes. Our final objective is to evaluate the discriminative potential of the MB model fit to all OAC users for GIB and NGIB.

Methods

Data source

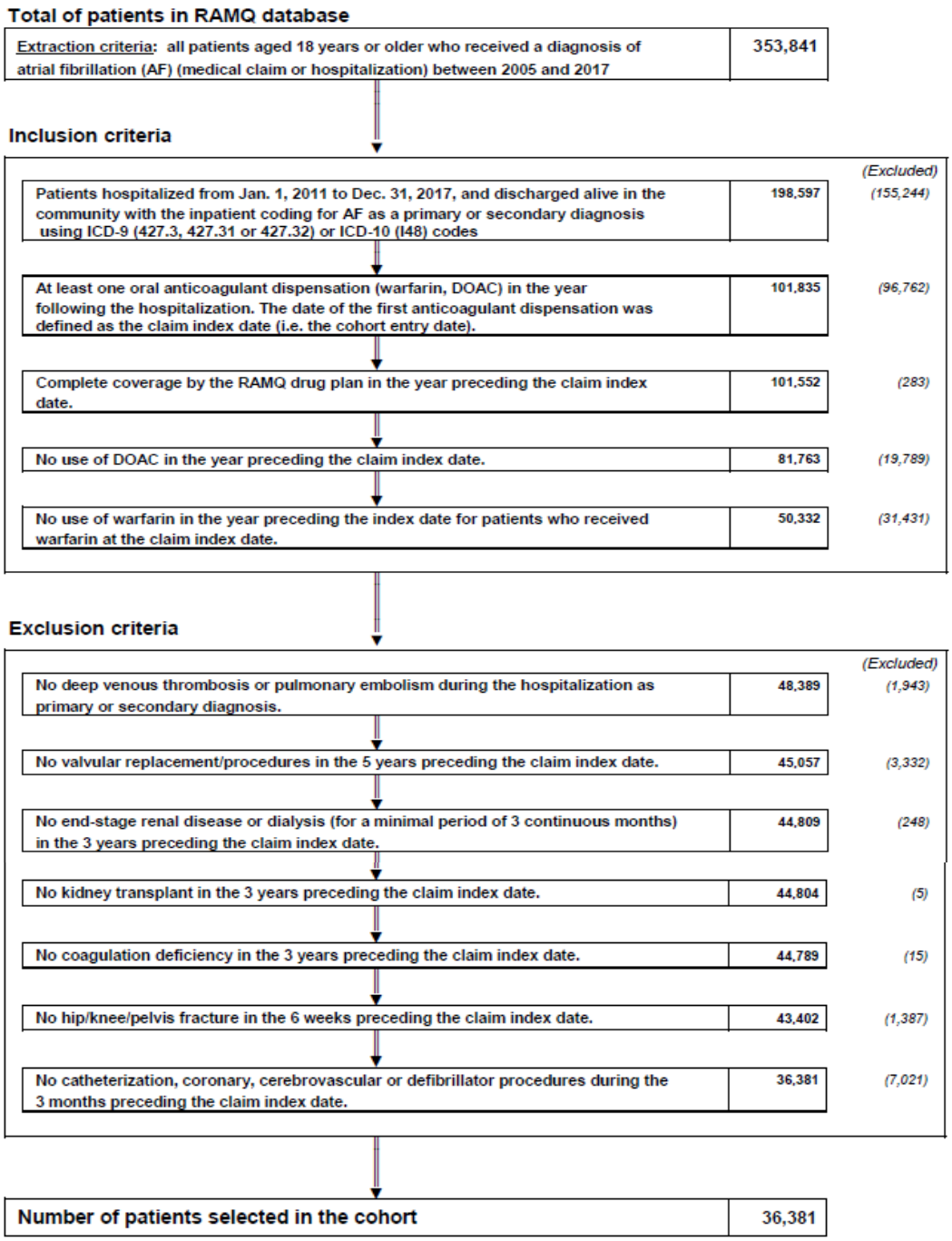
Administrative databases have proven to be a widely available and useful tool for pharmacoepidemiologic studies [31, 32]. The data for our study were compiled from a subset of the Régie de l'Assurance Maladie du Québec (RAMQ) drug and medical services database linked to the Med-Echo hospitalization database using encrypted patient healthcare insurance numbers [31, 33-36]. Quebec prescription and hospitalization data have been shown to have a high degree of completeness (with only 0 to 0.4% of data that was missing) and accuracy [31]. Thus, our cohort did not have any missing data.

Population-based cohort definition

We conducted a cohort study using drug claims and diagnostic coding data from the Quebec RAMQ and Med-Echo administrative databases. We identified adult patients who were hospitalized for all cause and discharged alive in the community from January 1, 2011 to December 31, 2017 with a primary or a secondary diagnosis of AF. They were identified using ICD-9 (427.3, 427.31 or 427.32) or ICD-10 (I48) codes [37, 38]. For patients with more than one admission with an AF diagnosis, we used the first date of admission. The ICD-9 codes displayed median positive predictive values of 89% and 95.7% in two distinct validation studies [37, 38].

Patients included in the cohort had to have a filled prescription of at least one of the DOACs (dabigatran, rivaroxaban and apixaban) or warfarin in the year following hospitalization, but could not have used any OAC one year prior to this claim. For this reason, they also had to have continuous RAMQ drug plan coverage for at least one year prior to cohort entry (see Fig 1). The date of cohort entry (or study index) was defined as the first filled OAC prescription after hospital discharge.

Fig 1. Population-based cohort definition flowchart.



AF: atrial fibrillation; OAC: oral anticoagulant, DOAC: direct oral anticoagulant, RAMQ: Régie d'Assurance-Maladie du Québec.

We excluded patients with OAC contraindications (end-stage chronic renal disease [ESRD] or dialysis for a minimum of 3 months) followed by kidney transplantation within 3 years before cohort entry. We also excluded patients with a non-AF indication for DOAC anticoagulation such as post-orthopedic surgery (hip or knee replacement 6 weeks before cohort entry) and a diagnosis of venous thromboembolism (defined as either deep vein thrombosis or pulmonary embolism) during the hospitalization period. Finally, we excluded those having undergone cardiac valve replacement up to 5 years prior to cohort entry.

Oral anticoagulant exposure

OAC exposure was defined as filing a new claim for warfarin or a DOAC (all dosages approved in Canada included) after hospital discharge. Given that the database had very few users of edoxaban, these patients were not included in our cohort. Patient treatment initiation was determined using dispensation dates of the OAC prescriptions. All individuals were new users, i.e., individuals who had not been exposed to any OAC at least one year prior to cohort entry.

Study Outcomes

The primary outcomes were MB including GIB, NGIB and ICH. MB, GIB, NGIB and ICH were defined as the first instance of each respective bleeding event leading to a hospitalization during follow-up and identified using ICD-9 and ICD-10 codes from inpatient claims (S1 Table). These outcomes were defined using 6 distinct observational studies [39-45]. When multiple of either MB subtypes occurred, only the first of that respective MB subtype was evaluated as the primary outcome (e.g. GIB was defined as the first GIB during the follow-up period). These codes have been externally validated with positive predictive value ranging from 85% to 95% [46-48]. Patient follow-up began from the first OAC claim until the earliest occurrence of one of the following events: MB event, end of coverage of the RAMQ drug insurance, date of death, 1 year of follow-up or end of the study.

Baseline characteristics and predictor candidates

Sociodemographic variables (age, sex, and material and social deprivation indices) were defined at cohort entry [49]. Associated morbidities were assessed up to 3 years prior to cohort entry. They included stroke/transient ischemic attack, hypertension, dyslipidemia, cardiomyopathy, coronary artery disease, acute myocardial infarction, peripheral vascular disease (PVD), chronic heart failure, anemia, chronic kidney disease (CKD), severe kidney disease (creatinine clearance < 30 ml /min), acute renal failure, liver disease, diabetes mellitus, asthma and chronic obstructive pulmonary disease (COPD), history of MB, and prior Helicobacter *Pylori* infection [40, 50, 51]. The CHA_2DS_2-VASc score (stroke risk), a modified HAS-BLED (bleeding risk) excluding labile INR, and the Charlson-Deyo comorbidity index, were assessed up to 3-years prior to cohort entry (S2 and S3 Tables for coding algorithms). Finally, we documented baseline medication use, which included antiplatelets, proton pump inhibitors (PPIs), non-steroidal anti-inflammatory agents (NSAIDs), digoxin, amiodarone, antidepressants, β-blockers, calcium channel blockers, inhibitors of renin-angiotensin system, diuretics, loop diuretics, antidiabetics up to 2 weeks prior to cohort entry.

Statistical analyses

First, we generated descriptive data for warfarin, DOAC and OAC new users with and without GIB, NGIB and MB. We calculated percentages for binary and categorical variables and means with standard deviations for continuous ones.

We determined the cumulative incidence of MB, GIB, NGIB and ICH (events per 100 person-years), respectively. We then generated Kaplan-Meier curves for each dose-stratified OAC treatment group to assess cumulative MB, GIB and NGIB incidences within the first year after cohort entry. We used the log rank test to compare each of the MB, GIB and NGIB cumulative incidences of each DOAC treatment group to those of warfarin users.

We selected candidate variables to be evaluated as predictors of any MB or MB subtypes based on availability in our dataset and clinical relevance, which was defined as inclusion in bleeding scores, significant differences in baseline measurements, or a strong association with MB based on narrative review [25, 29, 52]. We used the Least Absolute Shrinkage and Selection Operator (LASSO) method, which introduces a penalty/bias to each coefficient of a regression model to select relevant predictors and to minimize overfitting, and the adaptive LASSO (adaLASSO), which uses the same principle while applying a larger penalty to smaller coefficients than to larger ones [53, 54].

Both LASSO and adaLASSO penalties can be incorporated into logistic regression (logistic-LASSO and logistic-adaLASSO, respectively), which perform well when the true model is sparse [53, 54]. Given that the 10 events per predictor rule, proposed to be too conservative for penalty-based regression, was respected for each outcome in the OAC models, we deemed the sample size of this cohort to be sufficiently large to derive robust prediction models (S4 Table) [55]. Most notably, all available data were used to maximize the power and generalizability of the results.

For each outcome, we calculated odds ratios (ORs) for each covariate for the warfarin, DOAC and OAC treatment groups using logistic-LASSO and logistic-adaLASSO regressions (R v3.6.2, package "glmnet"). We did not include 95% confidence intervals (CIs) as it is challenging to interpret them in log-LASSO and log-adaLASSO modelling. We calculated cross-validated concordance statistics (c-statistics) and their 95% CIs using the area under Receiving Operator Curves (auROC) to determine model discrimination (R v3.6.2, package cvAUC) [56]. Finally, the calibration of each model was quantitatively and qualitatively characterized using Hosmer-Lemeshow tests, a chi-squared test of mean squared differences of true and predicted outcomes between quantiles of outcome measurements, and their corresponding calibration plots (R v3.6.2, packages "generalhoslem" and "PredictABEL").

We then identified the best model, defined as having the best discrimination value, adequate calibration and having selected the least variables within each OAC subgroup (warfarin, DOAC and OAC). Ultimately, we evaluated the final MB model's performance and evaluated its ability to detect MB

subtypes (GIB and NGIB) via discrimination and calibration testing using the previously discussed methods.

Ethics statement

The protocol was approved by the University of Montreal Health Research Ethics Committee (cert. 17-068-CERESD) and the Committee of Access to Personal Information (CAI).

Results

Demographic and clinical characteristics

The cohort of OAC new users diagnosed with AF that have met all inclusion and exclusion criteria comprised of 36,381 patients. The two treatment subgroups consisted of warfarin users (n=14,741) and DOAC users (n=21,640). The mean age of patients who experienced bleeding during follow-up and those that did not ranged from 78.9 to 80.9 years old as shown in Table 1. Whether or not they experienced MB, OAC users were more likely to be over the age of 75 (68.3% to 77.4%), had numerous comorbidities (Charlson-Deyo co-morbidity scores from 4.5±3.4 to 5.9±3.9), had a high stroke risk (CHA_2DS_2-VASc scores from 3.7±1.4 to 4.0±1.3) and had a high bleeding risk (HAS-BLED scores from 3.1±1.3 to 3.5±1.3), as shown in Table 1. Patients who experienced MB within the year of follow-up were more likely to be over 75 years old (76.1%), had over 5 comorbidities on average (Charlson-Deyo score: 5.3 ± 3.6), a high bleeding risk (HAS-BLED: 3.4 ± 1.2) and a high stroke risk (CHA_2DS_2-VASc: 4.0 ± 1.3). Warfarin and DOAC users had a total of 499 and 528 MB events, respectively (Table 1; S5 and S6 Tables).

Table 1. Baseline characteristics of OAC new user with and without major bleed in the year of follow-up from 2011 to 2018.

	No major bleeding (n=35,354)	**GI bleeding** (n=438)	**Non-GI extracranial bleeding** [a] (n=363)	**All major bleeding** [b] (n=1,027)
Sociodemographics				
Age (mean ± SD)	78.9 ± 9.4	80.6 ± 8.0	80.2 ± 8.2	80.9 ± 8.2
Age (%) [d]				
≥ 75	68.3%	77.4%	72.7%	76.1%
Male (%)	45.9 %	45.4 %	52.9 %	49.1 %
Pampalon index elevated social	26.6%	26.6%	26.5%	26.6%
Pampalon index elevated material	25.8%	25.8%	25.8%	25.8%
CHA_2DS_2-VASc Score (mean ± SD)	3.7 ± 1.4	4.0 ± 1.3	4.0 ± 1.4	4.0 ± 1.3
CHA_2DS_2-VASc Score (%) [d]				
0 - 1	5.9%	2.3%	2.5%	2.3%
2 - 3	37.7%	31.7%	32.5%	32.3%
4	29.0%	33.8%	31.7%	32.6%
≥ 5	27.4%	32.2%	33.3%	32.7%
HAS-BLED score (mean ± SD)	3.1 ± 1.3	3.3 ± 1.2	3.5 ± 1.3	3.4 ± 1.2
HAS-BLED score (%) [d]				
< 3	34.5%	24.2%	22.0%	23.7%
≥ 3	65.5%	75.8%	78.0%	77.3%
Co-morbidities within 3 years before cohort entry				
Hypertension	81.6%	87.7 %	86.8 %	86.6 %
Coronary artery disease (excl. MI)	56.0 %	51.4 %	58.4 %	53.9 %
Acute myocardial infarction	12.9 %	16.0 %	23.4 %	17.8 %
Chronic heart failure	37.4 %	47.5 %	45.6 %	45.9 %
Cardiomyopathy	6.2 %	6.2 %	13.0 %	8.3 %
Other dysrhythmias	19.8 %	17.8 %	20.7 %	20.1 %
Valvular heart disease	18.7 %	24.0 %	26.5 %	23.4 %
Stroke/TIA	19.0 %	16.2 %	19.3 %	20.0 %
Peripheral vascular (arterial) disease	20.9 %	26.7 %	31.7 %	28.6 %
Dyslipidemia	52.2 %	56.4 %	58.7 %	56.7 %
Diabetes	34.7 %	40.2 %	48.5 %	42.5 %
History of major bleeding [c]	29.0 %	43.6 %	47.7 %	42.9 %
History of intracranial bleeding	3.8 %	2.5 %	4.4 %	5.0 %
History of GI bleeding	7.4 %	19.0 %	11.9 %	13.8 %
History of other bleeding [a]	21.8 %	32.7 %	39.4 %	32.5 %
Chronic renal failure	35.1 %	39.7 %	49.0 %	42.4 %
Chronic renal failure ≤ 30 mL/min	0.5 %	0.7 %	1.1 %	0.8 %

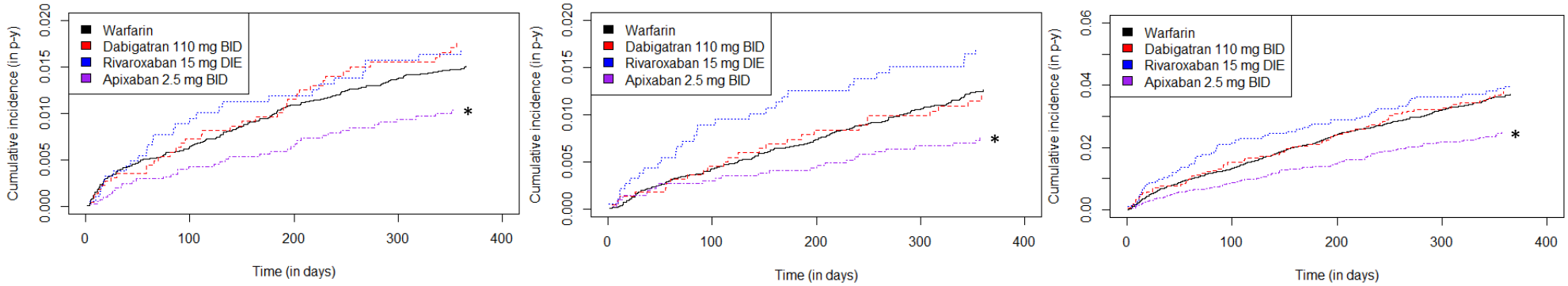
Acute renal failure	22.3 %	26.7 %	34.4 %	28.4 %
Liver disease	2.1 %	5.7 %	3.6 %	4.0 %
Chronic obstructive pulmonary	36.5 %	47.0 %	49.0 %	43.1 %
Infection par Helicobacter pylori	0.7 %	0.9 %	1.4 %	0.9 %
Depression	11.3 %	10.3 %	12.7 %	13.4 %
Concomitant medication use (within 2 weeks before cohort entry) (%)				
Statin	44.7 %	48.2 %	54.3 %	51.0 %
All antiplatelets [c]	29.6 %	39.0 %	40.2 %	39.1 %
Low dose aspirin (ASA)	26.4 %	35.4 %	35.8 %	35.2 %
Oth. antiplatelets (without ASA)	4.8 %	6.9 %	7.2 %	6.3 %
Proton pump inhibitors (PPIs)	45.8 %	48.2 %	56.2 %	50.1 %
NSAIDs	1.4 %	1.1 %	0.6 %	1.2 %
Digoxin	11.6 %	12.3 %	13.2 %	12.6 %
Amiodarone	8.7 %	8.5 %	11.6 %	9.8 %
Antidepressants	16.5 %	18.5 %	20.1 %	20.2 %
B-Blockers	62.9 %	58.2 %	59.2 %	60.5 %
Calcium channel blockers	37.3 %	39.5 %	36.4 %	38.6 %
Inhibitors of renin-angiotensin system	36.8 %	36.5 %	42.4 %	39.8 %
Diuretics	38.4 %	45.4 %	49.9 %	45.4 %
Loop diuretics	31.2 %	38.6 %	41.6 %	37.8 %
Antidiabetics	20.4 %	24.0 %	30.3 %	26.2 %
OAC type at cohort entry				
Warfarin	40.3 %	46.6 %	46.0 %	48.6 %
Dabigatran 110 mg	6.2 %	8.5 %	6.9 %	7.8 %
Dabigatran 150 mg	4.1 %	3.4 %	2.5 %	2.9 %
Rivaroxaban 15 mg	5.0 %	6.6 %	8.0 %	6.7 %
Rivaroxaban 20 mg	13.5 %	12.6 %	14.3 %	11.6 %
Apixaban 2.5 mg	11.4 %	8.9 %	7.7 %	8.9 %
Apixaban 5 mg	19.6 %	13.5 %	14.6 %	13.5 %
Charlson score (mean ± SD)	4.5 ± 3.4	5.2 ± 3.4	5.9 ± 3.9	5.3 ± 3.6
Charlson score < 4 (%) [d]	45.7 %	36.1 %	29.2 %	34.5 %
Charlson score ≥ 4 (%) [d]	54.3 %	63.9 %	70.8 %	65.5 %

[a] Non-GI extracranial major bleeding as an outcome or a predictor includes vitreous, urogenital, hemoperitoneal and unspecified major bleeding as well as hemoarthrosis, hemopericardium, hemoptysis, hematuria and post-bleeding anemia. [b] All major bleedings included GI, non-GI extracranial major bleeding and intracranial bleeding. [c] Represents a history of at least one of the bleeding subcategories OR at least one prescription of antiplatelet subcategory. Although each subcategory is mutually exclusive, the totals will not add up to the parent variable. [d] Each categorization is clinically justifiable. A HAS-BLED≥3 implies high bleeding risk, a CHA_2DS_2-VASc≥2 implies high stroke risk and an age≥75 guarantees oral anticoagulation in accordance to AF guidelines. Lastly, a Charlson score cut-off of 4 was chosen since it was close to the lowest average value for any of the subgroups.

Treatment-specific cumulative incidence measurements

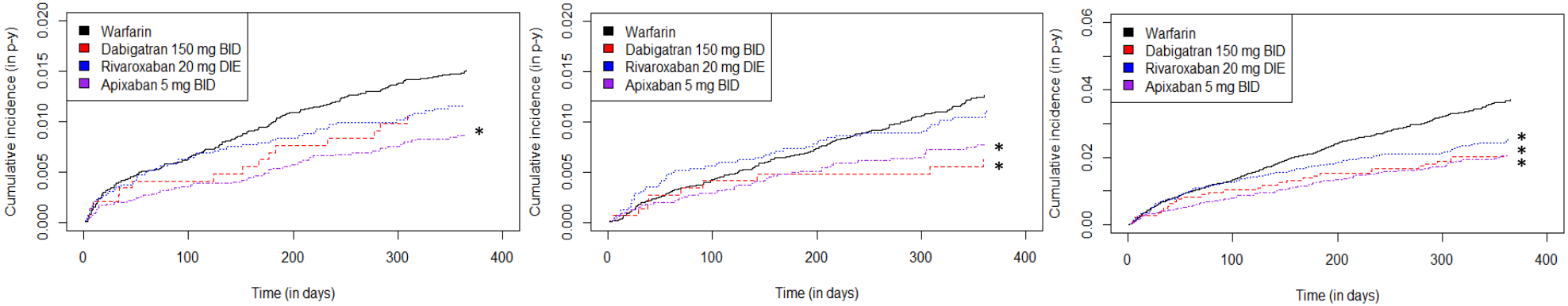
Including both approved dosages, DOAC users had cumulative ICH, GIB, NGIB, and MB incidences ranging from 0.35 to 0.92, 0.89 to 1.80, 0.64 to 1.77 and 2.11 to 4.27 events per 100 person-years, respectively (Table 2). Warfarin users had cumulative ICH, GIB, NGIB and MB incidences of 1.05, 1.57, 1.28 and 2.84 events per 100 person-years, respectively (Table 2). As shown in Figs 2 and 3, apixaban users had lower incidences of all bleeding subtypes relative to warfarin users for both dosages (log rank $p<0.05$).

Fig 2. Gastrointestinal, non-gastrointestinal extracranial and all major bleeding cumulative incidence curves for each direct oral anticoagulant at low dose relative to warfarin.



Warfarin, dabigatran, rivaroxaban and apixaban are shown in black, red, blue and purple, respectively. Gastrointestinal, non-gastrointestinal and all major bleeding are shown from left to right. * statistically significant difference relative to warfarin ($p<0.05$).

Fig 3. Gastrointestinal, non-gastrointestinal extracranial and all major bleeding cumulative incidence curves for each direct oral anticoagulant at high dose relative to warfarin.



Warfarin, dabigatran, rivaroxaban and apixaban are shown in black, red, blue and purple, respectively. Gastrointestinal, non-gastrointestinal and all major bleeding are shown from left to right. * statistically significant difference relative to warfarin ($p<0.05$).

Table 2. Crude cumulative incidence of all major bleeds among warfarin, low dose and high dose OAC users with each major bleeding subtype one year after cohort entry between 2011 and 2018.

	Warfarin DIE (n=14,741)	Dabigatran 110 mg BID (n=2,255)	Dabigatran 150 mg BID (n=1,467)	Rivaroxaban 15 mg DIE (n=1,846)	Rivaroxaban 20 mg DIE (n=4,876)	Apixaban 2.5 mg BID (n=4,127)	Apixaban 5 mg BID (n=7,069)
Major gastrointestinal bleeding							
Number with bleeds	204	37	15	29	55	39	59
Total person-years	13,021.8	2,049.9	1,404.6	1,618.8	4,565.5	3,566.4	6,606.5
Rate of bleed (per 100 person-years) [b]	1.57 (1.36-1.79)	1.80 (1.28-2.44)	1.01 (0.61-1.70)	1.79 (1.22-2.52)	1.20 (0.91-1.55)	1.09 (0.78-1.47)	0.89 (0.68-1.14)
Major non-GI extracranial bleeding [a]							
Number with bleeds	167	25	9	29	52	28	53
Total person-years	13,048.9	2,057.0	1,409.6	1,638.6	4,594.0	3,589.5	6,522.7
Rate of bleed (per 100 person-years) [b]	1.28 (1.11-1.49)	1.21 (0.80-1.18)	0.64 (0.31-1.15)	1.77 (1.22-2.52)	1.11 (0.86-1.48)	0.78 (0.53-1.11)	0.81 (0.60-1.04)
Major intracranial bleeding							
Number with bleeds	138	19	6	11	16	27	33
Total person-years	13156.4	2073.4	1414.6	1647.9	4621.8	3589.8	6649.1
Rate of bleed (per 100 person-years) [b]	1.05 (0.88-1.91)	0.92 (0.55-1.43)	0.42 (0.16-0.92)	0.67 (0.33-1.19)	0.35 (0.20-0.56)	0.75 (0.50-1.10)	0.50 (0.34-0.70)
Any major bleeding (GIB, other extracranial and intracranial bleeding)							
Number with bleeds	499	80	30	69	119	91	139
Total person-years	12978.1	2042.9	1402.1	1615.3	4560.0	3559.4	6591.7
Rate of bleed (per 100 person-years) [b]	3.84 (3.51-4.19)	3.92 (3.12-4.83)	2.14 (1.46-3.00)	4.27 (3.33-5.36)	2.61 (2.17-3.10)	2.56 (2.07-3.12)	2.11 (1.78-2.48)

[a] Non-GI extracranial bleeding includes vitreous, urogenital, hemoperitoneal and unspecified bleeding as well as hemoarthrosis, hemopericardium, hemoptysis, hematuria and post-bleeding anemia. [b] Incidence rate estimates are followed by exact Poisson 95% confidence intervals.

Logistic-LASSO and logistic-adaLASSO prediction models

The ORs of the selected predictors for the warfarin, DOAC and OAC models assessing GIB, NGIB and MB under the logistic-LASSO and logistic-adaLASSO regressions are presented in S7 and S8 Tables, respectively. The models for GIB, NGIB and MB had concordance statistics ranging from 0.60 (95% CI 0.58-0.62) to 0.66 (95% CI 0.63-0.70) with no statistically significant difference between logistic-LASSO and logistic-adaLASSO models (S7 and S8 Tables, S2 Fig). All models were adequately calibrated (Hosmer Lemeshow test: $p>0.05$) except for the logistic-LASSO selected OAC model for NGIB (S7 and S8 Tables, S1 Fig). There was little difference in discrimination or calibration between logistic-LASSO selected models and their logistic-adaLASSO counterparts. This was the case for all treatment groups and outcomes (S7 and S8 Tables, S1 and S2 Figs).

With the exception of NGIB, the predictors of each bleeding outcome were similar between the DOAC and warfarin treatment groups. Since the logistic-LASSO MB model derived from OAC user data selected marginally less variables than the logistic-adaLASSO MB model and the performance of the models did not differ significantly across methods, we chose the former as the final model fit. The most important MB predictors in our final MB model were liver disease (OR = 1.64), MB history (OR = 1.57), age $\geq$ 75 vs < 75 (OR = 1.37) antiplatelet use (OR = 1.28), cardiomyopathy (OR = 1.22), PVD (OR = 1.21) and COPD (OR = 1.21).

The selected model had a c-statistic of 0.63 (95% CI 0.61-0.65) and was well-calibrated (Table 3). The formula representing this model can be seen in Table 3. The final MB model performed just as well in detecting GIB and NGIB as it did for MB (GIB c-statistic: 0.65, 95% CI 0.63-0.66; NGIB c-statistic: 0.67, 95% CI 0.64-0.70; Table 3). However, with regards to calibration, the model underpredicted GIB and NGIB among patients at moderate and high risk of each respective MB subtype (see Fig S4). To understand how to apply and interpret the selected model, you may

refer to the formula for the risk of major bleeding in the year following OAC initiation derived for any OAC new user with AF (Table 3).

Table 3. The predictors selected into the primary prediction model of major bleeding and its performance.

	Model coefficients	Model ORs
Sociodemographic criteria at cohort entry		
Age ≥ 75 years (ref. <75 years)	0.31	1.37
Female sex	0.08	1.09
Co-morbidities within 3 years before cohort entry		
Liver disease	0.49	1.64
History of major bleeding	0.45	1.57
Cardiomyopathy	0.2	1.22
Peripheral vascular (arterial) disease	0.2	1.21
Hypertension	0.14	1.15
Congestive heart failure	0.12	1.14
Chronic obstructive pulmonary disease/asthma	0.12	1.13
Valvular heart disease	0.10	1.10
Acute myocardial infarction	0.09	1.09
Coronary artery disease (excl. MI)	0	-
Other dysrhythmias	0	-
Stroke/TIA	0	-
Dyslipidemia	0	-
Chronic renal failure	0	-
Chronic renal failure ≤ 30 mL/min	0	-
Acute renal failure	0	-
Infection by Helicobacter pylori	0	-
Concomitant medication use within 2 weeks before cohort entry		
Antiplatelet	0.25	1.28
Antidiabetics	0.17	1.19
Antidepressants	0.10	1.10
Statin	0	-
NSAIDs	0	-
Proton pump inhibitors	0	-
OAC type at cohort entry (ref. warfarin)		
OAC type (apixaban)	-0.37	0.69
OAC type (rivaroxaban)	0	-
OAC type (dabigatran)	0	-
Model statistics (MB)		

Cross-val. C-Statistic (95% CI)	N/A	0.63 (0.60-0.65)
Hosmer-Lemeshow test (p-value)	N/A	p>0.05
Model sensitivity (GIB)		
Cross-val. C-Statistic (95% CI)	N/A	0.65 (0.63-0.66)
Hosmer-Lemeshow test (p-value)	N/A	p<0.001
Model sensitivity (NGIB)		
Cross-val. C-Statistic (95% CI)	N/A	0.67 (0.64-0.70)
Hosmer-Lemeshow test (p-value)	N/A	0.01<p<0.05

The risk of major bleeding in the year following oral anticoagulant initiation as defined by the prediction model derived from a population of all oral anticoagulant users with atrial fibrillation using logistic-LASSO regression can be estimated with $\frac{e^x}{1+e^x}$ where x = -4.51 + 0.31*age_75_and_more + 0.08*is_female + 0.49*liver_disease + 0.45*prior_major_bleeding + 0.2*cardiomyopathy + 0.2*peripheral_vascular_disease + 0.14*hypertension + 0.12*heart_failure + 0.12*chronic_obstructive_pulmonary_disorder_or_asthma + 0.10*valvular_heart_disease + 0.09*myocardial_infarction + 0.25*antiplatelets + 0.17*antidiabetics + 0.10*antidepressants - 0.37*apixaban

Discussion

Our study is the first to derive prediction models for MB and MB subtypes from a cohort of DOAC and warfarin new users with AF. It did so using a robust statistical prediction tool. Our MB and MB subtype models were well-calibrated and performed similarly to previously published MB scores. Warfarin and DOAC users presented similar predictors of MB and GIB, not NGIB. This was likely due to the variable locations of bleeding included in the definition of NGIB. We then built a final MB model derived from data from all OAC users. Due to the marginally superior discrimination of the OAC model relative to the warfarin model, it was deemed that the OAC model was more useful than having separate models for DOAC and warfarin users. The most important MB predictors in our final MB model were liver disease, MB history, age≥75, antiplatelet use, cardiomyopathy, PVD and COPD with ORs ranging from 1.21 to 1.64. Notably, the selection of apixaban as a protective factor (OR=0.69) relative to warfarin corroborates previous observational studies [57, 58]. These findings may be attributable to the superior bleeding profile of apixaban relative to warfarin.

The OR values for the most important predictors of our final model were largely similar to those reported in the analyses used to derive existing MB scores. For the ABS, the population had a similar stroke risk, but was younger (mean age ranging from 68.1 to 73.7) and less at risk of bleeding (mean HAS-BLED ranging from 2.1 to 2.8). The ABS score, which, like us, was derived from OAC users, selected analogous predictors to our model, including prior MB (HR=1.27, 95% CI 1.18-1.36), antiplatelet therapy (HR=1.25, 95% CI 1.16-1.35), and COPD (HR=1.21, 95% CI 1.13-1.30). The most important difference between our model and the ABS score is their selection of CKD. This difference is most likely due to the continuous definition of age given the association between our age categories, kidney function as well as OAC prescription guidelines.

Furthermore, the ORBIT-AF population had a similar age to ours, but a higher stroke risk (a median CHA_2DS_2-VASC ranging from 4.0 to 5.0) and lower bleeding risk (a median HAS-BLED of 2.0). The analyses used to create the ORBIT-AF score used warfarin and dabigatran user data, provided similar point estimates and predictors such as age≥75 (HR=1.38, 95% CI 1.17-1.61), any prior bleeding excluding NGIB (HR=1.73, 95% CI 1.34-2.23), and antiplatelet therapy (HR=1.51, 95% CI 1.30-1.75). Like with the ABS score, the selection of CKD is a major distinction to our model. This may be due to their prediction method, the omission of NGIB in the MB history definition or the lower bleeding risk of the derivation cohort.

On the other hand, for each existing MB score, we found differences between some of their OR values and our own. Most notably, the HAS-BLED study presented a significantly different OR estimate for prior MB (OR=7.51, 95% CI 3.00- 18.78), while all other models selected CKD and omitted liver disease. The CKD discrepancy is most likely due to the contraindication of DOAC use among patients with renal dysfunction in our cohort. Moreover, the high prior MB point estimate may be attributable to the small sample size or selection bias attributable to the substantial missing data. However, despite these differences to our model, the HAS-BLED similarly incorporated age≥65 (OR=2.66, 95% CI 1.33-5.32). Given that the HAS-BLED was derived from warfarin data, it may exclude important MB predictors

among DOAC users, hence the need for a score that is derived from a cohort encompassing all types of OAC users.

Our model performed similarly to other MB scores in the literature with a c-statistic of 0.63 (0.60-0.65) and had adequate calibration. The HAS-BLED, (c-statistic: 0.65 [0.61-0.69]) performed better than existing scores in a meta-analysis of observational studies (c-statistics of 0.63 (0.61-0.66) and 0.63 (0.56-0.72) for HEMORR2AGES and ATRIA, respectively) with Net Reclassification and Integrated Discrimination Improvement values exceeding 7% ($p<0.001$) [24, 59-62]. However, unlike our model, few of the studies used cross-validation or bootstrapping to evaluate model performance, which may have led to overconfident assessments if the models were not independently validated [24, 59-63]. Although our model performed similarly to the HAS-BLED, we evaluated its discrimination more robustly and the HAS-BLED was inadequately calibrated [64]. MB prediction scores, such as the ORBIT score and the ABS, which included DOAC user data in their derivation cohort, have performed similarly or slightly better than our model with c-statistics of 0.65 (0.64-0.66) and 0.68 (0.67-0.69), respectively [27, 28].

Our study was one of the few to have tested the ability of its MB prediction model to detect MB subtypes. A real-world study compared the HAS-BLED's ability to discriminate MB subtypes to that of the Age Biomarker Clinical history score and found that the HAS-BLED performed better in detecting MB (c-statistics: 0.583 and 0.518, respectively) and GIB (c-statistics: 0.596 and 0.519, respectively) [65]. However, these findings were neither cross-validated, nor externally validated [60, 65]. Our own MB risk score overperformed relative to the HAS-BLED in this study (c-statistic: 0.65 95% CI 0.63-0.66), but further research is needed for confirmation. Furthermore, while the HAS-BLED outperformed other scores in predicting ICH, we were unable to evaluate this outcome due to a paucity of events-per-predictors [60, 65]. Finally, despite encompassing approximately half of MB cases, NGIB, which predominantly included genitourinary bleeding and gross hematuria, has been poorly studied [66-68]. Our model predicted NGIB as well as it did MB (c-statistic: 0.67 95% CI 0.64-0.70). Thus, one of the

advantages of our MB model is that it also had a good discrimination in terms of GIB and NGIB. Nonetheless, these findings need to be validated with inpatient data.

Furthermore, no study has identified the predictors for the most prevalent MB subtypes among DOAC and warfarin users. Two prediction schemes (the Qbleed models) and one observational study evaluated predictors of upper GIB and ICH as well as all GIB, respectively. However, neither model accounted for all DOAC users [69, 70]. Our study is the first to identify predictors of GIB and NGIB using a derivation cohort of DOAC and warfarin users. Our final model identified similar predictors to existing MB scores, but may be more robust. Clinical scores that effectively predict common MB subtypes like GIB are essential as they can significantly impact patient quality of life, DOAC adherence, and mortality [29, 71].

Our study has several advantages. Firstly, it is the only study to have developed MB and MB subtype prediction models derived from DOAC and warfarin user data. Secondly, this is one of the few studies to calculate cumulative incidence of MB, GIB, ICH and NGIB stratified by dosage for all DOACs. Thirdly, we used a prediction method that minimized the likelihood of overfitting the regression to its derivation dataset, theoretically leading to a more robust model than existing ones [24, 27, 28, 60-62, 64, 72]. Fourth, unlike previous studies, our model's performance indices have been cross-validated to avoid inflated c-statistics [24, 27, 60-62, 64, 72]. Fifth, we used a dataset large enough to establish models in each treatment subgroup. Sixth, our predictor candidates were well-defined and clinically useful (non-redundant) variables with externally validated coding algorithms. Moreover, we made sure that our outcome definitions were consistent with previous claims-based observational studies. Seventh, patient loss-to-follow-up (mainly death), OAC non-adherence and OAC switching during follow-up could limit model performance. However, our sensitivity analyses suggested that none of these factors have hindered model performance (S9 Table). Ultimately, the observational nature of our data allowed us to characterize real-world predictors of our outcomes.

Our findings presented some limitations. Firstly, prediction modelling is not designed for causal inference, thereby precluding conclusions regarding the impacts of hypothetical interventions on the risk factors. Secondly, due to the nature of our prediction models, these findings are not directly generalizable to any other common OAC indications or edoxaban users. Thirdly, important candidate predictors may not have been evaluated in our models. Specifically, our source data does not include information on alcohol use, tobacco use, ethnicity, over-the-counter aspirin use or labile INR (factors highly associated with bleeding) [24, 73, 74]. Despite the large populational data source, our sample size constrained our ability to identify ICH predictors. Fourth, some patients with prior cardiovascular diseases may not have been identified due to errors in diagnostic coding. Fifth, medication dispensation does not necessarily amount to medication use, resulting in a potential misclassification bias in our cumulative incidence findings and prediction error in our prediction model. Sixth, given our use of real-world data, our findings require external validation using inpatient data [28]. Seventh, our comparisons to published MB models were only speculative given the differences in MB and predictor definitions between models derived from administrative claims data and those derived from inpatient data. Lastly, given our selection of patients who were hospitalized, it is likely that our cohort was older, sicker and used more medications than the general population of anticoagulant users with AF. External validation will be required to ensure the generalizability of our findings to this population.

Our findings have several implications. Due to the overall similarity of MB predictors across treatment groups, our findings suggest that it would be ideal to create an MB risk score that groups together all OAC users rather than generating separate scores for DOACs and warfarin. Moreover, the paucity of RCT and observational data pertaining to GIB and NGIB predictors within an AF population of OAC users makes it difficult to assess whether existing prediction models, such as the HAS-BLED takes into account risk factors for the most prevalent MB subtypes in a real-world population. Thus, although it requires further validation using clinical data and real-world data from other AF patient populations, this study may inform the development of a much-needed monitoring tool that encompasses

a more diverse range of MB risk factors adapted to the heterogeneity of OAC user and MB subtype characteristics. Ultimately, our derivation model is well-calibrated and has a similar discriminative potential relative to the other MB scores in the literature (most notably, the HAS-BLED, ABS, and ORBIT-AF), but will require further validation. Future studies will involve using inpatient data to compare our model to the HAS-BLED using adequate comparative performance metrics and seeing how well it stratifies the risk for each MB subtype relative to the HAS-BLED.

Acknowledgments

Jakub Qazi was the first author. He wrote the article, ran the analyses, contributed to part of the conceptualization of the project and participated in interpreting the data in conjunction with the members of the advisory committee (Dr. Sylvie Perreault, Dr. Mireille Schnitzer and Dr. Marie-Josée Martel) as well as Dr. Robert Côté. Sylvie Perreault is the supervising author. In addition to providing training, revisions and final approval of the published article, she created a conceptual framework for the study design and data analysis and provided access to her data. Mireille Schnitzer provided a statistical framework and guidance for the prediction modelling. Marc Dorais provided database training and programming guidance. Robert Côté contributed clinical validation of the study's findings. Marie-Josée Martel provided guidance regarding improvements to the study during advisory committee meetings. Marie-Josee Martel is also an employee of Xcenda UK Ltd.

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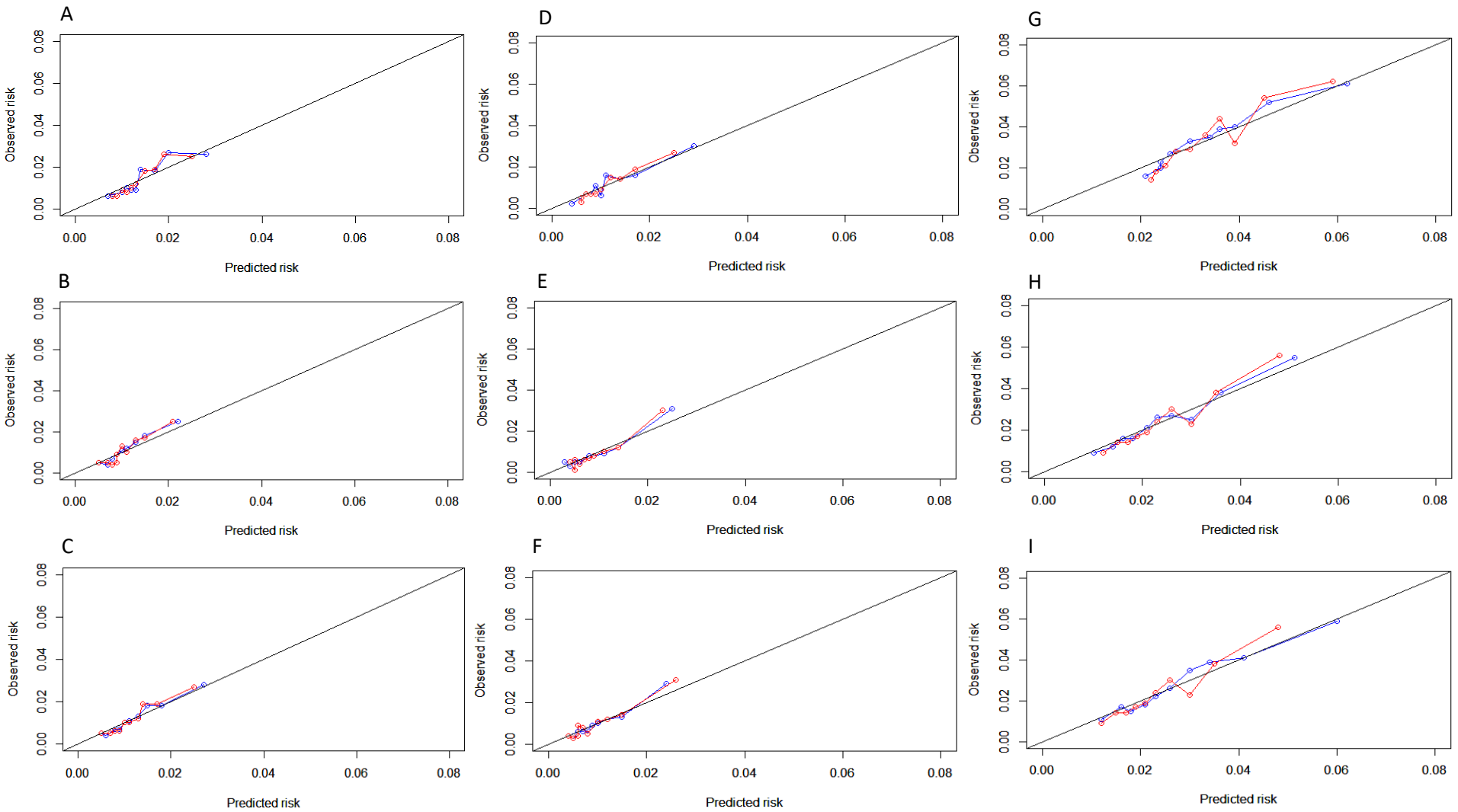
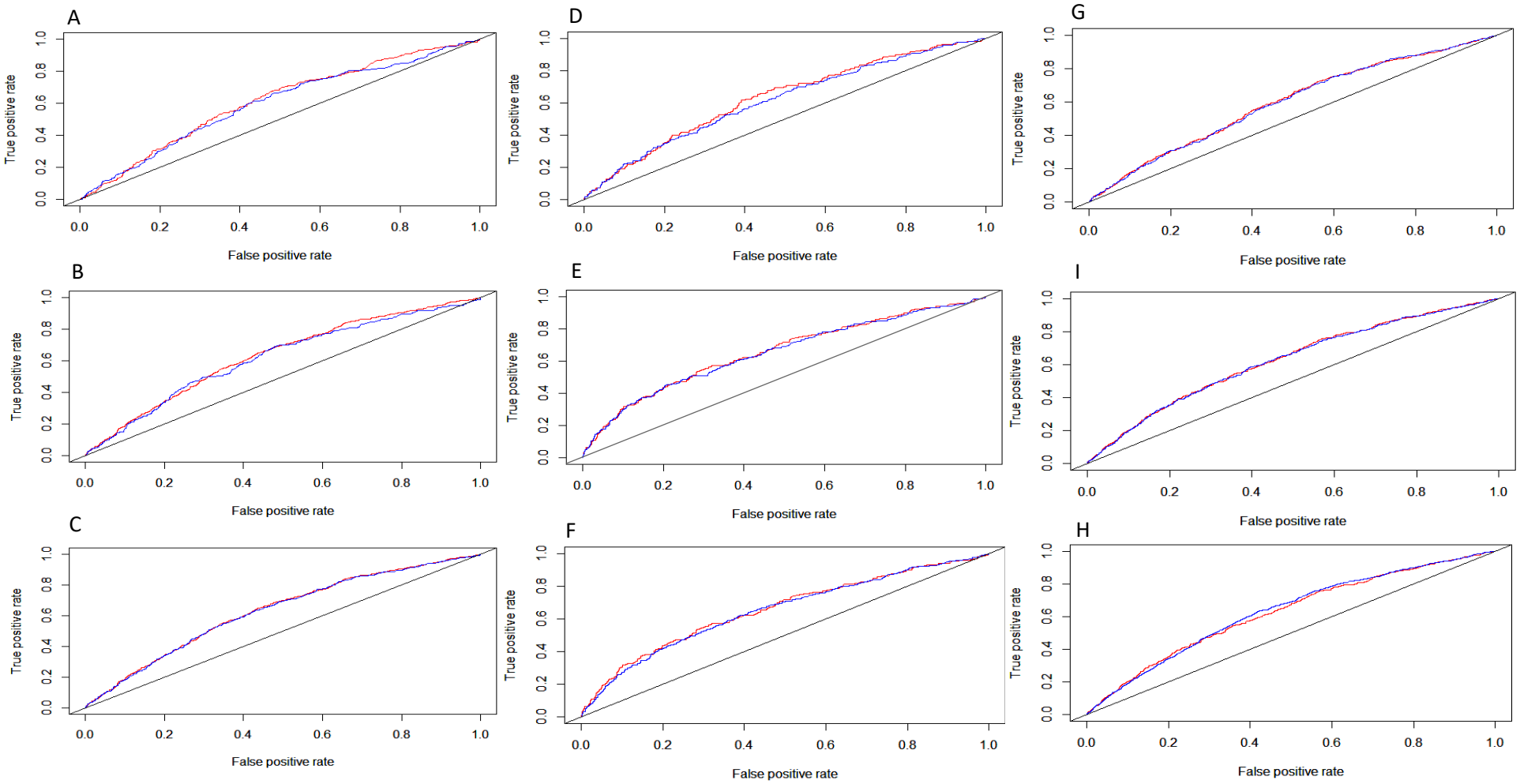
Supporting information

S1 Fig. Calibration plots.



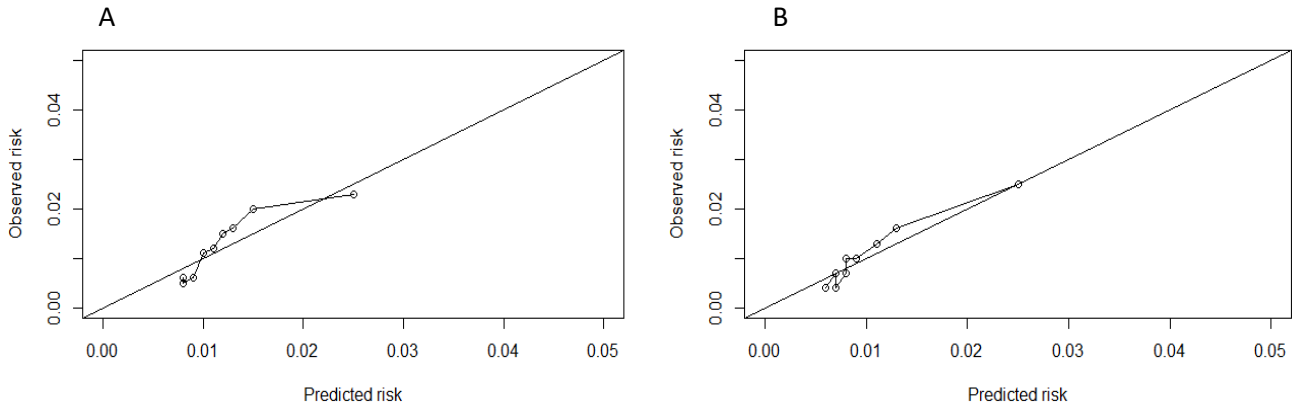
Calibration plots of LASSO (red) and adaptive LASSO (blue) logistic regression models for GIB among users of A) Warfarin, B) DOACs, C) all OACs; NGIB among users of D) Warfarin, E) DOACs, F) all OACs; and MB among users of G) Warfarin, H) DOACs, I) all OACs.

S2 Fig. Cross-validated ROC curves.



Cross-validated ROC curves of LASSO (red) and adaptive LASSO (blue) logistic regression models for GIB among users of A) Warfarin, B) DOACs, C) all OACs; NGIB among users of D) Warfarin, E) DOACs, F) all OACs; and MB among users of G) Warfarin, H) DOACs, I) all OACs.

S3 Fig. Calibration of plots of the global MB model tested for MB subtypes.



Calibration plots of the global MB model tested for its ability to predict A. GIB and B. NGIB.

S1 Table. Major bleeding outcome definition.

	ICD-9 codes	ICD-10 codes
Major Bleed (MB)		
Haemorrhagic stroke intracranial (non-traumatic; ICH)	430, 431, 432.x	I60, I61, I62
Haemorrhagic stroke intracranial (traumatic; ICH)	852x, 853x	S063, S064, S065, S066
Major GI bleeding (GIB)	Upper GI: 456.1, 530.7, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x. 532.6x, 533.0x. 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 537.83, 578.0 Lower GI: 562.02, 562.03, 562.12, 562.13, 569.3x, 569.85, 578.1x, 578.9	Upper GI: I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K2901, K290, K31811, K920 Lower GI: K921, K922, K5711, K5713, K5731, K5733, K625, K5521
Major Non-GI Extracranial Bleed (NGIB)	Hematuria: 599.7 Hemoptysis: 786.3x Vitreous bleeding: 379.23 Urogenital bleeding: 626.2x,280.0 285.1,285.9 Hemarthrosis: 719.1x Hemopericardium: 423.0x Hemoperitoneal MB: 568.8 Unspecified MB: 459.0x Post-bleed anemia: 285.1x	Hematuria: R31 Hemoptysis: R042, R0489, R049 Vitreous bleeding: H43.13 Urogenital bleeding: N92.0, D50.0, D62, D64.9 Hemarthrosis: M250x Hemopericardium: I31.2 Hemoperitoneal MB: K66.1 Unspecified MB: R58.0 Post-bleed anemia: D62

ICD-9 and ICD-10 codes for GIB, NGIB, ICH and MB. These outcomes were defined using 6 observational studies [1-6].

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3. Lauffenburger JC,Farley JF,Gehi AK,Rhoney DH,Brookhart MA, Fang G. Effectiveness and safety of dabigatran and warfarin in real-world us patients with non-valvular atrial fibrillation: A retrospective cohort study. J Am Heart Assoc. 2015;

4. Maura G,Blotière PO,Bouillon K,Billionnet C,Ricordeau P,Alla F, Zureik M. Comparison of the short-term risk of bleeding and arterial thromboembolic events in nonvalvular atrial fibrillation patients newly treated with dabigatran or rivaroxaban versus vitamin k antagonists: A french nationwide propensity-matched cohort study. Circulation. 2015; 132: 1252-1260.

5. Graham DJ,Reichman ME,Wernecke M,Zhang R,Southworth MR,Levenson M,Sheu TC,Mott K,Goulding MR,Houstoun M,MaCurdy TE,Worrall C, Kelman JA. Cardiovascular, bleeding, and mortality risks in elderly medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. Circulation. 2015; 131: 157-164.

6. Outcomes of dabigatran and warfarin for atrial fibrillation in contemporary practice. Annals of internal medicine. 2017; 167: 845-854.

S2 Table. Definition of CHA_2DS_2-$VASc_2$, modified HAS-BLED, ATRIA, $HEMORR_2HAGES$ and ORBIT-AF risk scores along with their scoring algorithms.

Risk score definition	Points, if present
CHA_2DS_2-VASc stroke risk score	
Congestive heart failure or left ventricular dysfunction	1
Hypertension	1
Age	1
Age ≥ 75 years	2
Diabetes Mellitus	1
Stroke (ischemic stroke, transient ischemic disease or systemic embolism	2
Vascular disease (myocardial infarction, peripheral arterial disease or aortic plaque	1
Sex category (female)	1
HAS-BLED bleeding risk score	
Hypertension	1
Abnormal renal function	1
Abnormal hepatic function	
Abnormal Stroke (ischemic stroke, transient ischemic disease	1
Bleeding	1
Older than > 65 years	1
Labile 65 - 74 years international normalized ratio (not available)	1
Drugs (ASA, clopidogrel, prasugrel, ticagrelor, ticlopidine, or non-steroidal anti-inflammatory drugs) in the 1 month preceding the ICH hospitalization or 1month after discharge	1
Alcohol intake	1
ATRIA bleeding risk score	
Anemia (Male: Hemoglobin <13 g/dL; Female: Hemoglobin <12 g/dL)	3
Severe Renal Disease (Glomerular filtration rate <30 mL/min or dialysis)	3
Age ≥ 75 years	2
Any Prior Hemorrhage Diagnosis	1
Hypertension History	1
$HEMORR_2HAGES$ bleeding risk core	1
Hepatic or Renal Disease	1
Ethanol (Alcohol) Abuse	1
Malignancy History	1
Older (Age > 75)	1
Reduced Platelet Count or Function	1
Rebleeding Risk (bleeding history)	1
Hypertension (Uncontrolled)	1
Anemia (Male: Hemoglobin <13 g/dL; Female: Hemoglobin <12 g/dL)	1
Genetic Factors (CYP 2C9 single-nucleotide polymorphisms)	1
Excessive Fall Risk	1
Stroke History	1
ORBIT-AF bleeding risk score	
Anemia (Male: Hemoglobin <13 g/dL; Female: Hemoglobin <12 g/dL)	2
Age >74 years	1
Bleeding history	2
GFR <60 mL/min/1.73 m2	1
Antiplatelet agent use	1

S3 Table. Definition of co-morbidity and concomitant medication variables used for CHA_2DS_2-VASc and HAS-BLED risk score calculation according to ICD-9 and ICD-10 codes from the Med-Echo databases.

	ICD-9 codes	**ICD-10 codes**
CHA_2DS_2VASc		
Congestive heart failure	402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 425.4, 428.0	I11.0, I13.0, I13.2, I42.0, I50
Left ventricular dysfunction	428.1, 428.9	I50.1, I50.9
Hypertension	401	I10
Diabetes	250.x	E08, E10, E11, E13
Ischemic stroke	433.xx, 434.xx, 436	I63 except 63.6, I67.89
Systemic embolism	444.x, 557.0, 362.31, 362.32, 598.31	I74, K55.0, H34.1, H34.2, N28.0
Transient ischemic stroke (TIA)	435.x	G45
Aortic plaque	440.0	I70.0
Peripheral arterial disease	440 (except 440.0), 441, 443.0, 443.89, 443.9	I70.1 to I70.9, I71, I73.0, I73.89, I73.9
Myocardial infarction	410.xx	I21, I22, I23
Modified HAS-BLEED		
Ischemic stroke	433.xx, 434.xx, 436	I63 except I63.6, I67.89
Transient ischemic-attack	435.x	G45
Moderate to severe renal disease	404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 580.0, 580.4, 581.0, 581.1, 581.2, 581.3, 581.89, 581.9, 582.0, 582.1, 582.2, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.7, 583.6, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 586, 590.0, 590.01, 590.80	I12, I13, N00, N01, N02, N03, N04, N05, N07, N11, N12, N14, N17, N18, N19
Moderate to severe liver disease	570, 572.3, 070.0, 070.21, 070.20, 070.60	K7200, K762, K766, B150, B160, B162, B190, K704, I85
Haemorrhagic stroke intracranial (non-traumatic)	430, 431, 432.x	I60, I61, I62
Extracranial major or unclassified major bleeding	Upper GI: 456.1, 530.7, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x. 532.6x, 533.0x. 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 537.83, 578.0 Lower GI: 562.02, 562.03, 562.12, 562.13, 569.3x, 569.85, 578.1x, 578.9 Other sites: Hematuria: 599.7 Hemoptysis: 786.3x Vitreous bleeding: 379.23 Urogenital bleeding: 626.2x,280.0 285.1,285.9 Hemarthrosis: 719.1x Hemopericardium: 423.0x	Upper GI: I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K2901, K290, K31811, K920 Lower GI: K921, K922, K5711, K5713, K5731, K5733, K625, K5521 Other sites: Hematuria: R31 Hemoptysis: R042, R0489, R049 Vitreous bleeding: H43.13 Urogenital bleeding: N92.0, D50.0, D62, D64.9 Hemarthrosis: M250x Hemopericardium: I31.2

	Hemoperitoneal MB: 568.8 Unspecified MB: 459.0x Post-bleed anemia: 285.1x	Hemoperitoneal MB: K66.1 Unspecified MB: R58.0 Post-bleed anemia: D62
Traumatic intracranial bleeding	852x, 853x	S063, S064, S065, S066
Clopidogrel, ticlopidine, prasugrel, ticagrelor	46486, 47307, 45617, 47402, 47834, 47866	46486, 47307, 45617, 47402, 47834, 47866
Low dose ASA	00143, 46353 (daily dose < 100 mg)	00143, 46353 (daily dose < 100 mg)
Non steroidal anti-inflammatory drugs (NSAIDs)	46353, 38184, 47327, 47078, 41694, 47059, 43150, 47122, 33803, 44749, 04745, 46654, 47506, 04810, 38691, 44359, 47385, 47084, 19752, 47890, 07462, 42019, 47346, 47107, 40381, 45592, 45407, 03766	46353, 38184, 47327, 47078, 41694, 47059, 43150, 47122, 33803, 44749, 04745, 46654, 47506, 04810, 38691, 44359, 47385, 47084, 19752, 47890, 07462, 42019, 47346, 47107, 40381, 45592, 45407, 03766
Alcohol	331.7, 359.4, 425.5, 577.1	E224, E529A, F10, G312, G612, G721, I426, K292, K70, K860, L278A, O354, T51, Z714, Z721

S4 Table. Sample size justification.

	MB	GIB	NGIB	MB	GIB	NGIB	MB	GIB	NGIB
	All OACs			Warfarin			DOACs		
10 events per candidate predictor	280[a]	280[a]	280[a]	280	280	280	280	280	280
5 events per candidate predictor[b]	140[a]	140[a]	140[a]	140[a]	140[a]	140[a]	140[a]	140[a]	140[a]

Assuming 28 candidate predictors, these are the event requirements for each subgroup. [a] The number of outcomes in these groups would be sufficient to yield robust prediction models. [b] In a simulation study, it was found that under the assumption that outcomes are rare and that noise predictors (predictors presenting redundant information) are present, LASSO regression was shown to yield stable predictions (neither overfitted, nor underfitted models) with an events per candidate predictor ratio of 5 [7].

7. Pavlou M,Ambler G,Seaman S,De Iorio M, Omar RZ. Review and evaluation of penalised regression methods for risk prediction in low-dimensional data with few events. *Statistics in Medicine*. 2016; **35**: 1159-1177.

S5 Table. Baseline characteristics of OAC new user with specific types of major bleeds in the year of follow-up from 2011 to 2018.

	GI bleeding			Non-GI extracranial bleeding [a]			All major bleeding [a]		
	Warfarin (n=204)	DOAC [b] (n=234)	OAC [c] (n=438)	Warfarin (n=167)	DOAC [b] (n=196)	OAC [c] (n=363)	Warfarin (n=499)	DOAC [b] (n=528)	OAC [c] (n=1,027)
Sociodemographics									
Age (mean ± SD)	80.9 ± 8.5	80.3 ± 7.5	80.6 ± 8.0	80.4 ± 8.5	80.0 ± 8.0	80.2 ± 8.2	81.1 ± 8.5	80.7 ± 7.9	80.9 ± 8.2
Age (%)									
≥ 75 years old	79.9%	75.2%	77.4%	71.9%	73.5%	72.7%	76.0%	76.1%	76.1%
Male (%)	45.1 %	45.7 %	45.4 %	53.3 %	52.6 %	52.9 %	49.9 %	48.3 %	49.1 %
Pampalon index elevated social	26.7%	26.5%	26.6%	26.5%	26.5%	26.5%	26.6%	26.5%	26.6%
Pampalon index elevated material	25.7%	25.8%	25.8%	25.8%	25.7%	25.8%	25.8%	25.8%	25.8%
CHA_2DS_2-VASc Score (mean ±	4.1 ± 1.3	3.8 ± 1.2	4.0 ± 1.3	4.1 ± 1.4	3.9 ± 1.4	4.0 ± 1.4	4.1 ± 1.3	3.9 ± 1.3	4.0 ± 1.3
CHA_2DS_2-VASc Score (%)									
0 - 1	2.9%	1.7%	2.3%	1.2%	3.6%	2.5%	2.0%	2.7%	2.3%
2 - 3	25.5%	37.2%	31.7%	31.1%	33.7%	32.5%	28.5%	36.0%	32.3%
4	32.8%	34.6%	33.8%	29.9%	33.2%	31.7%	32.7%	32.6%	32.6%
≥ 5	38.7%	26.5%	32.2%	37.7%	29.6%	33.3%	36.9%	28.8%	32.7%
HAS-BLED score (mean ± SD)	3.5 ± 1.2	3.1 ± 1.2	3.3 ± 1.2	3.7 ± 1.3	3.3 ± 1.3	3.5 ± 1.3	3.6 ± 1.2	3.2 ± 1.2	3.4 ± 1.2
HAS-BLED score (%)									
< 3	17.7%	29.9%	24.2%	16.2%	27.0%	22.0%	17.8%	29.2%	23.7%
≥ 3	82.3%	70.1%	75.8%	83.8%	73.0%	78.0%	82.2%	70.8%	77.3%
Co-morbidities within 3 years before cohort entry									
Hypertension	90.2 %	85.5 %	87.7 %	89.2 %	84.7 %	86.8 %	88.8 %	84.5%	86.6 %
Coronary artery disease (excl. MI)	58.8 %	44.9 %	51.4 %	58.9 %	56.1 %	58.4 %	61.1 %	49.1 %	53.9 %
Acute myocardial infarction	16.2 %	15.8 %	16.0 %	23.4 %	19.4 %	23.4 %	20.2 %	15.5 %	17.8 %
Chronic heart failure	53.9 %	41.9 %	47.5 %	50.3 %	41.3 %	45.6 %	49.9 %	42.1 %	45.9 %
Cardiomyopathy	5.9 %	6.4 %	6.2 %	11.4 %	14.3 %	13.0 %	8.0 %	8.5 %	8.3 %
Other dysrhythmias	21.1 %	15.0 %	17.8 %	20.4 %	20.9 %	20.7 %	21.4 %	18.8 %	20.1 %
Valvular heart disease	26.5 %	21.8 %	24.0 %	33.5 %	20.4 %	26.5 %	26.1 %	20.8 %	23.4 %
Stroke/TIA	17.2 %	15.4 %	16.2 %	20.4 %	18.4 %	19.3 %	21.6 %	18.4 %	20.0 %

Peripheral vascular (arterial)	30.9 %	23.1 %	26.7 %	35.9 %	28.1 %	31.7 %	31.9 %	25.6 %	28.6 %
Dyslipidemia	56.4 %	56.4 %	56.4 %	62.3 %	55.6 %	58.7 %	58.9 %	54.6 %	56.7 %
Diabetes	41.2 %	39.3 %	40.2 %	47.3 %	49.5 %	48.5 %	44.1 %	40.9 %	42.5 %
History of major bleeding [a, d]	48.0 %	39.7 %	43.6 %	51.5 %	44.4 %	47.7 %	45.7 %	40.3 %	42.9 %
History of intracranial bleeding	1.5 %	3.4 %	2.5 %	4.2 %	4.6 %	4.4 %	4.0 %	5.9 %	5.0 %
History of GI bleeding	19.1 %	18.8 %	19.0 %	13.8 %	10.2 %	11.9 %	14.6 %	13.1 %	13.8 %
History of other bleeding [a]	39.7 %	26.5 %	32.7 %	41.9 %	37.2 %	39.4 %	35.7 %	29.6 %	32.5 %
Chronic renal failure	52.5 %	28.6 %	39.7 %	57.5 %	41.8 %	49.0 %	51.9 %	33.3 %	42.4 %
Chronic renal failure ≤ 30 mL/min	1.0 %	0.4 %	0.7 %	1.8 %	0.5 %	1.1 %	1.2 %	0.4 %	0.8 %
Acute renal failure	36.3 %	18.4 %	26.7 %	42.5 %	27.6 %	34.4 %	35.3 %	22.0 %	28.4 %
Liver disease	5.4 %	6.0 %	5.7 %	4.8 %	2.6 %	3.6 %	4.8 %	3.2 %	4.0 %
Chronic obstructive pulmonary	51.5 %	43.2 %	47.0 %	47.3 %	50.5 %	49.0 %	43.3 %	43.0 %	43.1 %
Infection by Helicobacter pylori	1.5 %	0.4 %	0.9 %	1.2 %	1.5 %	1.4 %	1.0 %	0.8 %	0.9 %
Depression	8.3 %	12.0 %	10.3 %	11.4 %	13.8 %	12.7 %	12.2 %	14.6 %	13.4 %
Concomitant medication use (within 2 weeks before cohort entry) (%)									
Statin	48.0 %	48.3 %	48.2 %	56.9 %	52.0 %	54.3 %	53.1 %	49.1 %	51.0 %
All antiplatelets [d]	46.1 %	32.9 %	39.0 %	47.9 %	33.7 %	40.2 %	46.3 %	32.2 %	39.1 %
Low dose aspirin (ASA)	41.7 %	29.9 %	35.4 %	41.3 %	31.6 %	35.8 %	40.7 %	29.4 %	35.2 %
Oth. antiplatelets (without ASA)	6.9 %	6.8 %	6.9 %	8.2 %	2.6 %	7.2 %	12.6 %	4.6 %	6.3 %
Proton pump inhibitors (PPIs)	52.0 %	44.9 %	48.2 %	61.7 %	51.5 %	56.2 %	53.9 %	46.4 %	50.1 %
NSAIDs	1.5 %	0.9 %	1.1 %	0 %	1.0 %	0.6 %	0.8 %	1.5 %	1.2 %
Digoxin	13.7 %	11.1 %	12.3 %	15.0 %	11.7 %	13.2 %	13.4 %	11.7 %	12.6 %
Amiodarone	7.8 %	9.0 %	8.5 %	10.9 %	12.2 %	11.6 %	9.6 %	10.0 %	9.8 %
Antidepressants	20.1 %	17.1 %	18.5 %	19.8 %	20.4 %	20.1 %	21.6 %	18.8 %	20.2 %
B-Blockers	58.3 %	58.1 %	58.2 %	63.5 %	55.6 %	59.2 %	62.9 %	58.2 %	60.5 %
Calcium channel blockers	41.2 %	38.0 %	39.5 %	36.5 %	36.2 %	36.4 %	40.7 %	36.6 %	38.6 %
Inhibitors of renin-angiotensin	37.3 %	35.9 %	36.5 %	46.7 %	38.8 %	42.4 %	42.3 %	37.5 %	39.8 %
Diuretics	47.6 %	43.6 %	45.4 %	52.1 %	48.0 %	49.9 %	47.7 %	43.2 %	45.4 %
Loop diuretics	44.6 %	33.3 %	38.6 %	46.1 %	37.8 %	41.6 %	42.1 %	33.7 %	37.8 %
Antidiabetics	26.0 %	22.2 %	24.0 %	31.7 %	29.1 %	30.3 %	29.7 %	22.9 %	26.2 %
OAC type at cohort entry									
Warfarin	100%	NA	46.6 %	100%	NA	46.0 %	100%	NA	48.6 %
Dabigatran 110 mg	NA	15.9 %	8.5 %	NA	12.8 %	6.9 %	NA	26.3 %	7.8 %

Rivaroxaban 150 mg	NA	6.4 %	3.4 %	NA	4.6 %	2.5 %	NA	15.2 %	2.9 %
Rivaroxaban 15 mg	NA	12.3 %	6.6 %	NA	14.8 %	8.0 %	NA	5.6 %	6.7 %
Rivaroxaban 20 mg	NA	23.6 %	12.6 %	NA	26.5 %	14.3 %	NA	13.0 %	11.6 %
Apixaban 2.5 mg	NA	16.7 %	8.9 %	NA	14.3 %	7.7 %	NA	22.6 %	8.9 %
Apixaban 5 mg	NA	25.2 %	13.5 %	NA	27.0 %	14.6 %	NA	17.3 %	13.5 %
Charlson score (mean, ± SD)	5.9 ± 3.5	4.6 ± 3.2	5.2 ± 3.4	6.3 ± 3.8	5.5 ± 3.9	5.9 ± 3.9	5.8 ± 3.6	4.9 ± 3.5	5.3 ± 3.6
Charlson score < 4 (%)	28.9 %	42.3 %	36.1 %	75.5 %	33.2 %	29.2 %	28.3 %	40.3 %	34.5 %
Charlson score ≥ 4 (%)	62.1 %	57.7 %	63.9 %	24.5 %	66.8 %	70.8 %	71.7 %	59.7 %	65.5 %

[a] Non-GI extracranial major bleeding as an outcome or a predictor includes vitreous, urogenital, hemoperitoneal and unspecified major bleeding as well as hemoarthrosis, hemopericardium, hemoptysis, hematuria and post-bleeding anemia. All major bleedings included GI, Non-GI extracranial major bleeding and intracranial bleeding. [b] DOAC users include all doses of dabigatran, rivaroxaban and apixaban. [c] OAC users include all doses of warfarin, dabigatran, rivaroxaban and apixaban. [d] Represents a history of at least one of the bleeding subcategories OR at least one prescription of antiplatelet subcategory. Although each subcategory is mutually exclusive, the totals will not add up to the parent variable.

S6 Table. Baseline characteristics of OAC new users without specific types of major bleeds in the year of follow-up from 2011 to 2018.

	Non GI bleeders			Non GI extracranial bleeder [a]			-Non major bleeders (all types) [a]		
	Warfarin (n=14,537)	DOAC [b] (n=21,406)	OAC [c] (n=35,943)	Warfarin (n=14,574)	DOAC [b] (n=21,444)	OAC [c] (n=36,018)	Warfarin (n=14,242)	DOAC [b] (n=21,112)	OAC [c] (n=35,354)
Sociodemographics									
Age (mean ± SD)	80.1 ± 9.2	78.2 ± 9.5	79.0 ± 9.4	80.1 ± 9.2	78.2 ± 9.5	79.0 ± 9.4	78.9 ± 9.4	78.2 ± 9.5	78.9 ± 9.4
Age (%)									
≥ 75	73.5%	64.9%	68.4%	73.6%	64.9%	68.5%	68.3%	64.7%	68.3%
Male (%)	44.6 %	46.9 %	46.0 %	44.5 %	46.9 %	45.9 %	45.9 %	46.9 %	45.9 %
Pampalon index elevated social	26.6%	26.6%	26.6%	26.6%	26.6%	26.6%	26.6%	26.6%	26.6%
Pampalon index elevated material	25.9%	25.8%	25.8%	25.9%	25.8%	25.8%	25.8%	25.8%	25.8%
CHA_2DS_2-VASc Score (mean ±	4.0 ± 1.4	3.5 ± 1.4	3.7 ± 1.4	4.0 ± 1.4	3.5 ± 1.4	3.7 ± 1.4	3.7 ± 1.4	3.5 ± 1.4	3.7 ± 1.4
CHA_2DS_2-VASc Score (%)									
0 - 1	4.0%	7.1%	5.9%	4.0%	7.1%	5.8%	5.9%	7.2%	5.9%
2 - 3	31.8%	41.7%	37.6%	31.7%	41.6%	37.6%	37.7%	41.7%	37.7%
4	30.8%	27.9%	29.1%	30.8%	27.9%	29.1%	29.0%	27.9%	29.0%
≥ 5	33.5%	23.4%	27.5%	33.5%	23.4%	27.5%	27.4%	23.3%	27.4%
HAS-BLED score (mean ± SD)	3.3 ± 1.3	2.9 ± 1.3	3.1 ± 1.3	3.3 ± 1.3	2.9 ± 1.3	3.1 ± 1.3	3.1 ± 1.3	2.9 ± 1.3	3.1 ± 1.3
HAS-BLED score (%)									
< 3	26.7%	39.5%	34.3%	26.7%	39.5%	34.3%	34.5%	39.7%	34.5%
≥ 3	73.3%	60.5%	65.7%	73.3%	60.5%	65.7%	65.5%	60.3%	65.5%
Co-morbidities within 3 years before cohort entry									
Hypertension	84.7%	79.5%	81.7%	84.8%	79.6%	81.7%	81.6%	79.5%	81.6%
Coronary artery disease (excl. MI)	52.5 %	48.2 %	56.2 %	52.3%	41.8%	46.1 %	52.5 %	41.8 %	56.0 %
Acute myocardial infarction	15.6 %	11.2 %	13.0 %	12.9 %	11.2 %	12.9 %	12.9 %	11.1 %	12.9 %
Chronic heart failure	43.9 %	33.2 %	37.5 %	44.0 %	33.2 %	37.6 %	37.4 %	33.1 %	37.4 %
Cardiomyopathy	6.4 %	6.1 %	6.2 %	6.4 %	6.0 %	6.1 %	6.2 %	6.0 %	6.2 %
Other dysrhythmias	20.4 %	19.4 %	19.8 %	20.5 %	19.4 %	19.8 %	19.8 %	19.4 %	19.8 %
Valvular heart disease	22.8 %	16.1 %	18.8 %	22.8 %	16.1 %	18.8 %	18.7 %	16.0 %	18.7 %
Stroke/TIA	21.0 %	17.7 %	19.1 %	20.9 %	17.7 %	19.0 %	19.0 %	17.7 %	19.0 %

Peripheral vascular (arterial)	25.0 %	18.4 %	21.0 %	24.9 %	18.3 %	21.0 %	20.9 %	18.3 %	20.9 %
Dyslipidemia	53.8 %	51.2 %	52.2 %	53.7 %	51.2 %	52.2 %	52.2 %	51.2 %	52.2 %
Diabetes	38.8 %	32.2 %	34.9 %	38.7 %	32.2 %	34.8 %	34.7 %	32.1 %	34.7 %
History of major bleeding [a,d]	32.7 %	26.8 %	29.2 %	32.7 %	26.8 %	29.2 %	29.0 %	26.6 %	29.0 %
History of intracranial bleeding	3.4 %	4.2 %	3.9 %	3.3 %	4.2 %	3.8 %	3.8 %	4.1 %	3.8 %
History of GI bleeding	8.0 %	7.1 %	7.5 %	8.1 %	7.2 %	7.6 %	7.4 %	7.0 %	7.4 %
History of other bleeding [a]	25.8 %	19.3 %	21.9 %	25.9 %	19.2 %	21.9 %	21.8 %	19.1 %	21.8 %
Chronic renal failure	45.4 %	28.4 %	35.3 %	45.4 %	28.3 %	35.2 %	35.1 %	28.3 %	35.1 %
Chronic renal failure ≤ 30 mL/min	0.9 %	0.3 %	0.5 %	0.9 %	0.3 %	0.5 %	0.5 %	0.3 %	0.5 %
Acute renal failure	29.4 %	17.7 %	22.4 %	29.3 %	17.6 %	22.3 %	22.3 %	17.6 %	22.3 %
Liver disease	2.2 %	2.0 %	2.1 %	2.2 %	2.0 %	2.1 %	2.1 %	2.0 %	2.1 %
Chronic obstructive pulmonary	38.7 %	35.2 %	36.6 %	38.8 %	35.1 %	36.6 %	36.5 %	35.0 %	36.5 %
Infection by Helicobacter pylori	0.8 %	0.7 %	0.7 %	0.8 %	0.7 %	0.7 %	0.7 %	0.7 %	0.7 %
Depression	11.3 %	11.4 %	11.3 %	11.3 %	11.3 %	11.3 %	11.3 %	11.3 %	11.3 %
Concomitant medication use (within 2 weeks before cohort entry) (%)									
Statin	47.8 %	42.9 %	44.9 %	47.7 %	42.8 %	44.8 %	44.7 %	42.8 %	44.7 %
All Antiplatelets [d]	35.7 %	25.7 %	29.7 %	35.7 %	25.7 %	29.7 %	29.6 %	25.6 %	29.6 %
Low dose aspirin (ASA)	31.8 %	23.0 %	26.5 %	31.6 %	23.0 %	26.6 %	31.8 %	22.9 %	26.4 %
Oth. antiplatelets (without ASA)	6.2 %	3.8 %	4.8 %	6.1 %	3.9 %	4.8 %	6.1 %	3.8 %	4.8 %
Proton pump inhibitors (PPIs)	49.8 %	43.3 %	45.9 %	49.7 %	43.2 %	45.8 %	45.8 %	43.2 %	45.8 %
NSAIDs	1.3 %	1.4 %	1.4 %	1.4 %	1.3 %	1.4 %	1.4 %	1.4 %	1.4 %
Digoxin	13.4 %	10.4 %	11.6 %	13.4 %	10.4 %	11.6 %	11.6 %	10.4 %	11.6 %
Amiodarone	9.3 %	8.5 %	8.8 %	9.2 %	8.4 %	8.7 %	8.7 %	8.4 %	8.7 %
Antidepressants	16.6 %	16.5 %	16.6 %	16.6 %	16.5 %	16.5 %	16.5 %	16.5 %	16.5 %
B-Blockers	62.3 %	63.4 %	62.9 %	62.2 %	63.4 %	62.9 %	62.9 %	63.4 %	62.9 %
Calcium channel blockers	39.9 %	35.5 %	37.3 %	40.0 %	35.6 %	37.4 %	37.3 %	35.5 %	37.3 %
Inhibitors of renin-angiotensin	37.8 %	36.2 %	36.9 %	37.7 %	36.2 %	36.8 %	36.8 %	36.2 %	36.8 %
Diuretics	44.3 %	34.6 %	38.5 %	44.2 %	34.6 %	38.5 %	38.4 %	34.5 %	38.4 %
Loop diuretics	37.1 %	27.4 %	31.3 %	37.1 %	27.4 %	31.3 %	31.2 %	27.3 %	31.2 %
Antidiabetics	23.0 %	18.8 %	20.5 %	22.9 %	18.8 %	20.4 %	20.4 %	18.7 %	20.4 %
OAC type at cohort entry									
Warfarin	100 %	0 %	40.4 %	100 %	0 %	40.5 %	100 %	0 %	40.3 %
Dabigatran 110 mg	NA	8.9 %	6.2 %	NA	10.4 %	6.2 %	NA	10.4 %	6.2 %

Dabigatran 150 mg	NA	5.7 %	4.0 %	NA	6.9 %	4.1 %	NA	6.9 %	4.1 %
Rivaroxaban 15 mg	NA	7.3 %	5.1 %	NA	8.4 %	5.0 %	NA	8.4 %	5.0 %
Rivaroxaban 20 mg	NA	19.2 %	13.4 %	NA	22.5 %	13.4 %	NA	22.6 %	13.5 %
Apixaban 2.5 mg	NA	16.3 %	11.4 %	NA	19.1 %	11.4 %	NA	19.1 %	11.4 %
Apixaban 5 mg	NA	27.9 %	19.5 %	NA	32.7 %	19.5 %	NA	32.8 %	19.6 %
Charlson score (mean, ± SD)	5.0 ± 3.4	4.2 ± 3.4	4.5 ± 3.4	5.0 ± 3.4	4.2 ± 3.4	4.5 ± 3.4	4.5 ± 3.4	4.2 ± 3.4	4.5 ± 3.4
Charlson score < 4 (%)	37.9 %	50.7 %	45.5 %	62.0 %	50.8 %	45.6 %	45.7 %	50.9 %	45.7 %
Charlson score ≥ 4 (%)	71.1 %	49.3 %	54.5 %	38.0 %	49.2 %	54.4 %	54.3 %	49.1 %	54.3 %

[a] Non-GI extracranial major bleeding as an outcome or a predictor includes vitreous, urogenital, hemoperitoneal and unspecified major bleeding as well as hemoarthrosis, hemopericardium, hemoptysis, hematuria and post-bleeding anemia. [b] DOAC users include all doses of dabigatran, rivaroxaban and apixaban. [c] OAC users include all doses of warfarin, dabigatran, rivaroxaban and apixaban. [d] Represents a history of at least one of the bleeding subcategories OR at least one prescription of antiplatelet subcategory. Although each subcategory is mutually exclusive, the totals will not add up to the parent variable.

S7 Table. Logistic Regression LASSO analyses of Major Bleeding Subtype Predictors among OAC new users from 2011 to 2018.

	GI bleeding			Non-GI extracranial bleeding			Major bleeding (all types)		
	Warfarin (n=14,741)	DOAC [b] (n=21,640)	OACs [c] (n=36,381)	Warfarin (n=14,741)	DOAC [b] (n=21,640)	OACs [c] (n=36,381)	Warfarin (n=14,741)	DOAC [b] (n=21,640)	OACs [c] (n=36,381)
Age (%)									
≥75	1.13	1.42	1.39	-	1.32	1.13	1.05	1.60	1.37
Female (%)	-	-	-	1.20	-	1.14	1.14	-	1.09
Co-morbidities within 3 years before cohort entry									
Hypertension	1.12	1.13	1.21	1.02	-	1.08	1.14	1.09	1.15
Coronary artery disease (excl.	-	-	-	-	1.22	1.06	-	1.02	-
Acute myocardial infarction	-	1.10	-	1.43	1.25	1.41	1.04	1.11	1.09
Chronic heart failure	1.12	1.14	1.17	-	-	-	1.04	1.18	1.14
Cardiomyopathy	-	-	-	1.36	2.15	1.86	1.04	1.26	1.22
Other dysrhythmias	-	0.85	0.93	-	-	-	-	0.99	-
Valvular heart disease	-	1.15	1.09	1.36	-	1.24	1.05	1.12	1.10
Stroke/TIA	0.96	0.97	0.87	-	-	-	-	-	-
Peripheral vascular (arterial)	-	1.01	1.07	1.20	1.21	1.26	1.15	1.23	1.21
Dyslipidemia	-	1.02	-	-	-	-	-	-	-
History of major bleeding	1.53	1.49	1.58	1.65	1.65	1.72	1.51	1.59	1.57
Chronic renal failure	-	0.98	-	-	1.21	1.12	-	-	-
Chronic renal failure ≤ 30	-	-	-	1.08	-	1.21	-	-	-
Acute renal failure	-	-	-	1.14	-	1.07	-	-	-
Liver disease	1.78	2.53	2.38	1.39	-	1.12	1.81	1.28	1.64
Chronic obstructive pulmonary	1.33	1.15	1.29	1.08	1.49	1.34	1.02	1.21	1.13
Infection by Helicobacter	-	-	-	-	1.20	1.29	-	-	-
Concomitant medication use (within 2 weeks before cohort entry) (%)									
Statin	-	-	-	-	-	1.03	-	1.06	-
Antiplatelet	1.27	1.16	1.29	1.23	1.02	1.16	1.37	1.12	1.28
Proton pump inhibitors (PPIs)	-	-	0.95	1.12	-	1.07	-	-	-
NSAIDs	-	-	-	0.62	-	0.79	0.97	-	-
Antidepressants	-	-	-	-	-	-	1.16	-	1.10

Antidiabetics	-	-	1.05	1.17	1.39	1.33	1.17	1.10	1.19
OAC used at cohort entry									
DOAC type (dabigatran) [a]	NA	1.43	1.06	NA	1.05	-	NA	1.47	-
DOAC type (rivaroxaban) [a]	NA	-	-	NA	1.52	1.28	NA	-	-
DOAC type (apixaban) [a]	NA	1.0 (ref)	0.73	NA	1.0 (ref)	0.71	NA	1.0 (ref)	0.69
Model statistics									
Cross-val. C-Statistic (95% CI)	0.61 (0.57-0.64)	0.63 (0.60-0.66)	0.63 (0.61-0.66)	0.61 (0.57-64)	0.66(0.62-0.70)	0.64 (0.61-0.67)	0.60 (0.58-0.62)	0.63 (0.61-0.65)	0.63 (0.60-0.65)
Hosmer-Lemeshow p-value	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	0.01<p<0.0	p>0.05	p>0.05	p>0.05

All values are ORs. [a] In the DOAC group, the rivaroxaban and apixaban variables are compared to dabigatran. In the OAC group, dabigatran, rivaroxaban and apixaban are compared to warfarin. [b] DOAC users include all doses of dabigatran, rivaroxaban and apixaban. [c] OAC users include all doses of warfarin, dabigatran, rivaroxaban and apixaban.

S8 Table. Logistic Regression Adaptive LASSO analyses of Major Bleeding Subtype Predictors among OAC new users from 2011 to 2018.

	GI bleeding			Non-GI extracranial bleeding			Major bleeding (all types)		
	Warfarin (n=14,741)	DOAC [b] (n=21,640)	OACs [c] (n=36,381)	Warfarin (n=14,741)	DOAC [b] (n=21,640)	OACs [c] (n=36,381)	Warfarin (n=14,741)	DOAC [b] (n=21,640)	OACs [c] (n=36,381)
Age (%)									
≥ 75	1.23	1.54	1.50	-	1.47	-	-	1.71	1.44
Female (%)	-	-	-	1.16	-	-	1.11	-	1.10
Co-morbidities within 3 years before cohort entry									
Hypertension	1.24	1.13	1.30	-	-	-	1.13	1.08	1.18
Coronary artery disease (excl. MI)	-	-	-	-	1.22	-	-	-	-
Acute myocardial infarction	-	1.11	-	1.52	1.33	1.51	-	1.10	1.10
Chronic heart failure	1.13	1.13	1.19	-	-	-	-	1.18	1.12
Cardiomyopathy	-	-	-	1.46	2.43	1.96	-	1.34	1.25
Other dysrhythmias	-	0.81	0.89	-	-	-	-	-	-
Valvular heart disease	-	1.18	1.12	1.39	-	1.16	-	1.11	1.12
Stroke/TIA	0.91	-	0.82	-	-	-	-	-	-
Peripheral vascular (arterial)	-	-	1.07	1.20	1.26	1.26	1.13	1.26	1.23
Dyslipidemia	-	-	-	-	-	-	-	-	-
History of major bleeding	1.65	1.58	1.67	1.76	1.76	1.83	1.58	1.66	1.61
Chronic renal failure	-	-	-	-	1.22	1.02	-	-	-
Chronic renal failure ≤ 30 mL/min	-	-	-	1.32	1.02	1.21	-	-	1.09
Acute renal failure	-	-	-	1.07	-	-	-	-	-
Liver disease	2.21	2.98	2.65	1.57	-	-	1.97	1.41	1.75
Chronic obstructive pulmonary	1.51	1.15	1.35	-	1.60	1.32	-	1.23	1.15
Infection by Helicobacter pylori	1.42	-	-	-	1.65	1.26	-	-	-
Concomitant medications (within 2 weeks before cohort entry) (%)									
Statin	-	-	-	-	-	-	-	1.02	-
Antiplatelet	1.37	1.15	1.35	1.23	-	1.06	1.41	1.11	1.30
Proton pump inhibitors (PPIs)	-	-	0.91	1.07	-	-	-	-	0.94
NSAIDs	-	-	-	0.22	-	0.83	0.87	-	-

Antidepressants	-	-	-	-	-	-	1.15	-	1.11
Antidiabetics	-	-	-	1.14	1.51	1.34	1.16	1.10	1.21
OAC used at cohort entry									
DOAC_type (dabigatran) [a]	NA	1.51	1.10	NA	1.37	-	NA	1.50	-
DOAC_type (rivaroxaban) [a]	NA	-	-	NA	1.75	1.15	NA	-	-
DOAC_type (apixaban) [a]	NA	1.0 (ref)	0.69	NA	1.0 (ref)	0.81	NA	1.0 (ref)	0.65
Model statistics									
Cross-val. C-Statistic (95% CI)	0.61 (0.57-0.64)	0.62 (0.59-0.65)	0.63 (0.60-0.66)	0.61 (0.57-0.65)	0.65 (0.61-0.69)	0.65 (0.62-0.68)	0.60 (0.58-0.62)	0.62 (0.60-0.64)	0.63 (0.61-0.65)
Hosmer-Lemeshow p-value	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05

All values are ORs. [a] In the DOAC group, the rivaroxaban and apixaban variables are compared to dabigatran. In the OAC group, dabigatran, rivaroxaban and apixaban are compared to warfarin. [b] DOAC users include all doses of dabigatran, rivaroxaban and apixaban. [c] OAC users include all doses of warfarin, dabigatran, rivaroxaban and apixaban

S9 Table. Sensitivity analyses of the global MB model for all OAC users.

	Discrimination (cross-validated c-statistics)
Full cohort	0.63 (0.61-0.65)
Patients excluding deaths during follow-up	0.65 (0.64-0.67)
Adherent patients (PDC≥0.80)	0.62 (0.60-0.64)
Non-adherent patients (PDC<0.80)	0.63 (0.61-0.65)
OAC switchers during follow-up	0.61 (0.57-0.64)
OAC non-switchers during follow-up	0.64 (0.62-0.66)

Discrimination values for the global score in patients who did not die during follow-up, adherent patients (PDC≥0.80), non-adherent patients (PDC<0.80), patients who switched OAC in the year of follow-up and patients who did not switch OAC in the year of follow-up.

Discussion

Summary of important findings

There is a knowledge gap pertaining to the predictors of major bleeding for current populations of oral anticoagulant users with atrial fibrillation. This knowledge gap is even more significant with regards to major bleeding subtypes. Consequently, our study's main purpose was to derive prediction models for major bleeding and major bleeding subtypes from a cohort of direct oral anticoagulant and warfarin new users with atrial fibrillation. Our global major bleeding model had moderate discrimination (c-statistic 0.63 95% CI 0.60-0.65) and was adequately calibrated (Hosmer-Lemeshow p-value>0.05). The same model also had moderate discrimination for gastrointestinal bleeding and non-gastrointestinal extracranial bleeding. The selected predictors associated with the final model were liver disease (OR=1.64), major bleeding history (OR=1.57), age ≥ 75 (OR=1.37, relative to age < 75), antiplatelet use (OR=1.28), cardiomyopathy (OR=1.22), peripheral vascular disease (OR=1.21) and chronic obstructive pulmonary disease or asthma (OR=1.13).

Like the global model, the gastrointestinal bleeding model derived from all oral anticoagulant users in our cohort had moderate discrimination (c-statistic 0.63 95% CI 0.61-0.66). The important predictors analogous to both treatment groups (warfarin and direct oral anticoagulants) were all selected in the model derived from all oral anticoagulants. The gastrointestinal predictors identified in all treatment groups consisted of old age (OR=1.39), hypertension (OR=1.21), congestive heart failure (OR=1.17), major bleeding history (OR=1.58), liver disease (OR=1.38), chronic obstructive pulmonary disease or asthma (OR=1.29), and antiplatelet use (OR=1.29), while apixaban use was protective relative to warfarin use (OR=0.73). Likewise, our non-gastrointestinal extracranial bleeding model had moderate discrimination (c-statistic 0.64 95% CI 0.61-0.67) but was the first of its kind to be derived from any population of anticoagulated patients. It also selected a broader range of predictors than the gastrointestinal bleeding model of which the most significant ones were myocardial infarction (OR=1.41), cardiomyopathy (OR=1.86), valvular heart disease (OR=1.24), peripheral vascular disease (OR=1.26), major bleeding history (OR=1.72), chronic obstructive pulmonary disease or asthma (OR=1.34), prior H. Pylori infection (OR=1.29), antidiabetics (OR=1.33), and rivaroxaban use (OR=1.28), while apixaban (OR=0.71) was protective.

Of note, despite some shared predictors of GIB and NGIB in the "all oral anticoagulant" treatment group (age, peripheral vascular disease, valvular heart disease, prior major bleeding, liver disease, COPD, antiplatelet use, antidiabetic use and apixaban use), there were more differences than similarities between the models as shown by the predictors that were selected for only one of either outcome. These included sex, coronary artery disease, prior myocardial infarction, congestive heart failure, cardiomyopathy, prior stroke/TIA, all definitions of renal failure, H. pylori infection, NSAID use and rivaroxaban use).

This statistical prediction study was also one of the first to identify the predictors of major bleeding and major bleeding subtypes in warfarin and direct oral anticoagulant user populations from a single study. Our findings suggest that the predictors of any major bleeding presented similar trends between both treatment groups. Most of the important major bleeding predictors that were selected in both warfarin and direct oral anticoagulant users were those selected in the final model derived from a population of all oral anticoagulant users in the cohort. Likewise, the gastrointestinal bleeding predictors were similar between warfarin and direct oral anticoagulant users. The important predictors analogously selected in both treatment groups consisted of old age (OR=1.13 vs 1.42), hypertension (OR=1.12 vs 1.13), congestive heart failure (OR=1.12 vs 1.14), major bleeding history (OR=1.53 vs 1.49), liver disease (OR=1.78 vs 2.53), chronic obstructive pulmonary disease or asthma (OR=1.33 vs 1.15), and antiplatelet use (OR=1.27 vs 1.16) for warfarin and direct oral anticoagulant users, respectively. These models mirrored the important predictors selected in the gastrointestinal model derived from all oral anticoagulant users from the cohort. However, these results only pertain to observed trends as no conclusion can be made about how the variables compare to each other on account of the absence of confidence intervals and the nature of prediction modelling.

On the other hand, the selected predictors of non-gastrointestinal extracranial bleeding were generally different between the treatment groups in large part due to the selection of distinct predictors. However, as mentioned previously, these comparisons can just be reported as trends as per the absence of confidence intervals. The main warfarin-associated predictors were female sex (OR=1.20), acute myocardial infarction (OR=1.43), cardiomyopathy (OR=1.36), valvular heart disease (OR=1.36), perivascular vascular disease (OR=1.20), major bleeding history (OR=1.65), liver disease (OR=1.39), antiplatelet use (OR=1.23), use of NSAIDs (OR=0.62, protective) and use of antidiabetics (OR=1.17), while direct oral anticoagulant-associated predictors were old age (OR=1.32), coronary artery disease

(OR=1.22), acute myocardial infarction (OR=1.25), cardiomyopathy (OR=2.15), peripheral vascular disease (OR=1.21), major bleeding history (OR=1.65), liver disease (OR=1.49), prior H. Pylori infection (OR=1.20), use of antidiabetics (OR=1.39) and use of rivaroxaban (OR=1.52, relative to apixaban). This was most probably due to the variable sources of bleeding included in the definition of non-gastrointestinal extracranial bleeding, of which the most prevalent ones were genitourinary bleeding and hematuria.

Comparison of model performance to published major bleeding models

Our selected major bleeding prediction model performed similarly to other major bleeding scores. Most significantly, our model's c-statistic of 0.63 (0.60-0.65) were concordant with meta-analysis findings for the HAS-BLED, (pooled c-statistic=0.65 95% CI 0.61-0.69), the HEMORR$_2$HAGES (pooled c-statistic=0.63 95% CI 0.61-0.66) and the ATRIA (pooled c-statistic=0.63 95% CI 0.56-0.72) [117]. However, it is important to note that the comparisons of our score's performance to that of other risk scores are only hypothetical and require further testing.

Furthermore, given that the HAS-BLED was derived from warfarin data, it may exclude important predictors of direct oral anticoagulant-associated major bleeding. Consequently, there is a need for a score that is derived from a cohort which includes all types of oral anticoagulant users as opposed to only being validated for direct oral anticoagulant users. Two scores were derived from post-warfarin era anticoagulant user data, the ORBIT-AF and the ABS score. While the discriminatory potential of the ORBIT-AF score (c-statistic 95% CI 0.65 0.64-0.66) was similar to ours, the ABS score performed somewhat better (c-statistic 95% CI 0.67-0.69) [113, 114]. However, its ability to predict major bleeding subtypes has yet to be evaluated.

Our study was also one of the few to have tested the ability of its major bleeding prediction model to detect major bleeding subtypes. The availability of scores that can accurately predict major bleeding subtypes is essential to patient care, since common ones like gastrointestinal bleeding can significantly impact patient quality of life, post-bleeding direct oral anticoagulant adherence, and mortality [166, 167]. A study that used direct oral anticoagulant user data from three hospitals has compared the HAS-BLED's ability to detect bleeding subtypes to that of other scores. It concluded that the HAS-BLED performed best in detecting major gastrointestinal bleeding relative to ATRIA and ORBIT (c-statistics:

0.74 [95% CI 0.71-0.76] vs 0.71 [95% CI 0.68-0.74], and 0.69 [95% CI 0.66-0.72], respectively) [129]. When considering this major bleeding subtype, the model performance of the HAS-BLED and ATRIA superseded that of ours (c-statistic=0.65 95% CI 0.63-0.66). However, the interpretability of the study was severely constrained by its limited generalizability to a North American real-world oral anticoagulant user population, its limited generalizability to warfarin users, its small sample size and the low frequency of bleeding outcomes. Moreover, according to the ABC score's derivation study, the HAS-BLED performed better than the ABC score in detecting gastrointestinal bleeding (c-statistics: 0.596 and 0.519, respectively, $p<0.05$) [125]. In conflict with the findings from Caro-Martinez et al., our own major bleeding risk score (c-statistic 0.65, 95% CI 0.66-0.72) overperformed relative to both scores.

Finally, no existing score has been tested for its ability to detect non-gastrointestinal extracranial bleeding, despite its prevalence rivaling that of gastrointestinal bleeding [129, 168, 169]. Our model predicted non-gastrointestinal extracranial bleeding as well as it did major bleeding and gastrointestinal bleeding (c-statistic 0.67 95% CI 0.64-0.70). Thus, one of the advantages of our major bleeding model is that, according to our preliminary findings, it predicted gastrointestinal bleeding and non-gastrointestinal extracranial bleeding as well as it does major bleeding.

However, our study has two important advantages. First, although we did not yet have the opportunity to validate our findings with independent data, very few studies used cross-validation or bootstrapping on model performance indices as is recommended by the TRIPOD guidelines for clinical prediction studies despite incorporating bootstrapping in their regression methods [25, 112, 113, 160]. This could lead to an overestimation of the discriminatory potential of the model (a greater c-statistic relative to the true value) due the model being overfit to the derivation data. Secondly, our models are theoretically robust due to the nature of the methods used in this study. Lastly, our findings preliminarily suggest that our global model is well calibrated, although this will require further validation. Conversely, meta-analysis findings suggest that the HAS-BLED displayed inadequate calibration, and most significantly so, for patient at moderate risk of major bleeding [117]. Therefore, our model has the potential to predict MB more stably than existing ones.

Similarities of predictors with published prediction models

The OR values for the most important predictors identified in our final model mirrored the relative risk of the predictors selected in the models used to derive existing major bleeding scores. Firstly, the ABS score selected analogous predictors to our own model. Analogously selected predictors included age, albeit defined continuously (HR=1.02, 95% CI 1.02-1.03), prior major bleeding (HR=1.27, 95% CI 1.18-1.36), antiplatelet therapy (HR=1.25, 95% CI 1.16-1.35), and chronic obstructive pulmonary disorder (HR=1.21, 95% CI 1.13-1.30) [114]. Furthermore, the analyses used to derive the ORBIT-AF score, derived from a population of warfarin and dabigatran users, also selected comparable predictors. These included age ≥ 75 (HR=1.38, 95% CI 1.17-1.61), any prior bleeding (HR=1.73, 95% CI 1.34-2.23), and antiplatelet therapy (HR=1.51, 95% CI 1.30-1.75) [113]. Similarly, the analyses used to derive the HAS-BLED selected age ≥ 65 (OR=2.66, 95% CI 1.33-5.32) as a predictor of major bleeding [25].

Lastly, a registry-based cohort study of rivaroxaban users with atrial fibrillation identified similar modifiable and non-modifiable major bleeding predictors. The former consisted of uncontrolled hypertension (HR=1.79, 95% CI 1.05-3.05) and use of antiplatelets, NSAIDs, or paracetamol (HR=1.80, 95% CI 1.24-2.61), while heart failure and vascular disease were reported as important nonmodifiable risk factors (HR=1.97 95% CI 1.36-2.86 and 1.91, 95% CI, 1.32-2.77, respectively). Although increased age was defined differently than in our cohort (per 5-year increments), it was also selected (HR=1.25; 95% CI 1.12-1.38) [110].

Although, in prediction studies, the predictors are not usually considered beyond the performance of the models they constitute, these similarities are worth mentioning as their consistent selection across studies speaks to their relevance to different populations of oral anticoagulant users with atrial fibrillation. Although this will need to be tested further, it also speaks to the potential generalizability of our models beyond a population of Quebec oral anticoagulant users diagnosed with atrial fibrillation.

Differences with published prediction models

Conversely, there were also differences in the predictors selected by the analyses used to derive existing major bleeding scores and our own model. The analyses used to derive the HAS-BLED score yielded an estimate for prior major bleeding (OR=7.51, 95% CI 3.00-18.78) that deviated significantly from ours [25]. The high prior major bleeding point estimate may be attributable to the small sample size, which

may have led to an unstable prediction model or the missing data (25%), which may have led to selection bias given that at-risk patients with multiple comorbidities were more likely to be lost to follow-up. However, it is not possible to attribute this difference to the characteristics of the HAS-BLED's derivation cohort population, since its patients were, on average, younger and at lower risk of major bleeding than ours. Moreover, the HAS-BLED models also selected renal failure (OR=2.86, 95% CI, 1.33-6.18), while this variable was not selected in ours. Since the use of warfarin was (and still is) indicated in patients with renal failure at any degree of severity, the analyses used to derive the HAS-BLED are more likely to select it as a predictor in the HAS-BLED derivation cohort. The non-selection of this variable may be due to the contraindication of direct oral anticoagulant use for patients with renal failure in our cohort. Moreover, the approval of direct oral anticoagulants led to more stringent monitoring and dosing guidelines in patients with different degrees of renal failure [14, 15, 19]. This may explain that patients with this co-morbidity are less at risk of major bleeding in our derivation cohort, relative to the HAS-BLED's.

For the ABS score, renal failure was also selected as a predictor [114]. This may be due to the different variable selection processes between the logistic-LASSO regression and the bootstrapped Cox proportional hazard regression. However, unlike the HAS-BLED's derivation model, in which age was categorical, the ABS score defined age continuously. Since oral anticoagulant prescription is associated with age categories and kidney function, the impact of renal failure on major bleeding is most likely masked by the association between age categories and major bleeding as well as its association to renal failure [15, 23].

With regards to the ORBIT-AF, it could be due to the fact that there was a much greater proportion of warfarin users in their study (~90%) relative to ours (~40%). Therefore, like with the ABS score, given that age categories are not used in warfarin prescription and the association between age categories, renal failure and direct oral anticoagulant prescription practices, the association between renal failure and major bleeding was not masked in the analyses used to derive the ORBIT score, while it may have been in our study [113].

Meanwhile, a study identifying percutaneous coronary intervention patients at high bleeding risk presented some conflicting findings to ours. Unlike our study, it identified severe kidney disease as a major bleeding risk factor ($p<0.05$), mild to moderate kidney disease, NSAID or steroids use and prior

stroke as minor bleeding risk factors ($p<0.05$), but did not identify liver disease as a major bleeding risk factor ($p>0.05$). In addition to differences in our study population and different bleeding outcome definitions, it was evaluating each risk factor only if it was present individually [170].

Finally, two potential reasons that can explain all of these differences that is common to all the existing major bleeding scores are the differences in candidate predictors that were considered and differences in the derivation cohort characteristics. For instance, almost all models omitted liver disease in their analyses. Additionally, the HAS-BLED's derivation and validation cohorts had a much lower mean age relative to our patient population, a lower risk of stroke and a lower rate of prior major bleeding [25]. The ORBIT-AF's derivation cohort had a slightly higher risk of stroke and a lower bleeding risk [113]. Meanwhile, for the ABS, the cohort was younger and less at risk of bleeding [114].

Comparison to published major bleeding subtype models

Meanwhile, no study has identified the predictors for the most prevalent major bleeding subtypes among direct oral anticoagulant and warfarin users, thereby making it difficult to know what variables may be important to consider when designing a major bleeding risk score. Although the sample size of our cohort constrained our ability to identify predictors of intracranial hemorrhage, our study is the first to identify predictors of gastrointestinal bleeding and non-gastrointestinal extracranial bleeding using a derivation cohort of direct oral anticoagulant and warfarin users as well as robust prediction methods. Although its generalizability to other direct oral anticoagulant users is limited, an observational study identified the predictors of gastrointestinal bleeding in a patient population of dabigatran users with atrial fibrillation. Like our model, theirs selected heart failure (HR=1.25, 95% CI 1.01-1.56) and antiplatelet therapy (HR=1.49, 95% CI 1.19-1.88). However, unlike ours, it selected renal impairment (HR=1.67, 95% CI 1.24-2.25) and previous Helicobacter pylori infection (HR=4.75, 95% CI 1.93-11.68) as significant gastrointestinal bleeding predictors. Our model may not have selected H. Pylori infection on account of the low percentage of affected patients in our cohort, while renal impairment may have been selected because of their categorization of age which, unlike ours, did not mask the associations between direct oral anticoagulant prescription, CKD and major bleeding in the year of follow-up. Notably, it did not consider major bleeding history or liver disease as candidate predictors. However, neither calibration, nor discrimination were assessed, and robust prediction methods were not used [95]. Two other prediction schemes (the Qbleed prediction models) were designed to predict upper

gastrointestinal bleeding and intracranial hemorrhage. Despite performing well (c-statistic > 0.70), only 1% of the derivation cohort were oral anticoagulant users and less than 0.04% were direct oral anticoagulant users. Thus, the generalizability of these findings to warfarin users and, most significantly, direct oral anticoagulant users is questionable [131]. However, despite this important difference, in concordance with the predictors of gastrointestinal bleeding of our models, their study still identified prior bleeding, congestive heart failure and hypertension as important predictors of upper gastrointestinal bleeding. The lack of understanding of the predictors of major bleeding subtypes both limits the quality of monitoring for at-risk patients and are associated with significant costs [36].

Internal validity

In accordance with the "The Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines, we can address the quality of our study by considering the data source, the cohort definition, variable definitions, sources of bias, study size, missing data and statistical methods [171].

Firstly, as stated previously, while our data source is notorious for its accuracy and lack of missing data, none of our patient selection criteria were associated with both the study exposures and outcomes. Other types of selection biases were also unlikely. Immortal time bias, for instance, was likely negligeable, if present, since 85% of patients had their first oral anticoagulant claim two weeks after hospital discharge and follow-up only began after the first oral anticoagulant exposure. Likewise, competing risk bias was also improbable, since the only possible event that could have realistically modified the risk of our outcome of interest was bleeding, itself. While competing risk is inconsequential to major bleeding events at the same location since only the first event is under study, only 24 patients (2.4% of those with major bleeding) had 2 or more major bleeding events at different locations. However, as we used a method that did not account for survival time, loss-to-follow-up bias may have occurred since our cohort patents were generally older and had multiple co-morbidities, while those prone to major bleeding were even more so. Nevertheless, we do not expect this limitation to impact model performance. This will be further discussed in the next section.

Information bias was likely minimal since both outcomes were evaluated using diagnostic codes with positive predictive values consistently exceeding 85% and exposures were clearly defined. However, our estimation of drug use using claims data may have led to a differential misclassification bias since

patients more prone to bleeding, who are older and sicker, are less likely to claim prescribed medications.

However, since explanatory modelling was not the goal of our study, confounding was inevitably present in our models. As a result, variables which were reported to be highly and independantly associated with bleeding in multiple studies such as renal failure were not consistently included in our models [60, 114]. Unmeasured confounding may also be attributable to the absence of variables highly predictive of bleeding such as alcohol use, tobacco use and over-the-counter ASA use in our source data [42, 172, 173]. Lastly, due to the nature of penalty-based regression, our regression coefficients are inherently biased, thus speaking to why it is not advisable to interpret the individual estimates causally. Since the goals of prediction modelling are inherently different from those of explanatory modelling, it is important to separately discuss how the model derivation strategy used in this study maximized the performance of the associated predictive models.

Strengths and limitations of our predictive model derivation strategy

To evaluate the quality of a predictive model derivation or validation study, the "Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis" (TRIPOD) guidelines are mainstay and, interestingly, still mirror the important methodological steps for dealing with selection, indication and confounding bias [160]. Generally, we can categorize these steps as such: an adequate cohort definition, adequate variable definitions, use of robust prediction tools and the use of adequate performance evaluation metrics.

We specifically defined the derivation cohort in function of our population of interest by excluding other indications for oral anticoagulant use and contraindications for direct oral anticoagulant use. In doing so, we ensured that our prediction models would perform consistently with independent data that still originates from our population of interest. Furthermore, the size of our cohort was sufficiently large to establish robust prediction models and evaluate over 25 candidate predictors for each outcome in each subgroup. It is, however, important to note that, due to the observational nature of our data, our models are only applicable to a real-world setting.

We also clearly defined our outcomes of interest using validated diagnostic codes and only evaluated well-defined and clinically useful variables as candidate predictors. This step was imperative since an

inaccurate or unclear variable definition would have hindered prediction model performance or limited the reproducibility of the study findings, respectively [174]. Conversely, the definitions of some of the candidate predictors may have led to suboptimal model performance since drug dispensation does not necessarily represent drug utilization and patients with prior cardiovascular diseases may not have been identified due to errors in diagnostic coding. Nonetheless, this limitation is unlikely to be significantly impactful in our population of interest as exemplified by a study suggesting that significant predictor misclassification only marginally hindered the performance of the CHA_2DS_2-VASc [175]. Lastly, given the nature of our cohort, we could not use adherence at baseline as a candidate predictor. Our outcome definition also did not consider oral anticoagulant switching and patient loss-to-follow-up. However sensitivity analyses, suggest that neither of oral anticoagulant non-adherence, oral anticoagulant switching, nor patient loss-to-follow-up impacted the performance of our global model (Table S4)

Moreover, unlike our study, previous major bleeding prediction model derivation studies only relied on pre-existing risk scores in their selection of candidate predictors instead of fully reviewing major bleeding risk factors identified in the literature and did not consider candidate predictors of important clinical relevance (i.e. liver disease). However, while our source data did include a wide array of useful variables, we could not use detailed inpatient data such as weight, glomerular filtration rate, blood pressure, and labile INR to validate our models due to their absence in our source dataset.

Most significantly, compared to the methods used to derive existing major bleeding prediction models, log-LASSO regression could theoretically select more robust models by reducing overfitting and make the model easier to interpret by removing redundant or uninformative variables [25, 111-114, 165]. Moreover, unlike previous studies, our model's performance indices were cross-validated [25, 111-115]. This means that our model performance metrics are less likely to be overestimated than they would be in other studies that did not validate their findings using independent data. However, there may be theoretical limitations associated with the use of LASSO-logistic regression as a prediction method in our population of interest, since most relevant prediction studies used cox proportional hazard models and our cohort was inherently susceptible to loss-to-follow-up. However, as stated previously, our sensitivity analyses suggest that model performance was not limited by patient loss-to-follow-up (Table S4).

External validity

It is important to identify the populations with which our prediction model may perform effectively. Our findings are not generalizable to any other common oral anticoagulant indication. The use of oral anticoagulants in orthopedic surgery, for instance, would be the most obvious example of an oral anticoagulant indication in which our models lack generalizability to. In addition to being significantly different to atrial fibrillation patients, orthopedic surgery patients present major differences in underlying conditions and a different set of potential major bleeding predictors associated with the operation itself. For this reason, the use of major bleeding risk scores like the HAS-BLED is categorically discouraged in this patient population and not even discussed in the literature.

When used to treat venous thromboembolism, oral anticoagulant anticoagulation is typically used for 3 months, but it can occur over different treatments phases which are each associated with a different risk of bleeding. Moreover, the use of low-molecular-weight-heparin also needs to be factored in the prediction models. Finally, although similar major bleeding predictors have been reported in a population of patient with venous thromboembolism, there are significant populational differences to oral anticoagulant users with atrial fibrillation that are attributable to demographics, underlying conditions, concomitant medication use, difference in oral anticoagulant initial dosing [176]. Typically, other models have been developed to predict major bleeding in this population [177].

It is more likely that our findings are generalizable to edoxaban users with atrial fibrillation to the populational similarities among all patient population of direct oral anticoagulant users, the similarities in prescription guidelines and the similar mechanism of action [14, 33].

As our findings are derived from a Canadian patient population, it is possible that the models will perform well in an US patient population due to populational similarities (e.g. sex, age and prevalence of certain co-morbidities) [178]. However, the differences in healthcare access, poverty rates, and the approved direct oral anticoagulant dosages between the two countries could also limit the models' performance in that population. Our findings may also be generalizable to European oral anticoagulant users with atrial fibrillation since Europe's approved direct oral anticoagulant dosages are similar to Canada's. However, there are significantly greater populational differences in many relevant comorbidities. For similar reasons, our findings are most likely not generalizable to an African or Asian population. To this effect, although antiplatelet use and prior major bleeding were selected as predictor in models derived from a US population (the ORBIT and ABS score studies), a European population (the HAS-BLED) and a Canadian population (our model), there is lack of consistency in the definition

of variables across models. This is due to a lack of standardization in clinical definitions across the countries from which the models were derived from. This is not a study limitation, per se, but speaks to the importance of harmonizing clinical diagnostic recording worldwide and the potential challenge in creating a prediction model that is generalizable to other countries.

Furthermore, given that our cohort only included patients who were hospitalized, they are generally older and sicker than the general population of oral anticoagulant users with atrial fibrillation. Thus, although it is likely that our models are generalizable to it, our findings will need to be validated in a population of patients who were not hospitalized.

Lastly and most importantly, to adequately compare our model to existing prediction scores or models, net reclassification improvement and integrated discrimination improvement analyses would need to be conducted with a dataset supplemented with clinical data. Thus, our interpretations about how our models compare to the existing scores and models are only hypothetical and need to be adequately validated. This is particularly true for the HAS-BLED, which has been extensively tested in different population of oral anticoagulant users and has the advantage of already being well-established clinically.

Future work

Future studies will predominantly involve model validation with independent data, risk stratification, and comparisons to other scores. Firstly, our models will need to be validated in a cohort of patient that was not hospitalized, one that includes edoxaban users and, potentially, one that is external to Quebec. Secondly, risk stratification, which involves assigning a predefined major bleeding risk status (low, moderate, high) to each individual on the basis of important predictors and thresholds of estimated risks, is especially important, because one of the key barriers to oral anticoagulant prescription was reported to be the overestimation of the risk of bleeding on the part of physicians [179]. Finally, it will be important to compare the discriminatory potential of the HAS-BLED and other pre-existing scores to our model fit using adequate comparative model performance metrics for both major bleeding and its subtypes. Since the HAS-BLED incorporates data that can only be determined in a clinical setting such as labile INR, it will be important to use a dataset that includes the relevant inpatient data.

Of note, any causal interpretation of the association between our predictors and major bleeding or its subtypes are speculative due to the nature of prediction modelling. However, our findings could lead to future studies aimed at evaluating major bleeding risk factors individually to confirm our speculations.

Conclusion

This is the first study to have developed a major bleeding prediction model that was derived from all oral anticoagulants users that has been tested for non-gastrointestinal extracranial bleeding and gastrointestinal bleeding. It is also the only study to have identified predictors of non-gastrointestinal extracranial bleeding and gastrointestinal bleeding. In spite of minor differences, our analyses identified similar major bleeding, most notably, were liver disease, major bleeding history, old age ≥ 75, antiplatelet use, peripheral vascular disease and chronic obstructive pulmonary disease. The discriminative potential of our final model and its associated predictors are concordant with published data on the HAS-BLED, ORBIT-atrial fibrillation and ABS scores. Moreover, our final model was well-calibrated and performed as reliably in predicting major bleeding as it did gastrointestinal bleeding and non-gastrointestinal extracranial bleeding. Finally, we have confirmed that the predictors of major bleeding are largely similar between direct oral anticoagulant and warfarin user. Significantly, our models were generated using a method that is more robust that any of the existing major bleeding scores. For this reason, we lay the groundwork for the development of a much-needed monitoring tool that encompasses a more diverse range of major bleeding risk factors which better represent the heterogeneity of oral anticoagulant user and major bleeding subtype characteristics. However, although our models can be used with administrative data pertaining to older oral anticoagulant users with atrial fibrillation who have been hospitalized (e.g. to measure confounding), our models will need to be validated in other atrial fibrillation populations, and compared to the HAS-BLED using clinical data. In doing so, we hope to develop a tool that can lessen the burden of bleeding for oral anticoagulant users with atrial fibrillation.

Ethics

The protocol was approved by the University of Montreal Health Research Ethics Committee (cert. 17-068-CERESD) and the Comity of Access to Personal Information (CAI).

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Appendix

Tables

Table S1. Outcome definition (ICD-9 and ICD-10 codes for GIB, NGIB, MB)

	ICD-9 codes	**ICD-10 codes**
Major Bleed (MB)		
Haemorrhagic stroke intracranial (non-traumatic; ICH)	430, 431, 432.x	I60, I61, I62
Haemorrhagic stroke intracranial (traumatic; ICH)	852x, 853x	S063, S064, S065, S066
Major GI bleeding (GIB)	Upper GI: 456.1, 530.7, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x. 532.6x, 533.0x. 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 537.83, 578.0 Lower GI: 562.02, 562.03, 562.12, 562.13, 569.3x, 569.85, 578.1x, 578.9	Upper GI: I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K2901, K290, K31811, K920 Lower GI: K921, K922, K5711, K5713, K5731, K5733, K625, K5521
Major Non-GI Extracranial Bleed (NGIB)	Hematuria: 599.7 Hemoptysis: 786.3x Vitreous bleeding: 379.23 Urogenital bleeding: 626.2x,280.0 285.1,285.9 Hemarthrosis: 719.1x Hemopericardium: 423.0x Hemoperitoneal MB: 568.8 Unspecified MB: 459.0x Post-bleed anemia: 285.1x	Hematuria: R31 Hemoptysis: R042, R0489, R049 Vitreous bleeding: H43.13 Urogenital bleeding: N92.0, D50.0, D62, D64.9 Hemarthrosis: M250x Hemopericardium: I31.2 Hemoperitoneal MB: K66.1 Unspecified MB: R58.0 Post-bleed anemia: D62

Table S2. Definition of CHADS2-VASc2, modified HAS-BLED, ATRIA, HEMORR$_2$HAGES and ORBIT-AF risk scores along with their scoring algorithms.

Risk score definition	Points, if present
CHA$_2$DS$_2$-VASc stroke risk score	
Congestive heart failure or left ventricular dysfunction	1
Hypertension	1
Age	1
Age ≥ 75 years	2
Diabetes Mellitus	1
Stroke (ischemic stroke, transient ischemic disease or systemic embolism	2
Vascular disease (myocardial infarction, peripheral arterial disease or aortic plaque	1
Sex category (female)	1
HAS-BLED bleeding risk score	
Hypertension	1
Abnormal renal function	1
Abnormal hepatic function	
Abnormal Stroke (ischemic stroke, transient ischemic disease	1
Bleeding	1
Older than > 65 years	1
Labile 65 – 74 years international normalized ratio (not available)	1
Drugs (ASA, clopidogrel, prasugrel, ticagrelor, ticlopidine, or non-steroidal anti-inflammatory drugs) in the 1 month preceding the ICH hospitalization or 1month after discharge	1
Alcohol intake	1
ATRIA bleeding risk score	
Anemia (Male: Hemoglobin <13 g/dL; Female: Hemoglobin <12 g/dL)	3
Severe Renal Disease (Glomerular filtration rate <30 mL/min or dialysis)	3
Age ≥ 75 years	2
Any Prior Hemorrhage Diagnosis	1
Hypertension History	1
HEMORR$_2$HAGES bleeding risk core	1
Hepatic or Renal Disease	1
Ethanol (Alcohol) Abuse	1
Malignancy History	1
Older (Age > 75)	1
Reduced Platelet Count or Function	1
Rebleeding Risk (bleeding history)	1
Hypertension (Uncontrolled)	1
Anemia (Male: Hemoglobin <13 g/dL; Female: Hemoglobin <12 g/dL)	1
Genetic Factors (CYP 2C9 single-nucleotide polymorphisms)	1
Excessive Fall Risk	1
Stroke History	1
ORBIT-AF bleeding risk score	
Anemia (Male: Hemoglobin <13 g/dL; Female: Hemoglobin <12 g/dL)	2
Age >74 years	1
Bleeding history	2
GFR <60 mL/min/1.73 m2	1
Antiplatelet agent use	1

Table S3. Definition of co-morbidity and concomitant medication variables used for CHA$_2$DS$_2$-VASc and HAS-BLED risk score calculation according to ICD-9 and ICD-10 codes from the Med-Echo databases.

	ICD-9 codes	ICD-10 codes
CHA_2DS_2-VASc		
Congestive heart failure	402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 425.4, 428.0	I11.0, I13.0, I13.2, I42.0, I50
Left ventricular dysfunction	428.1, 428.9	I50.1, I50.9
Hypertension	401	I10
Diabetes	250.x	E08, E10, E11, E13
Ischemic stroke	433.xx, 434.xx, 436	I63 except 63.6, I67.89
Systemic embolism	444.x, 557.0, 362.31, 362.32, 598.31	I74, K55.0, H34.1, H34.2, N28.0
Transient ischemic stroke (TIA)	435.x	G45
Aortic plaque	440.0	I70.0
Peripheral arterial disease	440 (except 440.0), 441, 443.0, 443.89, 443.9	I70.1 to I70.9, I71, I73.0, I73.89, I73.9
Myocardial infarction	410.xx	I21, I22, I23
Modified HAS-BLEED		
Ischemic stroke	433.xx, 434.xx, 436	I63 except I63.6, I67.89
Transient ischemic-attack	435.x	G45
Moderate to severe renal disease	404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 580.0, 580.4, 581.0, 581.1, 581.2, 581.3, 581.89, 581.9, 582.0, 582.1, 582.2, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.7, 583.6, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 586, 590.0, 590.01, 590.80	I12, I13, N00, N01, N02, N03, N04, N05, N07, N11, N12, N14, N17, N18, N19
Moderate to severe liver disease	570, 572.3, 070.0, 070.21, 070.20, 070.60	K7200, K762, K766, B150, B160, B162, B190, K704, I85
Haemorrhagic stroke intracranial (non-traumatic)	430, 431, 432.x	I60, I61, I62
Extracranial major or unclassified major bleeding	Upper GI: 456.1, 530.7, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x. 532.6x, 533.0x. 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 537.83, 578.0 Lower GI: 562.02, 562.03, 562.12, 562.13, 569.3x, 569.85, 578.1x, 578.9 Other sites: Hematuria: 599.7 Hemoptysis: 786.3x Vitreous bleeding: 379.23 Urogenital bleeding: 626.2x,280.0 285.1,285.9 Hemarthrosis: 719.1x Hemopericardium: 423.0x Hemoperitoneal MB: 568.8 Unspecified MB: 459.0x Post-bleed anemia: 285.1x	Upper GI: I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K2901, K290, K31811, K920 Lower GI: K921, K922, K5711, K5713, K5731, K5733, K625, K5521 Other sites: Hematuria: R31 Hemoptysis: R042, R0489, R049 Vitreous bleeding: H43.13 Urogenital bleeding: N92.0, D50.0, D62, D64.9 Hemarthrosis: M250x Hemopericardium: I31.2 Hemoperitoneal MB: K66.1 Unspecified MB: R58.0 Post-bleed anemia: D62
Traumatic intracranial bleeding	852x, 853x	S063, S064, S065, S066
Clopidogrel, ticlopidine, prasugrel, ticagrelor	46486, 47307, 45617, 47402, 47834, 47866	46486, 47307, 45617, 47402, 47834, 47866

Low dose ASA	00143, 46353 (daily dose < 100 mg)	00143, 46353 (daily dose < 100 mg)
Non steroidal anti-inflammatory drugs (NSAIDs)	46353, 38184, 47327, 47078, 41694, 47059, 43150, 47122, 33803, 44749, 04745, 46654, 47506, 04810, 38691, 44359, 47385, 47084, 19752, 47890, 07462, 42019, 47346, 47107, 40381, 45592, 45407, 03766	46353, 38184, 47327, 47078, 41694, 47059, 43150, 47122, 33803, 44749, 04745, 46654, 47506, 04810, 38691, 44359, 47385, 47084, 19752, 47890, 07462, 42019, 47346, 47107, 40381, 45592, 45407, 03766
Alcohol	331.7, 359.4, 425.5, 577.1	E224, E529A, F10, G312, G612, G721, I426, K292, K70, K860, L278A, O354, T51, Z714, Z721

Table S4. Sensitivity analyses of the global MB model for all OAC users.

	Discrimination (cross-validated c-statistics)
Full cohort (n=36,381)	0.63 (0.61-0.65)
Patients excluding deaths during follow-up (n=30,894)	0.65 (0.64-0.67)
Adherent patients (PDC≥0.80) (n=24,802)	0.62 (0.60-0.64)
Non-adherent patients (PDC<0.80) (n=11,579)	0.63 (0.61-0.65)
OAC switchers during follow-up (n=6,022)	0.61 (0.57-0.64)
OAC non-switchers during follow-up (n=30,359)	0.64 (0.62-0.66)

Discrimination values for the global score in patients who did not die during follow-up, adherent patients (PDC≥0.80), non-adherent patients (PDC<0.80), patients who switched OAC in the year of follow-up and patients who did not switch OAC in the year of follow-up.