Comparison of the efficacy, safety, and adherence of oral anticoagulants

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Samanburður á virkni, öryggi og meðferðarheldni blóðþynningarlyfja um munn

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“I've been to Hollywood

I've been to Redwood

I crossed the ocean for a heart of gold

I've been in my mind

It's such a fine line

That keeps my searching for a heart of gold

And I'm getting old”

Neil Young

Ágrip

Blóðþynningarlyf um munn eru meðal algengustu uppáskrifuðu lyfja á heimsvísu. Vítamín K-hemlar, eins og warfarín, voru einu blóðþynningarlyfin um munn í meira en 60 ár eða þar til beinir storkuhemlar komu á markað á árunum 2009-2013. Beinir storkuhemlar hindra blóðstorku með því að hemja annað hvort blóðstorkuþátt II (dabigatran) eða X (apixaban, edoxaban og rivaroxaban). Niðurstöður upphaflegra slembiraðaðra rannsókna sýndu að beinir storkuhemlar voru tengdir við svipaða tíðni blóðsega og lægri tíðni stórvægra blæðinga samanborið við warfarín. Í framhaldinu hefur verið mælt með notkun beinna storkuhemla sem fyrstu meðferðar hjá sjúklingum með gáttatif eða bláæðasega. Engar slembiraðaðar rannsóknir bera þó beina storkuhemla innbyrðis og fyrri áhorfsrannsóknir hafa haft mikilvægar takmarkanir. Auk þess eru til takmörkuð gögn um samanburð á tíðni efri og neðri meltingarvegsblæðinga og nefblæðinga milli blóðþynningarlyfja um munn. Að sama skapi er enn óljóst hvort meðferðarheldni sé frábrugðin milli warfaríns og beinna storkuhemla.

Markmið verkefnisins var að bera saman virkni, öryggi og meðferðarheldni mismunandi blóðþynningarlyfja um munn. Markmið greinar I var að bera saman tíðni blóðsega og stórvægra blæðinga milli beinna storkuhemla. Markmið greinar II var að bera saman tíðni meltingarvegsblæðinga milli beinna storkuhemla. Markmið greinar III var að bera saman tíðni efri og neðri meltingarvegsblæðinga milli warfaríns og beinna storkuhemla. Markmið greinar IV var að bera saman tíðni nefblæðinga milli warfaríns og beinna storkuhemla. Að lokum var markmið greinar V að bera saman meðferðarheldni milli mismunandi blóðþynningarlyfja um munn.

Rannsóknargagnagrunnur var búinn til sem innihélt upplýsingar um alla sjúklinga á Íslandi sem fylltu út blóðþynningarlyf um munn á tímabilinu 1. mars 2014 til 28. febrúar 2019. Gagnagrunnurinn samanstóð af upplýsingum frá lyfjagagnagrunni Landlæknis, dánarmeinaskrá og rafrænum gagnagrunnum Landspítalans, fjórðungssjúkrahúsunum á Akranesi, Akureyri, Ísafirði, Neskaupsstað og heilsugæslum víðs vegar um landið. Öll blóðsega- og blæðingartilfelli voru staðfest handvirkt með því að fara inn í sjúkraskrár sjúklinga. Rannsóknarþýðið samanstóð af öllum sjúklingum sem hófu meðferð með apixaban, dabigatran, rivaroxaban og warfarín á rannsóknartímabilinu. Líkindaskorsvigtun var notuð til að fá samanburðarhæfa hópa. Blæðingar- og blóðsegatíðni var borin saman með Cox aðhvarfsgreiningu og Kaplan-Meier lifunarmati. Léleg meðferðarheldni var skilgreind sem hlutfall daga á meðferð undir 80%. Logistísk

aðhvarfsgreining var notuð til að bera saman hlutfall sjúklinga með lélega meðferðarheldni milli lyfja. Logistísk aðhvarfsgreining var einnig notuð til að meta sjúklingaþætti tengda lélegri meðferðarheldni.

Rivaroxaban var tengt við lægri tíðni blóðsega og hjartadreps samanborið við dabigatran. Á sama hátt var apixaban tengt við lægri tíðni hjartadreps samanborið við dabigatran en sá samanburður hafnaði þó ekki núlltilgátunni. Rivaroxaban var tengt við aukna tíðni stórvægra blæðinga, klínískt mikilvægra meltingarvegsblæðinga og klínískt mikilvægra nefblæðinga samanborið við aðra beina storkuhemla. Tíðni heilablóðfalla og heildardánartíðni var svipuð milli mismunandi beinna storkuhemla. Warfarín var tengt við aukna tíðni efri en ekki neðri meltingarvegsblæðinga samanborið við beina storkuhemla. Warfarín var einnig tengt við hærri nefblæðingartíðni en beinir storkuhemlar. Dabigatran var tengt við auknar líkur á lélegri meðferðarheldni samanborið við apixaban, rivaroxaban og warfarín. Meðferðarheldni var svipuð hjá sjúklingum á apixaban, rivaroxaban og warfarín. Kvenkyn, háþrýstingur, saga um heilablóðfall/heilablæðingu og samhliða notkun á statínum voru öll tengd við aukna hættu á lélegri meðferðarheldni.

Til samantektar var rivaroxaban tengt við hærri blæðingartíðni en aðrir beinir storkuhemlar en lægri tíðni blóðsega og hjartadreps samanborið við dabigatran. Warfarín var tengt við hærri tíðni efri meltingarvegsblæðinga og nefblæðinga samanborið við beina storkuhemla. Dabigatran var tengt við verri meðferðarheldni en önnur blóðþynningarlyf um munn.

Lykilorð:

Blóðþynningarlyf, blóðsegi, stórvæg blæðing, meðferðarheldni, meltingarvegsblæðing.

Abstract

Oral anticoagulants (OACs) are among the most commonly used medication worldwide. Vitamin K antagonists, such as warfarin, were the only available oral anticoagulants for over 60 years. However, in the 2010s, novel direct oral anticoagulants (DOACs) were approved that act by directly inhibiting either factor II (dabigatran) or factor X (apixaban, rivaroxaban, and edoxaban). The results of the initial randomized controlled trials demonstrated that DOACs were associated with similar thromboembolic rates and lower major bleeding rates compared to warfarin. As a result, DOACs are currently considered first-line therapy for patients with atrial fibrillation and venous thromboembolism. However, randomized controlled trials comparing DOACs head-to-head are currently lacking, and previous observational studies have important limitations. Additionally, data are largely lacking on other outcomes such as rates of upper and lower gastrointestinal bleeding (GIB) and epistaxis event rates. Similarly, it is still unknown whether medication adherence differs between warfarin and DOACs.

The aims of this thesis were to compare the efficacy, safety, and adherence of different oral anticoagulants. Therefore, 5 studies were designed and are presented in 5 distinct papers. Specifically, the aim of paper I was to compare rates of thromboembolism and major bleeding between different DOACs, the aim of paper II was to compare rates of any clinically relevant GIB between DOACs, the aim of paper III was to compare rates of upper and lower GIB between warfarin and DOACs, the aim of paper IV was to compare rates of epistaxis between warfarin and DOACs, and the aims of paper V was to compare the likelihood of nonadherence between different OACs.

A study outcome database was created that included all patients in Iceland who filled a prescription for an OAC from 1 March 2014 to 28 February 2019. The database combined data from the Icelandic Medicine Registry; the electronic healthcare databases of Landspitali University Hospital and the regional hospitals of Akranes, Akureyri, Ísafjörður, and Neskaupsstaður; the electronic healthcare databases of the primary healthcare centers around the country; and the Icelandic death registry. All thromboembolic and major bleeding events were manually verified by chart review. The study population included new users of apixaban, dabigatran,

rivaroxaban, and warfarin (for papers III-V). Inverse probability weighting was used to yield balanced study groups and bleeding and thromboembolic events were compared using Cox regression. Kaplan-Meier curves were used to visualize the data. Nonadherence, defined as proportion of days covered below 80%, was compared between groups using logistic regression. Similarly, logistic regression was used to estimate patient characteristics associated with nonadherence.

Rivaroxaban was associated with lower rates of any thromboembolism and myocardial infarction (MI) compared to dabigatran. Similarly, apixaban was associated with lower rates of MI compared to dabigatran, although this comparison did not reject the null hypothesis. Meanwhile, rivaroxaban was associated with higher rates of any major bleeding, any clinically relevant GIB, and any clinically relevant epistaxis compared to apixaban and dabigatran. Rates of stroke and all-cause mortality were similar between patients receiving different DOACs. Warfarin was associated with higher rates of upper but not lower or overall GIB compared to DOACs. Warfarin was also associated with higher epistaxis rates compared to DOACs. Dabigatran was associated with higher nonadherence compared to apixaban, rivaroxaban, and warfarin. Meanwhile, the odds of nonadherence was similar between apixaban, rivaroxaban, and warfarin. Apart from OAC type, female gender, hypertension, history of cerebrovascular accident, and concomitant statin use were all associated with lower odds of nonadherence.

In summary, rivaroxaban was associated with higher rates of bleeding compared to other DOACs but lower rates of any thromboembolism and MI compared to dabigatran. Warfarin was associated with high rates of upper GIB and epistaxis compared to DOACs. Dabigatran was associated with poorer adherence than other oral anticoagulants.

Keywords:

Oral anticoagulation, thromboembolism, major bleeding, adherence, gastrointestinal bleeding.

Acknowledgements

This doctoral thesis is the result of many years of hard work from a group of highly dedicated researchers, to whom I owe a great depth of gratitude. There is no doubt in my mind that I could not have done this without them.

First, I would like to thank my supervisor, Einar Stefán Björnsson. Einar and I initially met to discuss a possible PhD project in 2017 when I was a fifth-year medical student. Although I had previous background in basic research, I had never done clinical research before. Einar guided me through everything with unwavering support and patience. I've had the privilege to work with many great researchers throughout my short career, but I have never encountered one as dedicated and inspirational as him. One of Einar's signature traits is being incredibly accessible, he would frequently reply within minutes of receiving my Emails and would often send me manuscript revisions within 24 hours.

I would also like to thank my co-supervisor, Jóhann Páll Hreinsson. Jóhann has been involved in the project from the start, attending each meeting that Einar and I had, and was an enormous help in getting me through the stormy waters of applying for funding, bioethics approvals, and permissions for data acquisition. He also helped me navigate the even stormier waters of statistical analysis and coding in R. He has taught me (almost) everything I know in statistical analysis!

I would like to thank the doctoral committee for their input and help throughout this process. Two of whom, I especially owe a great deal of gratitude. Páll Torfi Önundarson was involved in this project from the start and immediately impressed me with his sharp scientific mind and invaluable suggestions. I have never met someone as critical of my work before, which was frustrating at times, but also critical in substantially improving our work. During the last year of the project, we held weekly meetings which were of invaluable help. Sigrún Helga Lund was also involved in this project from the start. I'm extremely grateful for her expertise and help. A good statistician is worth their weight in gold, and you don't find many better than Sigrún!

I would like to thank my colleagues, Arnar Snær Ágústsson, Daníel Alexander Pálsson, Edward Rumba, and Indriði Einar Reynisson, for their help during the data acquisition process. They worked tirelessly to help me

create an incredibly robust outcome database and I'm incredibly thankful for that. I would also like to thank Brynja R. Guðmundsdóttir and Geir Tryggvason for their input and help with this project.

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I would like to thank my family for their support during this project, I could not have done this without them. To my mother, who has been on oral anticoagulant treatment for most of her adult life, thank you for your genuine interest and support in everything I do. This work is dedicated to you.

Finally, I'd like to thank my wife, Björk Guðmundsdóttir, for her unconditional love and support. You make colors seem brighter, food taste sweeter, and impassible mountains (like a PhD project) feel like open fields. I love you with all my heart!

Contents

List of abbreviations

AF	Atrial fibrillation
AUC	Area under the curve
CI	Confidence interval
CYP2C9	Cytochrome P450 family 2 subfamily C member 9
DOAC	Direct oral anticoagulant
ESRD	End-stage renal disease
Fiix	Anticoagulation test that only reflects the activity of factors II and X
GI	Gastrointestinal
GIB	Gastrointestinal bleeding
ICD-9 CM	International classification of diseases, 9th revision, clinical modification
ICD-10	International classification of diseases, 10th revision
INR	International normalized ratio
IQR	Interquartile range
IPW	Inverse probability weighting
ISTH	International Society on Thrombosis and Haemostasis
NPV	Negative predictive value
NSAID	Nonsteroidal anti-inflammatory drug
OAC	Oral anticoagulant
PDC	Proportion of days covered
PPV	Positive predictive value
PT	Prothrombin time
RCT	Randomized controlled trial
SMD	Standardized mean difference
TIA	Transient ischemic attack
TTR	Time in therapeutic range
VKA	Vitamin K antagonist
VKORC1	Vitamin K epoxide reductase complex subunit 1
VTE	Venous thromboembolism

List of figures

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List of original papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I. Ingason AB, Hreinsson JP, Ágústsson AS, Lund SH, Rumba E, Pálsson DA, Reynisson IE, Guðmundsdóttir BR, Önundarson PT, Björnsson ES. Comparison of the efficacy and safety of direct oral anticoagulants: Nationwide propensity score-weighted study. Submitted.

II. Ingason AB, Hreinsson JP, Ágústsson AS, Lund SH, Rumba E, Pálsson DA, Reynisson IE, Guðmundsdóttir BR, Önundarson PT, Björnsson ES. Rivaroxaban is associated with higher rates of gastrointestinal bleeding than other direct oral anticoagulants: A nationwide propensity score-weighted study. *Ann Intern Med* 2021;174:1493-502.

III. Ingason AB, Hreinsson JP, Ágústsson AS, Lund SH, Rumba E, Pálsson DA, Reynisson IE, Guðmundsdóttir BR, Önundarson PT, Björnsson ES. Warfarin is associated with higher rates of upper but not lower gastrointestinal bleeding compared to direct oral anticoagulants: a population-based propensity-weighted cohort study. *Clinical Gastroenterology and Hepatology*. In revision.

IV. Ingason AB, Rumba E, Hreinsson JP, Ágústsson AS, Lund SH, Pálsson DA, Reynisson IE, Guðmundsdóttir BR, Önundarson PT, Björnsson ES, Tryggvason G. Warfarin is associated with higher rates of epistaxis compared to direct oral anticoagulants: a nationwide propensity score-weighted study. *Journal of Internal Medicine*. Article in press.

V. Ingason AB, Hreinsson JP, Lund SH, Ágústsson AS, Rumba E, Pálsson DA, Reynisson IE, Guðmundsdóttir BR, Önundarson PT, Björnsson ES. Comparison of medication adherence between different oral anticoagulants: a population-based propensity-weighted cohort study. Submitted.

In addition, some unpublished data may be presented.

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Declaration of contribution

The doctoral candidate designed the study along with his supervisors; Einar Stefán Björnsson, Jóhann Páll Hreinsson, and Páll Torfi Önundarson. The doctoral candidate created the oral anticoagulation database, performed the data acquisition, and manually verified all bleeding and thromboembolic events. Arnar Snær Ágústsson, Indriði Einar Reynisson, Daníel A. Pálsson, and Edward Rumba helped with the data acquisition process. The doctoral candidate analyzed the data with help from his supervisors and co-authors. He also wrote the first draft of each manuscript, which was subsequently revised and approved by each co-author prior to submission.

1 Introduction

1.1 The history of oral anticoagulants

Warfarin was discovered in the 1940s following the outbreak of “sweet clover disease”, a hemorrhagic disease where previously healthy cattle suddenly died from internal bleeding after eating molded hay (Link 1959). The causative agent was dicoumarol, an oxidized form of coumarin which formed in the moldy hay. Warfarin, a more potent derivate of dicoumarol, was subsequently isolated and marketed as a rodenticide in 1948 (Link 1959). In 1954, warfarin was approved for clinical application as an oral anticoagulant (OAC) and has since become one of the most commonly prescribed drugs in history. Warfarin and other coumarin derivatives act as vitamin K antagonists (VKAs). As vitamin K is essential for the formation of fully functional gamma-carboxylated blood clotting factors II, VII, IX, and X, inhibiting its effect leads to anticoagulation (Wadelius and Pirmohamed 2007). While high doses of warfarin had previously been demonstrated as poisonous, when dose-monitored it has served as an effective anticoagulant for decades.

VKAs, such as warfarin, were the only available OACs for more than 60 years. However, in the 2010s, new OACs were approved which act by directly inhibiting either factor IIa (dabigatran) or factor Xa (apixaban, rivaroxaban, and edoxaban) (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011, Giugliano, Ruff et al. 2013). The main advantage of these direct oral anticoagulants (DOACs), although controversial, is that routine control measurements are considered unnecessary. Since their emergence, DOACs have largely replaced VKAs in many countries (Loo, Dell'Aniello et al. 2017, van den Heuvel, Hövels et al. 2018).

1.2 Indications for oral anticoagulation

OACs are among the most commonly prescribed medications worldwide. OACs are used to prevent and treat thromboembolic events, the most common indications being atrial fibrillation (AF) and venous thromboembolism (VTE) (i.e., deep venous thrombosis and pulmonary embolism). The yearly incidence of VTE has been estimated to be as high as 0.4% in the United States (Virani, Alonso et al. 2020). Lifetime prevalence of AF has been estimated to be as high as 37% (Magnussen, Niiranen et al.

2017, Weng, Preis et al. 2018). With an aging world population, the prevalence of AF has been estimated to rise from 5.2 million in 2010 to 12.1 million in 2030 in the United States (Colilla, Crow et al. 2013), and from 8.8 million in 2010 to 17.9 million by 2060 in the European Union (Krijthe, Kunst et al. 2013). Similarly, the incidence of VTE increases with age (Silverstein, Heit et al. 1998). Concomitantly, the proportion of patients with AF receiving OACs has been increasing in recent years (Barnes, Lucas et al. 2015, Weitz, Semchuk et al. 2015, Gadsbøll, Staerk et al. 2017). Therefore, the use of OACs will likely continue to increase in the coming years.

1.3 Comparison of the efficacy and safety of oral anticoagulants in patients with atrial fibrillation

From 2009-2013, several phase 3 randomized controlled trials (RCTs) comparing the efficacy and safety of warfarin and DOACs for patients with AF were published. These included: the RE-LY trial, comparing dabigatran and warfarin (Connolly, Ezekowitz et al. 2009); the ARISTOTLE trial comparing apixaban and warfarin (Granger, Alexander et al. 2011); the ROCKET AF trial comparing rivaroxaban and warfarin (Patel, Mahaffey et al. 2011); and lastly, the ENGAGE AF-TIMI trial comparing edoxaban and warfarin (Giugliano, Ruff et al. 2013). The main outcomes of the trials are summarized in Table 1.

The primary efficacy outcome for these trials was defined as any stroke or systemic arterial embolism. This was significantly more common in warfarin-treated patients compared to those on apixaban, high-dose dabigatran, and rivaroxaban (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011). Low-dose dabigatran had similar efficacy compared to warfarin (Connolly, Ezekowitz et al. 2009). High-dose edoxaban trended towards lower rates of the primary efficacy outcome compared to warfarin, which was significant in a modified intention-to-treat analysis (Giugliano, Ruff et al. 2013). It is important to note that as systemic arterial embolism is a much rarer outcome than stroke, the primary efficacy outcome is essentially analogous to all-cause stroke rates. Indeed, in the RCTs, warfarin was associated with higher rates of stroke compared to apixaban and high-dose dabigatran, while warfarin trended towards higher stroke rates compared to rivaroxaban (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011). This observed difference was mainly driven by higher risk of hemorrhagic stroke, with similar rates of ischemic stroke between warfarin and individual DOACs (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011). Warfarin was associated with similar stroke rates compared to high-

Table 1: Results from randomized controlled trials comparing the efficacy and safety of warfarin and direct oral anticoagulants in patients with atrial fibrillation

Outcome	Apixaban HR (95% CI)	Dabigatran 110 mg RR (95% CI)	Dabigatran 150 mg RR (95% CI)	Rivaroxaban HR (95% CI)	Edoxaban 30 mg HR (95% CI)	Edoxaban 60 mg HR (95% CI)
Any stroke or systemic embolism	0.79 (0.66-0.95)	0.91 (0.74-1.11)	0.66 (0.53-0.82)	0.79 (0.66-0.96)	1.13 (0.96-1.34)	0.87 (0.73-1.04)*
Any stroke	0.79 (0.65-0.95)	0.92 (0.74-1.13)	0.64 (0.51-0.81)	0.85 (0.70-1.03)	1.13 (0.97-1.31)	0.88 (0.75-1.03)
Ischemic stroke†	0.92 (0.74-1.13)	1.11 (0.89-1.40)	0.76 (0.60-0.95)	0.94 (0.75-1.17)	1.41 (1.19-1.67)	1.00 (0.83-1.19)
Hemorrhagic stroke	0.51 (0.35-0.75)	0.31 (0.20-0.47)	0.26 (0.14-0.49)	0.59 (0.37-1.03)	0.33 (0.22-0.50)	0.54 (0.38-0.77)
Myocardial infarction	0.88 (0.66-1.17)	1.35 (0.98-1.87)	1.38 (1.00-1.91)	0.81 (0.63-1.06)	1.19 (0.95-1.49)	0.94 (0.74-1.19)
All-cause mortality	0.89 (0.80-0.998)	0.91 (0.80-1.03)	0.88 (0.77-1.00)‡	0.85 (0.70-1.02)	0.87 (0.79-0.96)	0.92 (0.83-1.01)
Major bleeding	0.69 (0.60-0.80)	0.80 (0.69-1.03)	0.93 (0.81-1.07)	1.04 (0.90-1.20)	0.47 (0.41-0.55)	0.80 (0.71-0.91)
Intracranial hemorrhage	0.42 (0.30-0.58)	0.31 (0.20-0.47)	0.40 (0.27-0.60)	0.67 (0.47-0.93)	0.30 (0.21-0.43)	0.47 (0.34-0.63)
Other bleeding	0.79 (0.68-0.93)	NR	NR	NR	0.40 (0.31-0.52)	0.62 (0.50-0.78)
Gastrointestinal bleeding	0.89 (0.70-1.15)	1.10 (0.86-1.41)	1.50 (1.19-1.89)	1.66 (1.34-2.05)§	0.67 (0.53-0.83)	1.23 (1.02-1.50)
Any bleeding	0.71 (0.68-0.75)	0.78 (0.74-0.83)	0.91 (0.86-0.97)		0.66 (0.62-0.71)	0.87 (0.82-0.92)
Major or clinically relevant bleeding	0.68 (0.61-0.75)	NR	NR	1.03 (0.96-1.11)	0.62 (0.57-0.67)	0.86 (0.80-0.92)
Net clinical outcome ¶	0.85 (0.78-0.92)	0.92 (0.84-1.02)	0.98 (0.89-1.08)	0.85 (0.74-0.96)	0.83 (0.77-0.90)	0.89 (0.83-0.96)

Please note that the results of these studies may not be directly comparable between direct oral anticoagulants as the selection criteria differed between trials.
*The modified intention-to-treat analysis was statistically significant (HR 0.87, 95% CI 0.63-0.99). †For the apixaban and dabigatran trials, this outcome included stroke of unspecified type as well. ‡P=0.051. §Results gathered from a post hoc analysis. ¶The net clinical outcome for the apixaban and rivaroxaban trials was defined as a composite of any stroke, systemic embolism, major bleeding, and death. For the dabigatran trial, it was defined as a composite of any stroke, systemic embolism, pulmonary embolism, myocardial infarct, major bleeding, and death. For the rivaroxaban trial, it was defined as a composite of any stroke, non-central nervous system embolism, and vascular death.

and low-dose edoxaban treatment (Giugliano, Ruff et al. 2013). Importantly, the risk of ischemic stroke was significantly higher for low-dose edoxaban compared to warfarin (Giugliano, Ruff et al. 2013). It is also worth noting that, the J-ROCKET AF, a Japanese RCT comparing warfarin and reduced-dose rivaroxaban (15 mg once daily) demonstrated significantly lower rates of ischemic stroke compared to warfarin (Hori, Matsumoto et al. 2012).

The primary safety outcome of the RCTs for apixaban, dabigatran, and edoxaban included any major bleeding, defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria as bleeding leading to hemoglobin drop of 20 g/L or more, transfusion of 2 units of packed red blood cells or more, bleeding into a critical area or organ (such as the retroperitoneal, intracranial, or intra-articular bleeding), or death (Schulman and Kearon 2005, Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Giugliano, Ruff et al. 2013). The primary safety outcome of the RCT for rivaroxaban was a composite of both major and clinically relevant non-major bleeding, although major bleeding rates were also reported separately (Patel, Mahaffey et al. 2011).

Warfarin was associated with higher rates of major bleeding compared to apixaban, low-dose dabigatran, and both high- and low-dose edoxaban treatment (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Giugliano, Ruff et al. 2013). Major bleeding rates were similar between warfarin and both high-dose dabigatran and rivaroxaban (Connolly, Ezekowitz et al. 2009, Patel, Mahaffey et al. 2011). Particularly, warfarin was associated with higher rates of intracranial hemorrhage compared to all DOACs (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011, Giugliano, Ruff et al. 2013). Additionally, warfarin was associated with higher rates of all-cause mortality compared to apixaban, and trended towards higher mortality rates compared to dabigatran, edoxaban, and rivaroxaban (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011, Giugliano, Ruff et al. 2013).

The above-mentioned studies were international multicenter studies with 8-10 thousand patients in each arm, and a mean follow-up period of nearly 2 years. This increases the generalizability of the studies and allows for comparison of multiple secondary outcomes. However, the studies are not without their limitations. First, hemorrhagic stroke is included in both the primary efficacy and safety outcome. Although oral anticoagulation is used to prevent stroke, it does so by decreasing the risk of ischemic stroke while the

rates of hemorrhagic stroke consequently increase. Additionally, the mean time in therapeutic range (TTR) for the warfarin groups, a major determinant of clinical outcomes, was only 55-65% (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011, Giugliano, Ruff et al. 2013), while TTR is over 70% in most Western countries (Le Heuzey, Ammentorp et al. 2014). Additionally, the DOAC trials have been criticized for two major oversights. First, dabigatran has been demonstrated to have inter-individual variation, similar to warfarin, information the pharmaceutical company seems to have withheld intentionally (Cohen 2014). Second, in the rivaroxaban trial, a faulty device was used to measure international normalized ratio (INR) for the warfarin control group, leading to falsely low INR measurements (Cohen 2016) and may have caused warfarin overdosing. Additionally, patients were excluded if they had $CHADS_2$ score lower than 1, if they had glomerular filtration rate below 25-30 mL/kg/h, or if they had significant liver disease. This limits the generalizability of the studies. Furthermore, 50-62% of patients in the RCTs had a prior history of VKA usage (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011, Giugliano, Ruff et al. 2013). This is important as patients are likely at the highest risk of complications when initiating VKA treatment for the first time. Therefore, population-based studies using a truly OAC naïve cohort and without selection of patients are important to analyze differences in the efficacy and safety of OACs.

Importantly, no RCT has made direct comparison of the efficacy and safety of DOACs. Furthermore, due to the different inclusion and exclusion criteria of previous RCTs, head-to-head comparisons of DOACs using these studies are unreliable. RCTs between individual DOACs are currently being undertaken (e.g., NCT04642430 and NCT03266783), but until then comparison of DOACs is limited to observational studies.

A previous registry study from the USA demonstrated that rivaroxaban was associated with both higher rates of major bleeding and ischemic stroke or systemic embolism compared to apixaban in patients with AF (Fralick, Colacci et al. 2020). Similarly, in an observational study from Scotland, rivaroxaban was associated with higher rates of major bleeding compared to apixaban (Mueller, Alvarez-Madrazo et al. 2019). An observational study from the UK, using a primary healthcare database, demonstrated that apixaban had lower rates of major bleeding compared to rivaroxaban and dabigatran, but similar rates of ischemic stroke (Vinogradova, Coupland et al. 2018). Contrastingly, a population-based study from Denmark demonstrated similar

risk of major bleeding and all-cause stroke or systemic embolism for apixaban, dabigatran, and rivaroxaban (Andersson, Svanstrom et al. 2018).

As mentioned above, all the initial RCTs defined major bleeding according to the ISTH criteria. To our best knowledge, no population-based observational study has used this definition. A nationwide Norwegian registry study used a modified version of the ISTH definition, omitting hemoglobin drop as one of the criteria (Halvorsen, Ghanima et al. 2017). A prospective French cohort study used a clinical definition of major bleeding, including vital signs and hemostatic procedures as a part of the criteria (Bouget, Balusson et al. 2020). Otherwise, most observational studies have defined major bleeding as a bleeding event requiring hospitalization (Larsen, Skjoth et al. 2017, Nielsen, Skjoth et al. 2017, Andersson, Svanstrom et al. 2018, Vinogradova, Coupland et al. 2018, Mueller, Alvarez-Madrazo et al. 2019, Souverein, van den Ham et al. 2020). How closely this resembles the ISTH criteria is unknown, especially for bleeding events that are typically less severe but have been included in previous studies, such as epistaxis, hematuria, postmenopausal bleeding, and anemia of unspecified cause (Larsen, Skjoth et al. 2017, Nielsen, Skjoth et al. 2017, Andersson, Svanstrom et al. 2018, Vinogradova, Coupland et al. 2018, Mueller, Alvarez-Madrazo et al. 2019, Souverein, van den Ham et al. 2020).

1.4 Comparison of the efficacy and safety of oral anticoagulants in patients with venous thromboembolism

RCTs in patients with symptomatic VTE demonstrated similar VTE recurrence rates for warfarin users and patients receiving apixaban (Agnelli, Buller et al. 2013), dabigatran (Schulman, Kearon et al. 2009, Schulman, Kakkar et al. 2014), edoxaban (Büller, Décousus et al. 2013), and rivaroxaban (Bauersachs, Berkowitz et al. 2010). Similarly, major bleeding rates for warfarin users were similar compared to patients receiving dabigatran, edoxaban, and rivaroxaban (Schulman, Kearon et al. 2009, Bauersachs, Berkowitz et al. 2010, Büller, Décousus et al. 2013, Schulman, Kakkar et al. 2014). However, another RCT that only included patients with pulmonary embolism demonstrated lower rates of major bleeding for rivaroxaban users compared to patients receiving warfarin (Büller, Prins et al. 2012). Additionally, apixaban users had markedly lower major bleeding rates compared to warfarin users (Agnelli, Buller et al. 2013). Interestingly, warfarin was associated with significantly higher rates of combined major and clinically relevant bleeding compared to apixaban, dabigatran, and edoxaban (Schulman, Kearon et al. 2009, Agnelli, Buller et al. 2013, Büller, Décousus

et al. 2013, Schulman, Kakkar et al. 2014), while bleeding rates were similar compared to rivaroxaban users (Bauersachs, Berkowitz et al. 2010, Büller, Prins et al. 2012).

A nationwide registry study from Denmark demonstrated that rivaroxaban was associated with lower rates of recurrent VTE compared to warfarin in patients with unprovoked VTE as treatment indication (Nielsen, Skjoth et al. 2017). Additionally, a study from the US, based on data from insurance claims, demonstrated lower major bleeding rates for rivaroxaban users compared to patients receiving warfarin (Kohn, Bunz et al. 2019). Another study from the US using insurance claims demonstrated that apixaban was associated with lower major bleeding and recurrent VTE rates than warfarin for patients with VTE as treatment indication (Dawwas, Smith et al. 2020). A couple of registry studies from the US, based on data from insurance claims, demonstrated lower major bleeding and recurrent VTE for apixaban than rivaroxaban in patients with VTE as treatment indication (Dawwas, Brown et al. 2019, Dawwas, Leonard et al. 2022).

1.5 Comparison of overall gastrointestinal bleeding rates between oral anticoagulants

Major bleeding during OAC treatment most commonly originates from the gastrointestinal tract (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011, Giugliano, Ruff et al. 2013). The initial RCTs for patients with AF demonstrated that warfarin was associated with lower rates of major gastrointestinal bleeding (GIB) compared to rivaroxaban, high-dose dabigatran, and high-dose edoxaban, while major GIB rates were similar compared to apixaban, low-dose dabigatran, and low-dose edoxaban treatment (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011, Giugliano, Ruff et al. 2013). In these initial RCTs, nonmajor GIB rates were not reported. However, post hoc analyses demonstrated that warfarin users had lower rates of clinically relevant GIB compared to rivaroxaban users (Sherwood, Nessel et al. 2015), while rates of nonmajor GIB were similar for warfarin and apixaban users (Bahit, Lopes et al. 2017).

In a meta-analysis of 28 observational nationwide or insurance database studies from 2017, warfarin was associated with lower rates of GIB compared to dabigatran and rivaroxaban, but higher rates compared to apixaban (Ntaios, Papavasileiou et al. 2017). In a more recent meta-analysis including 43 RCTs and 41 observational studies, warfarin was associated with lower

rates of major GIB compared to rivaroxaban (Gu, Wei et al. 2020). This was consistent for both RCTs and observational studies. Meanwhile, major GIB rates were similar for warfarin and dabigatran users in both RCTs and observational studies. Interestingly, apixaban was associated with lower major GIB rates compared to warfarin in observational studies, while the results from RCTs were not significantly different (Gu, Wei et al. 2020).

Results from previous population-based studies have suggested that rivaroxaban users had higher GIB rates than patients receiving other DOACs (Chan, Kuo et al. 2016, Abraham, Noseworthy et al. 2017, Adeboyeje, Sylwestrzak et al. 2017, Hernandez, Zhang et al. 2017, Lai, Chen et al. 2017, Vinogradova, Coupland et al. 2018, Mueller, Alvarez-Madrazo et al. 2019, Fralick, Colacci et al. 2020). In a study from the USA using data from the Medicare administrative database and a database of privately insured patients, rivaroxaban users had higher GIB rates compared to apixaban and dabigatran users (Abraham, Noseworthy et al. 2017). Another study using the Medicare administrative database demonstrated similar results (Hernandez, Zhang et al. 2017). A third registry study from USA demonstrated that rivaroxaban users had significantly higher GIB rates compared to dabigatran users (Fralick, Colacci et al. 2020). Another registry study based on commercially insured patients in USA demonstrated that rivaroxaban users had higher rates of major GIB compared to apixaban and dabigatran users (Adeboyeje, Sylwestrzak et al. 2017). In a study from primary care in the UK, age- and sex standardized GIB rates were highest among users of rivaroxaban compared with warfarin, apixaban, and dabigatran users (Vinogradova, Coupland et al. 2018). Cox regression adjusting for additional confounding factors demonstrated that rivaroxaban was associated with significantly higher GIB rates compared to apixaban but a direct comparison between rivaroxaban and dabigatran was not undertaken. Similarly, another registry study from Scotland based on administrative data demonstrated that rivaroxaban was associated with higher rates of GIB compared to apixaban (Mueller, Alvarez-Madrazo et al. 2019). Lastly, a couple of population-based studies from Taiwan based on a national insurance database demonstrated that rivaroxaban users had higher rates of GIB compared to dabigatran users (Chan, Kuo et al. 2016, Lai, Chen et al. 2017).

The above-mentioned studies have been based on administrative databases, with their inherent risk of selection bias due to insurance status, age, and comorbidities. For example, three of the studies from USA included data from the Medicare database, which only includes patients 65 years or older, patients with certain disabilities, or end-stage renal disease (Abraham,

Noseworthy et al. 2017, Hernandez, Zhang et al. 2017, Fralick, Colacci et al. 2020). Two of those studies were derived from the Optum database, which mostly includes employer-sponsored insurance (Abraham, Noseworthy et al. 2017, Fralick, Colacci et al. 2020). Additionally, most studies have been limited to patients with AF (Chan, Kuo et al. 2016, Adeboyeje, Sylwestrzak et al. 2017, Hernandez, Zhang et al. 2017, Lai, Chen et al. 2017, Nielsen, Skjoth et al. 2017, Sjalander, Sjogren et al. 2018, Mueller, Alvarez-Madrazo et al. 2019, Fralick, Colacci et al. 2020), and only a handful of studies have compared the risk of GIB between DOACs using a wider population (Chang, Zhou et al. 2015, Abraham, Noseworthy et al. 2017, Vinogradova, Coupland et al. 2018). Thus, there is clearly a medical need to explore differences in GIB rates between different OACs in population-based studies including well-characterized patient populations with a prolonged follow-up.

1.6 Comparison of upper and lower gastrointestinal bleeding rates between oral anticoagulants

It remains unclear whether rates of upper or lower GIB differ between patients receiving warfarin and DOACs. An RCT from Japan, the J-ROCKET AF trial, compared the efficacy and safety of warfarin and reduced dose rivaroxaban (15 mg x 1) for patients with AF. It demonstrated that major upper GIB rates were twice as common in warfarin users compared to rivaroxaban users (Hori, Matsumoto et al. 2012). Similarly, a post hoc analysis of the ARISTOTLE trial demonstrated a 50% higher rate of nonmajor upper GIB for warfarin users compared to apixaban users (Bahit, Lopes et al. 2017). A post hoc analysis of the RE-LY study found that 75% of major GIB originated in the upper GI tract in warfarin users, compared to 53% in patients receiving dabigatran (Eikelboom, Wallentin et al. 2011). Unfortunately, none of these three studies estimated whether these differences were statistically significant. In the ENGAGE AF-TIMI trial, low-dose edoxaban treatment was associated with lower rates of major lower GIB and trended towards lower rates of major upper GIB compared to warfarin (Giugliano, Ruff et al. 2013). Similarly, high-dose edoxaban treatment trended towards higher rates of major upper GIB compared to warfarin. Other RCTs have not estimated upper or lower GIB rates specifically (Schulman, Kearon et al. 2009, Bauersachs, Berkowitz et al. 2010, Büller, Prins et al. 2012, Agnelli, Buller et al. 2013, Büller, Décousus et al. 2013, Schulman, Kearon et al. 2013, Mao, Li et al. 2014, Schulman, Kakkar et al. 2014).

A study from the UK using population-based primary healthcare databases suggested that warfarin was associated with higher rates of upper

GIB compared to rivaroxaban but lower rates compared to apixaban (Vinogradova, Coupland et al. 2018). However, upper GIB events were identified by a handful of international classification of diseases 10th revision (ICD-10) codes only, including codes for melena and unspecified GIB. Furthermore, lower GIB events were identified using a single ICD-10 code only and GIB events were not verified. This limits the generalizability of the results. A study from the US, using the previously described Optum insurance database, demonstrated similar rates of upper and lower GIB for warfarin compared to both dabigatran and rivaroxaban (Abraham, Singh et al. 2015). This study identified events by ICD-9 CM codes only and without verification of GIB events. Other population-based studies comparing warfarin and DOACs have not compared upper or lower GIB rates specifically (Chang, Zhou et al. 2015, Chan, Kuo et al. 2016, Ellis, Neuman et al. 2016, Halvorsen, Ghanima et al. 2017, Hernandez, Zhang et al. 2017, Lai, Chen et al. 2017, Mentias, Shantha et al. 2018, Sjalander, Sjogren et al. 2018, Douros, Renoux et al. 2019, Lee, Choi et al. 2019, Li, Pathadka et al. 2020, Souverein, van den Ham et al. 2020, Dawwas, Dietrich et al. 2021, Halvorsen, Johnsen et al. 2021).

Compared to warfarin, DOACs have a shorter half-life, proportionally lower absorption in the GI tract, and have been hypothesized to cause direct caustic effect on the GI mucosa (Desai, Kolb et al. 2013, Cheung and Leung 2017). It is thus conceivable that these drugs might have different effects in the upper and lower GI tract.

1.7 Comparison of epistaxis rates between oral anticoagulants

Epistaxis is a common side effect of OACs and has been reported in up to 10-16% of patients in RCTs (Patel, Mahaffey et al. 2011, Hori, Matsumoto et al. 2012). In the ROCKET AF study, epistaxis was a more commonly reported adverse effect for rivaroxaban compared to warfarin, while the rates of major epistaxis were similar in patients taking the different drugs (Patel, Mahaffey et al. 2011). Similarly, epistaxis rates were higher for rivaroxaban users than warfarin users in the J-ROCKET AF trial, although the outcome was not tested for statistical significance (Hori, Matsumoto et al. 2012). Another RCT comparing rivaroxaban and warfarin in a Chinese population demonstrated no differences in epistaxis rates (Mao, Li et al. 2014). In contrast, apixaban had fourfold lower rates of any clinically relevant epistaxis events compared to warfarin treatment for patients with acute VTE (Agnelli, Buller et al. 2013). However, statistical significance was not estimated for this

outcome. Similarly, in a pooled analysis of 2 RCTs for patients with symptomatic VTE, dabigatran users had numerically lower rates of epistaxis compared to warfarin users which was not estimated for statistical significance (Schulman, Kakkar et al. 2014). Other large RCTs comparing warfarin to other DOACs have not specified epistaxis rates (Connolly, Ezekowitz et al. 2009, Bauersachs, Berkowitz et al. 2010, Granger, Alexander et al. 2011, Büller, Prins et al. 2012, Büller, Décousus et al. 2013, Giugliano, Ruff et al. 2013, Schulman, Kearon et al. 2013, Goldhaber, Schulman et al. 2017).

Importantly, observational studies have been limited to single-center studies studying the phenotypes of epistaxis events as well as comparing recurrence rates (García Callejo, Bécares Martínez et al. 2014, Buchberger, Baumann et al. 2018, L'Huillier, Badet et al. 2018, Sauter, Hegazy et al. 2018, Glikson, Chavkin et al. 2019, Send, Bertlich et al. 2019, Stankovic, Georgiew et al. 2019). These studies did not include data on OAC prescriptions for their target population and have therefore been unable to compare epistaxis incidence rates between patients receiving different OACs (García Callejo, Bécares Martínez et al. 2014, Buchberger, Baumann et al. 2018, L'Huillier, Badet et al. 2018, Sauter, Hegazy et al. 2018, Glikson, Chavkin et al. 2019, Send, Bertlich et al. 2019, Stankovic, Georgiew et al. 2019).

1.8 Warfarin monitoring

Due to its narrow therapeutic range, interindividual variability, and drug interactions, warfarin needs to be controlled by regular prothrombin time (PT) measurements approximately every 4-6 weeks. The PT, which is usually presented using the INR, measures the activity of three out of four vitamin K-dependent clotting factors, namely factors II, VII, and X, and is equally sensitive to reductions in each of the three factors (Gudmundsdottir, Francis et al. 2012). However, studies from *in vitro* and animal models have demonstrated that the antithrombotic effect of warfarin is primarily dependent on the activity of factors II and X (Xi, Béguin et al. 1989, Zivelin, Rao et al. 1993). Selective immunodepletion of factors II and X, but not other vitamin K-dependent factors, protected against tissue factor-induced coagulation in a rabbit model (Zivelin, Rao et al. 1993). Similarly, selective restoration of either factor II or X led to tissue factor-induced thrombosis in warfarin-treated rabbits infused with tissue factor.

Variable anticoagulation in individual patients has usually been blamed on food and drug interactions with warfarin. However, as factor VII has a much shorter half-life than factors II and X, it has been hypothesized that omitting the measurement of factor VII in PT measurements would lead to a more stable anticoagulation level and more accurate assessment of warfarin's anticoagulation activity (Gudmundsdottir, Francis et al. 2012). Therefore, the Fiix-test was developed which only measures the activity of factors II and X (Gudmundsdottir, Francis et al. 2012). A normalized ratio, the Fiix-NR, can be calculated based on the Fiix test in a manner similar to the PT-based INR. An RCT demonstrated that warfarin treatment monitored with Fiix was associated with similar rates of major bleeding but considerable, albeit nonsignificant, reduction in thromboembolic events compared to PT monitoring (HR 0.52, 95% CI 0.26-1.13) (Onundarson, Francis et al. 2015). Subsequently, warfarin treatment controlled through the anticoagulation center in Landspitali has been monitored using the Fiix-test since July 2016. The anticoagulation center at Landspitali monitors warfarin treatment in approximately 70-75% of all patients receiving warfarin in Iceland. Meanwhile, warfarin treatment outside Landspitali University Hospital is still monitored using conventional INR measurements. Since the change in monitoring, an observational study including experienced warfarin users only has been published and demonstrated similar results as well as reduced need for monitoring and dose adjustments (Oskarsdottir, Gudmundsdottir et al. 2021).

Apart from food and drug interactions, a significant cause of the large interpersonal difference in doses for warfarin is due to genetic polymorphisms. Around a third of the world's population carry one of two gene variants for CYP2C9, a liver enzyme that is responsible for warfarin metabolism (Aithal, Day et al. 1999, Burn and Pirmohamed 2018). Patients with two copies of these variants require much lower warfarin doses due to slower hepatic elimination. A third gene variant reduces the expression of *VKORC1*, which codes for warfarin's target enzyme, and is present in over half of the world population (Rieder, Reiner et al. 2005, Burn and Pirmohamed 2018). The presence of this variant increases the patient's sensitivity to warfarin, increasing the risk of complications, especially in tandem with the *CYP2C9* variants mentioned above. An RCT using genotyping for these variants demonstrated significantly higher TTR in the genotyped group compared to the control group (67% vs. 60%) (Pirmohamed, Burnside et al. 2013). Another possible improvement in warfarin treatment is self-monitoring which has been shown to reduce the

rates of thromboembolism, major bleeding, and all-cause mortality in RCTs (Heneghan, Alonso-Coello et al. 2006).

1.9 Comparison of medication adherence between different oral anticoagulants

The regular INR measurements required for monitoring warfarin treatment are inconvenient and time-consuming for patients and healthcare staff and this is one of the main reasons why many patients have been switched to DOACs where no such measurements are considered necessary. Nonetheless, monitoring not only secures optimal therapeutic dosing but also serves as a safety marker ensuring that the drug is used correctly. This has raised concerns that adherence and persistence to DOACs may be lower than for warfarin.

Adherence and persistence are both commonly used terms to study patients' medication-taking behavior. Adherence is defined as “the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen” (Cramer, Roy et al. 2008). The proportion of days covered (PDC) has been suggested as the golden standard in presenting adherence and signals the proportion of days the patient took his medication during his treatment period (Forbes, Deshpande et al. 2018). Meanwhile, persistence has been defined as “the duration of time from initiation to discontinuation of therapy” (Cramer, Roy et al. 2008). This is most often reported as the percentage of patients who still continue their treatment after a given time period. A related measurement is drug switching, i.e., the replacement of the currently prescribed drug with another similar medication.

A review of the literature suggests that the adherence for different DOACs is lowest for dabigatran (Crivera, Nelson et al. 2015, McHorney, Crivera et al. 2015, Brown, Shewale et al. 2016, Forslund, Wettermark et al. 2016, Yao, Abraham et al. 2016, Sorensen, Jamie Nielsen et al. 2017, Briasoulis, Inampudi et al. 2018, Banerjee, Benedetto et al. 2020). Dabigatran's low adherence has been speculated to be due to two factors; first, it requires two daily doses, and second, it has frequent gastrointestinal side effects that may lead to irregular intake or frequent treatment cessation (Connolly, Ezekowitz et al. 2009, Jackevicius, Tsadok et al. 2017). Indeed, during the RE-LY trial, 3 times as many patients discontinued dabigatran treatment due to gastrointestinal upset compared to warfarin (Connolly, Ezekowitz et al. 2009).

Whether adherence to warfarin is better than for other OACs is still unclear. Previous observational studies have yielded conflicting results when

comparing adherence rates between warfarin and DOACs (Yao, Abraham et al. 2016, Sorensen, Jamie Nielsen et al. 2017, Briasoulis, Inampudi et al. 2018, Banerjee, Benedetto et al. 2020). The major limitation of previous studies is that they do not account for warfarin dose adjustments (Yao, Abraham et al. 2016, Sorensen, Jamie Nielsen et al. 2017, Briasoulis, Inampudi et al. 2018, Banerjee, Benedetto et al. 2020). In contrast to DOACs which have fixed doses, warfarin dosage is being continuously modified according to INR measurements. If the dosage is increased before the next prescription that could lead to false results of nonadherence. Additionally, it must be kept in mind that the anticoagulant effect of warfarin lasts for about 2-5 days (O'Reilly and Aggeler 1968), while the effect of DOACs typically lasts for less than 24 hours (Stangier 2008, Weinz, Schwarz et al. 2009, Ogata, Mendell-Harary et al. 2010, Frost, Wang et al. 2013). This means that a lower adherence threshold may be acceptable for warfarin than DOACs.

1.10 Risk scores for thromboembolism and major bleeding used to guide oral anticoagulation treatment

In 2001, the $CHADS_2$ risk score was developed to estimate the risk of ischemic stroke in patients with AF (Gage, Waterman et al. 2001). It assigned 1 point for each of the following variables: congestive heart failure, hypertension, age over 75 years, and diabetes mellitus. Additionally, 2 points were assigned to patients with prior history of stroke or transient ischemic attack (TIA). The risk score was demonstrated to predict the risk of ischemic stroke better than previous risk scores (Gage, Waterman et al. 2001). However, it still omitted important risk factors such as vascular disease (Olesen, Lip et al. 2012). Consequently, an improved version of the risk score, the CHA_2DS_2-VASc score was developed (Lip, Nieuwlaat et al. 2010). It was expanded to estimate the risk of ischemic stroke, pulmonary embolism, or peripheral embolism. Consistent with the original $CHADS_2$ risk score, it assigned 1 point for congestive heart failure, hypertension, and diabetes mellitus. It assigned 2 points for prior history of ischemic stroke, TIA, or another thromboembolism. In addition, it assigned 1 point for vascular disease and 1 point for female sex. Finally, the improved system assigned 1 point for age over 65 years, and 2 points for age over 75. The risk score stratified patients with no points as low risk, patients with 1 point as intermediate risk, and patients with 2 points or higher as high risk. The validation of the risk score only performed marginally better than the original $CHADS_2$ score, with an area under the curve (AUC) of 0.61 compared to 0.56. However, it seemed to better estimate low-risk patients, with no low-risk

patients in the improved model developing thromboembolic events, compared to 1.4% of low-risk patients in the $CHADS_2$- model (Lip, Nieuwlaat et al. 2010). Both risk scores have been widely implemented clinically and in research. The $CHADS_2$ risk score or a modified version of it was used as an inclusion criterion for the initial RCTs for DOACs (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011, Giugliano, Ruff et al. 2013), and the CHA_2DS_2-VASc score has been implemented in guidelines for appropriate initiation of OAC treatment (January, Wann et al. 2019, Hindricks, Potpara et al. 2021). OAC treatment is recommended for males with a CHA_2DS_2-VASc score of 2 or higher and females with a score of 3 or higher. Additionally, OAC treatment may be considered for patients with a risk score of 1 for males and 2 for females (January, Wann et al. 2019, Hindricks, Potpara et al. 2021).

A few risk scores have been developed to estimate the risk of major bleeding in patients with AF receiving oral anticoagulation (Gage, Yan et al. 2006, Pisters, Lane et al. 2010, Fang, Go et al. 2011, O'Brien, Simon et al. 2015). The HEMORR2HAGES risk score was developed in 2006 using the national registry of AF in the USA (Gage, Yan et al. 2006), the same registry as the one used to develop the $CHADS_2$ score (Gage, Waterman et al. 2001). It estimated the risk of bleeding requiring hospitalization using ICD-9 CM codes. The model assigned 2 points for patients with a prior history of bleeding, and 1 point for each of the following variables: hepatic or renal disease, history of ethanol abuse, cancer, age over 75 years, reduced platelet count or function, hypertension, anemia, genetic factors, excessive risk of falling, and prior history of stroke. The AUC was 0.67 for this model (Gage, Yan et al. 2006).

The HAS-BLED risk score was developed in 2010 to estimate the risk of major bleeding in patients receiving OACs (Pisters, Lane et al. 2010). The definition of major bleeding was a bleeding event leading to hospitalization, hemoglobin drop of 20 g/L or more, and/or transfusion. The model was based on the Euro Heart Survey database, the same database as the one used to validate the CHA_2DS_2-VASc score (Lip, Nieuwlaat et al. 2010). The model included hypertension, reduced renal or liver function, history of stroke, prior history of major bleeding, labile INR values, age over 65 years, excessive alcohol consumption (defined as more than 8 units per week), and concomitant use of antiplatelets or nonsteroidal anti-inflammatory drugs (NSAIDs) as variables. The AUC for this model was 0.72 during internal validation (Pisters, Lane et al. 2010).

A year later, the ATRIA risk score was developed (Fang, Go et al. 2011). It identified major bleeding events using ICD-9 codes, with subsequent manual verification of each event. The study used a modified version of the ISTH criteria; i.e., a bleeding that was fatal, required transfusion of 2 or more units of packed red blood cells, or had a critical anatomic location (e.g., intracranial or retroperitoneal bleeding). In total, five variables were included in the model. Severe renal disease, defined as glomerular filtration rate >30 mL/min or dialysis dependence, was assigned 3 points. Similarly, 3 points were assigned to patients with anemia. Patients older than 75 years were assigned 2 points, and patients with hypertension or history of bleeding were assigned 1 point each. The AUC was 0.74 during internal validation (Fang, Go et al. 2011).

The ORBIT risk score was developed in 2015 (O'Brien, Simon et al. 2015). Similar, to the initial RCTs, it used the ISTH criteria for the definition of major bleeding. Using Cox regression, the five variables with the highest coefficient were selected for the final model. These included: age over 75 years, reduced hemoglobin/hematocrit or history of anemia, history of bleeding, reduced kidney function, and concomitant use of antiplatelets. The AUC for this model was 0.67 during internal validation. Additionally, external validation using the ROCKET AF database demonstrated an AUC of 0.62. This was comparable to both the HAS-BLED and ATRIA models which had an AUC of 0.60 and 0.59 respectively (O'Brien, Simon et al. 2015).

One of the limitations of the previous risk scores for major bleeding is that most of them were designed without including DOAC users (Gage, Yan et al. 2006, Pisters, Lane et al. 2010, Fang, Go et al. 2011). In addition, they have all been limited to patients with AF (Gage, Yan et al. 2006, Pisters, Lane et al. 2010, Fang, Go et al. 2011, O'Brien, Simon et al. 2015), which limits their generalizability. Furthermore, many of the variables included in the models, such as age and history of stroke, are risk factors for thromboembolism as well. Therefore, patients with high bleeding risk scores may still benefit from OACs due to their high thromboembolic risk. Finally, external validation of the studies has suggested lower predictive value than the original studies (Roldan, Marin et al. 2013, Fauchier, Chaize et al. 2016, Senoo, Proietti et al. 2016). Among the above-mentioned risk scores, HAS-BLED has performed the best, with an AUC of 0.54-0.68 (Roldan, Marin et al. 2013, Fauchier, Chaize et al. 2016, Senoo, Proietti et al. 2016).

1.11 Gender differences in oral anticoagulant use and outcomes

Although female sex has been associated with higher risk of thromboembolism in AF (Lip, Nieuwlaat et al. 2010), females have been

observed to be less likely to be treated with oral anticoagulation compared to males in some studies (Thompson, Maddox et al. 2017, Subramanya, Claxton et al. 2021). A US registry study from 2008-2014 demonstrated that this trend was independent of risk factors, with proportionally fewer females being treated with OACs for each $CHADS_2$ and CHA_2DS_2-VASc score stratification (Thompson, Maddox et al. 2017). Importantly, this study only included patients with a CHA_2DS_2-VASc score of 2 or higher. Similarly, another study from the US demonstrated that among patients aged 75 years or older, OAC prescription was proportionally more common for males than females (Subramanya, Claxton et al. 2021). Contrastingly, an international registry study demonstrated significantly lower OAC use for females compared to males in patients with CHA_2DS_2-VASc score of 1, while no difference was noted between the sexes for patients with higher risk scores (Mazurek, Huisman et al. 2018). As female sex does not appear to increase the risk of stroke in the absence of other risk factors (Friberg, Benson et al. 2012, Mikkelsen, Lindhardsen et al. 2012), the authors argued that females were not more likely to be undertreated compared to males (Friberg, Benson et al. 2012, Mazurek, Huisman et al. 2018). Interestingly, when stratified by geological location, females were less likely to receive OACs compared to males in North America, while no difference was noted between genders in other continents (Mazurek, Huisman et al. 2018). The proportion of OAC users being prescribed DOACs does not seem to differ between genders (Thompson, Maddox et al. 2017, Mazurek, Huisman et al. 2018, Subramanya, Claxton et al. 2021).

A meta-analysis of 5 RCTs demonstrated that among DOAC users with AF, females had lower rates of major bleeding but higher rates of stroke or systemic arterial embolism compared to males (Raccah, Perlman et al. 2018). However, there was notable heterogeneity in the results for different DOACs. Another meta-analysis demonstrated that women with AF receiving warfarin had higher risk of stroke or arterial embolism compared to males and similar major bleeding risk (Pancholy, Sharma et al. 2014).

An observational study from Italy suggested that females receiving DOACs had higher rates of GIB events requiring hospitalization than their male counterparts, while no differences were noted between the sexes in VKA users (Ferroni, Denas et al. 2022). Another observational study from Hong Kong demonstrated that DOAC use in females was associated with lower rates of intracranial hemorrhage and all-cause mortality compared to warfarin (Law, Lau et al. 2018). Similarly, rates of ischemic stroke and systemic embolism trended towards lower rates in female DOAC users, while

GIB rates were similar in DOAC users across sexes. Female warfarin users were associated with similar rates of the above-mentioned outcomes compared to male warfarin users (Law, Lau et al. 2018).

1.12 Oral anticoagulation selection for different populations

While warfarin is almost exclusively eliminated by hepatic metabolism, with renal elimination of less than 1%, around 80% of dabigatran, 50% of edoxaban, 36% of rivaroxaban, and 27% of apixaban is eliminated by the kidneys (Di Lullo, Ronco et al. 2017). This has raised questions on the appropriateness of DOAC treatment for patients with chronic kidney disease. The initial RCTs excluded patients with glomerular filtration rate (GFR) below 25-30 mL/min (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011, Giugliano, Ruff et al. 2013). However, guidelines from the Federal Drug Administration approve DOAC usage for patients with GFR as low as 15 mL/min (Di Lullo, Ronco et al. 2017). Additionally, observational studies have suggested that apixaban is at least noninferior to warfarin for patients with end-stage renal disease (ESRD); that is patients with GFR below 15 mL/min or dialysis dependence (Chokesuwattanaskul, Thongprayoon et al. 2018, Siontis, Zhang et al. 2018). A meta-analysis of five studies demonstrated that, in patients with ESRD, apixaban was associated with lower major bleeding rates compared to warfarin and similar rates of thromboembolism (Chokesuwattanaskul, Thongprayoon et al. 2018). Similarly, a study from the US, based on the Medicare database, demonstrated that apixaban was associated with lower major bleeding rates and similar rates of stroke or systemic embolism compared to warfarin in patients on dialysis (Siontis, Zhang et al. 2018). Another observational study from the US compared the efficacy and safety of rivaroxaban and warfarin in patients with GFR below 30 mL/min or dialysis dependence (Coleman, Kreutz et al. 2019). Of all the patients included in the study, 88% had ESRD. The study demonstrated that rivaroxaban was associated with lower rates of major bleeding and similar rates of ischemic stroke. Currently, apixaban is the only DOAC that is approved for patients with ESRD in the US. Conversely, no DOAC has been approved for patients with ESRD in Europe. That may change in the near future as RCTs comparing warfarin and apixaban use for patients on dialysis are currently in progress (NCT02933697, NCT03987711).

Patients with advanced liver dysfunction are at increased risk of bleeding and thromboembolism (Tripodi and Mannucci 2011). This might be partly

explained by the decreased capacity of the liver to synthesize pro- and anticoagulation factors (Tripodi and Mannucci 2011). Additionally, portal hypertension and associated esophageal varices, and thrombocytopenia can increase the risk of bleeding. Due to this increased risk, patients with significant liver disease were excluded from the initial RCTs (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011, Giugliano, Ruff et al. 2013). However, results from observational studies have suggested that DOAC treatment may be non-inferior to warfarin in patients with liver disease. A study from an insurance database in South Korea compared the efficacy and safety of warfarin and DOACs for patients with AF and significant liver disease; defined as viral hepatitis, cirrhosis, or a transaminase increase by more than twofold its upper limit (Lee, Lee et al. 2019). The results demonstrated that use of DOACs was associated with lower risk of ischemic stroke, intracranial hemorrhage, and bleeding leading to hospitalization compared to warfarin. However, this difference was less pronounced when the analysis was limited to patients with active liver disease. The results of this study must also be interpreted in the context that warfarin has been associated with significantly higher bleeding and thromboembolic rates in previous studies using the same database to study the whole AF population (Lee, Choi et al. 2019). A meta-analysis of patients with cirrhosis suggested that the efficacy and safety of warfarin and DOACs may be similar in this high-risk population (Hoolwerf, Kraaijpoel et al. 2018). However, this analysis was limited to only 239 patients, including 20 overlapping patients. The guidelines from the European Society of Cardiology recommend avoiding use of DOACs in patients with AF and severe liver disease; that is patients with a Child-Pugh class C (Hindricks, Potpara et al. 2021). According to these guidelines, rivaroxaban should also be avoided in patients with moderate liver disease (Child-Pugh class B) (Hindricks, Potpara et al. 2021). Of the DOACs, dabigatran may theoretically be most suitable for patients with significant liver disease due to the drug's high renal elimination. However, high-quality studies exploring this are currently lacking.

Lastly, optimal OAC treatment may also differ between patients of different ethnicities. Supporting this, the rates of the *CYP2C9* and *VKORC1* gene variants, partly responsible for the great interindividual variation in warfarin dose requirements, differ between Caucasians, Asians, and African Americans (Limdi, Wadelius et al. 2010). In the ROCKET AF trial, no differences were noted in treatment outcomes when stratified by race (Patel, Mahaffey et al. 2011). Similarly, in the ENGAGE AF-TIMI trial, the treatment effect was similar for Caucasians and non-Caucasians (Giugliano, Ruff et al.

2013). An observational study from the US demonstrated that rivaroxaban was associated with lower rates of ischemic stroke and major bleeding compared to warfarin in African American patients (Coleman, Thompson et al. 2020). Similarly, DOACs have generally compared favorably compared to warfarin in studies from Asia (Hori, Matsumoto et al. 2012, Lee, Choi et al. 2019, Chao, Chiang et al. 2021). However, this may be related to multiple factors other than ethnicity alone.

2 Aims

The aim of this doctoral thesis was to compare the efficacy, safety, and adherence of OACs in a nationwide cohort. The aim of each paper is listed below:

Paper I – to compare the rates of thromboembolism and major bleeding between apixaban, dabigatran, and rivaroxaban users.

Paper II – to compare the rates of clinically relevant GIB between apixaban, dabigatran, and rivaroxaban users.

Paper III – to compare the rates of upper and lower GIB between warfarin and DOAC users.

Paper IV – to compare the rates of epistaxis between warfarin and DOAC users.

Paper V – to compare the odds of nonadherence between warfarin, apixaban, dabigatran, and rivaroxaban users.

3 Materials and methods

3.1 Study design

The 5 papers were derived from a nationwide retrospective cohort database. Information was gathered on all patients who filled an OAC from 1 March 2014 to 28 February 2019 using the Icelandic Medicine Registry, which includes data on all outpatient drug prescriptions in the country. Using unique personal identification numbers that are assigned to each Icelander at birth, data on concomitant drug use, comorbidities, study outcomes, and area of residence were gathered and combined in a single outcome database. Apart from the Icelandic Medicine Registry, data were gathered from the Icelandic death registry; the electronic databases of Landspitali University Hospital; the four regional hospitals of Iceland (located at Akranes, Akureyri, Ísafjörður, and Neskaupsstaður); and the primary healthcare databases of the Capital Area, Westfjords, Eastern, Northern, and Western Iceland. The catchment area of each regional hospital is provided in Figure 1. The study was approved by the National Bioethics Committee of Iceland (VSN-16-057-V4 and VSN-18-111-V1).

3.2 Study population

The database included data on all patients in Iceland who filled a prescription for an OAC from 1 March 2014 to 28 February 2019. The study population being studied varied between individual papers. For papers I-II, new users of apixaban, dabigatran, and rivaroxaban were included. In these papers, patients were excluded if they had filled an OAC prescription in the preceding 12 months before the start of their eligibility in the study, if they had permanent residence outside Iceland, were receiving 2.5 mg of rivaroxaban, or if they had a mechanical heart valve, mitral stenosis, or ESRD. For papers III-IV, new users of warfarin, apixaban, dabigatran, and rivaroxaban were included. This analysis was limited to patients with AF, cryptogenic ischemic stroke, or VTE as treatment indication. Otherwise, the exclusion criteria were the same as for papers I-II. The study population for paper V was the same as for papers III-IV with the exception that only patients living in the capital area were included.

Figure 1: Location and catchment area of each regional hospital. Landspitali University Hospital is the only tertiary hospital in the country and serves as a regional hospital for both the capital area and southern Iceland. Republished with kind permission from Annals of Internal Medicine.

3.3 Study outcomes

For paper I, the primary efficacy outcome was any thromboembolism. Meanwhile, secondary efficacy outcomes included myocardial infarction (MI), VTE, arterial thromboembolism, and a composite outcome of either ischemic stroke or TIA. The primary safety outcome was major bleeding. Secondary safety outcomes were major GIB, intracranial hemorrhage, and major bleeding from other locations. Other outcomes were all-cause stroke, ischemic stroke, hemorrhagic stroke, all-cause mortality, and vascular mortality.

For paper II, the primary outcome was any clinically relevant GIB. Secondary outcomes were upper GIB, lower GIB, major GIB, and differences in causes of GIB.

Similarly, for paper III, the primary outcome was any clinically relevant upper, lower, or overall GIB. Secondary outcomes were major GIB and differences in causes of GIB. The analysis of cause of GIB was treated as exploratory for papers II and III.

For paper IV, the primary outcome was any clinically relevant epistaxis. Secondary outcomes were major epistaxis, subsequent major bleeding from any anatomical location following nonmajor epistaxis events, and differences in the presentation, treatment, and outcomes of epistaxis events.

For paper V, the primary outcome was nonadherence. Secondary outcomes were factors associated with nonadherence and rates of major bleeding and thromboembolism for adherent versus nonadherent patients.

3.4 Exposure of interest and follow-up period

The exposure of interest was treatment with apixaban, dabigatran, rivaroxaban, and warfarin. Patients were followed from the day they filled their index prescription until 28 February 2019 or earlier if death occurred, treatment was ceased, or the patient switched to another OAC.

Additionally, for paper I, follow-up was censored at the first occurrence of either primary study outcome.

For papers II-IV, follow-up was censored when the primary outcome was achieved. For paper V, follow-up was censored at the time of first major bleeding or thromboembolic event.

For paper IV, a separate analysis was performed where all patients, who continued their anticoagulation after an initial nonmajor epistaxis event, were followed for the risk of any major bleeding until the end of the study period or earlier if treatment was stopped, patient was switched to another OAC, or death occurred. Similarly, all patients who continued their anticoagulation after an initial epistaxis event were followed-up to identify rates of epistaxis recurrence.

3.5 Definition of study outcomes

Major bleeding was defined, according to the ISTH criteria, as bleeding leading to a hemoglobin drop of 20 g/L or more, transfusion of 2 or more units of red blood cells, symptomatic bleeding into a closed compartment, or death due to bleeding (Schulman and Kearon 2005). Any clinically relevant bleeding was defined as bleeding that led to unscheduled physician contact, or temporary treatment cessation (Onundarson, Francis et al. 2015). GIB was defined as bleeding that was overt or had a confirmed bleeding site on endoscopy. Upper GIB was defined as hematemesis or confirmed bleeding site on endoscopy. Similarly, lower GIB was defined as hematochezia or confirmed bleeding site on endoscopy. A patient presenting with massive

hematochezia and confirmed upper GI bleeding site on endoscopy would be classified as having an upper GIB. However, if that same patient would not have undergone an endoscopic procedure, he would have been classified as having a lower GIB. Patients with melena and uncertain bleeding site on endoscopy were classified as having a GIB of unknown location.

Stroke was defined as a focal neurological deficit in an area consistent with the findings of diagnostic imaging or autopsy. TIA was defined as a focal neurological deficit in an area corresponding to a major cerebral artery that lasted for less than 24 hours and, if applicable, no evidence of infarction or hemorrhage on diagnostic imaging. All ischemic stroke, intracranial hemorrhage, VTE, and arterial thromboembolism were confirmed by diagnostic imaging or autopsy.

Nonadherence was defined as PDC below 80%. This is consistent with previous studies (Karve, Cleves et al. 2009, Yao, Abraham et al. 2016, Sorensen, Jamie Nielsen et al. 2017, Banerjee, Benedetto et al. 2020).

3.6 Identification of study outcomes

Bleeding and thromboembolic events were identified by four separate pathways. First, a thorough “catch-all” ICD-10 code search was performed from the electronic databases of Landspitali University Hospital and the four regional hospitals of Iceland (Table 2). Second, results of all endoscopic procedures undergone by patients from these hospitals during the follow-up were manually reviewed. Third, results from computerized tomographies of the head and pulmonary arteries undertaken during the study period were examined. Fourth, the national death registry was queried. Importantly, all events were manually reviewed and verified.

For comparison, we identified events by using only previously verified ICD-10 codes (Maura, Blotiere et al. 2015, Nielsen, Skjoth et al. 2017, Sjalander, Sjogren et al. 2018), and without manual chart review. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for this method were calculated compared to our more robust searching algorithm.

3.7 Data extraction for baseline patient characteristics

Information on concomitant drug use was gathered from the Icelandic Medicine Registry using relevant anatomical therapeutic chemical classification codes (Table 3). Concomitant drug use was defined as filling a relevant prescription within 6 months of start of follow-up. Information was

collected on the following medications: antihistamines, antihypertensives, antiplatelets, corticosteroids, NSAIDs, proton-pump inhibitors, selective serotonin reuptake inhibitors, and statins.

The comorbidity burden of patients was estimated using the Charlson comorbidity index and CHA_2DS_2-VASc score, using previously validated ICD-10 codes (Charlson, Pompei et al. 1987, Quan, Khan et al. 2009, Lip, Nieuwlaat et al. 2010, Thygesen, Christiansen et al. 2011). All the variables in the CHA_2DS_2-VASc score are included in the Charlson comorbidity index except hypertension. Hypertension was defined by a relevant ICD-10 code or filling of at least two different types of antihypertensives (Quan, Khan et al. 2009, Nielsen, Skjoth et al. 2017). Additionally, data were collected on patients with underlying bleeding and coagulation disorders and prior history of bleeding or thromboembolic events using relevant ICD-10 codes (Table 2).

Data on treatment indication were gathered by searching for relevant ICD-10 codes from the electronic databases of Landspitali University Hospital, the four regional hospitals, and the primary healthcare databases of the Capital Area, the Westfjords, Eastern, Northern, Southern, and Western Iceland. If a diagnosis was missing or ambiguous, i.e., the ICD-10 codes suggested more than 1 possible treatment indication, treatment indication was identified by manual chart review. Treatment was classified as AF, VTE, cryptogenic ischemic stroke (i.e., without underlying disease processes such as AF), other, and unknown.

Data on all baseline characteristics were gathered from start of follow-up or earlier (Figure 2).

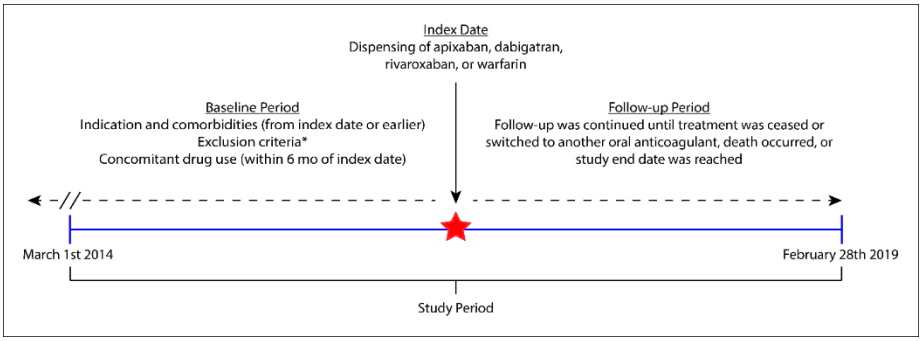

Figure 2: Chart depicting the data acquisition process for the thesis. *The exclusion criteria differ between individual papers and are described in detail in the Methods chapter.

Table 2: ICD-10 codes used

	ICD-10 codes
Major bleeding outcomes	
Gastrointestinal bleeding (specific search)	K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0, K92.1, K92.2, I85.0, I98.3
Gastrointestinal bleeding (sensitive search)	C15, C15.3, C15.4, C15.5, C15.8, C15.9, C16, C16.0, C16.1, C16.2, C16.3, C16.4, C16.5, C16.6, C16.8, C16.9, C17, C17.0, C17.1, C17.2, C17.3, C17.8, C17.9, C18, C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19, C20, C21, C21.0, C21.1, C21.2, C21.8, D37.1, D37.2, D37.3, D37.4, D37.5, I85, I85.0, I85.1, I98.3, K29, K29.2, K29.3, K29.4, K29.5, K29.6, K29.7, K29.8, K29.9, K50, K50.0, K50.1, K50.8, K50.9, K51, K51.0, K51.2, K51.3, K51.4, K51.5, K51.8, K51.9, K55.0, K55.1, K55.8 K55.9, K57.1, K57.3, K57.5, K57.9, K22.1, K22.3, K22.6, K25, K25.0, K25.1, K25.2, K25.3, K25.4, K25.5, K25.6, K25.7, K25.9, K26, K26.0, K26.1, K26.2, K26.3, K26.4, K26.5, K26.6, K26.7, K26.9, K27, K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9, K28, K28.0, K28.1, K28.2, K28.3, K28.4, K28.5, K28.6, K28.7, K28.9, K29.0, K55.2, K62.5, K62.6, K63.1, K63.3, K92.0, K92.1, K92.2

Intracranial hemorrhage	I60, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61, I61.0, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.7, I61.8, I61.9, I62, I62.0, I62.1, I62.9, S06.3, S06.4, S06.5, S06.6
Other bleeding	D50.0, D62, H11.3, H35.6, H43.1, J94.2, M25.0, N02, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N95.0, R04, R04.0, R04.1, R04.2, R04.8, R04.9, R31, R58
Thromboembolic outcomes	
Ischemic stroke	I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64
Transient ischemic attack	G45, G45.0, G45.1, G45.2, G45.3, G45.4, G45.8, G45.9
Myocardial infarction	I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.2, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8
Deep venous thrombosis	I63.6, I67.6, I80.2, I80.3, I80.8, I80.9, I81, I82, I82.2, I82.3, I82.4, I82.6, I82.8, I82.9
Pulmonary embolism	I26, I26.0, I26.9
Arterial thromboembolism	I74, I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9
Other thrombosis (sensitive search)	G08, G46, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8, G95.1, H34.9, I65, I65.0, I65.1, I65.2, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.8, I66.9, I67, I67.0, I67.1, I67.2, I67.3, I67.4, I67.5, I67.7, I67.8, I67.9, I68.8, I76, I79.0, I79.1, I82.0
Treatment indication	
Atrial fibrillation	I48, I48.0, I48.1, I48.2, I48.3, I48.4, I48.9
Venous thromboembolism	I26, I26.0, I26.9, I80.2, I80.3, I80.8, I80.9, I82, I82.2, I82.3, I82.4, I82.6, I82.8, I82.9
Ischemic stroke	G46, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8, I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5,

	I63.6, I63.8, I63.9, I64, I64.0, I64.1, I64.2, I64.3, I64.4, I64.5, I64.6, I64.8, I64.9, I69, I69.3, I69.8, 169.9
Mechanical heart valve	Z95.2, Z95.3, Z95.4
Comorbidities	
Prior history of gastrointestinal bleeding	K22.1, K22.3, K22.6, K25, K25.0, K25.1, K25.2, K25.3, K25.4, K25.5, K25.6, K25.7, K25.9, K26, K26.0, K26.1, K26.2, K26.3, K26.4, K26.5, K26.6, K26.7, K26.9, K27, K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9, K28, K28.0, K28.1, K28.2, K28.3, K28.4, K28.5, K28.6, K28.7, K28.9, K29.0, K55.2, K62.5, K62.6, K63.1, K63.3, K92.0, K92.1, K92.2, I85.0, I98.3
Venous thromboembolism	I26, I26.0, I26.9, I80.2, I80.3, I80.8, I80.9, I82, I82.2, I82.3, I82.4, I82.6, I82.8, I82.9
Ischemic heart disease	I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.2, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8
Heart failure	I11.0, I13.0, I13.2, I50, I50.1, I50.2, I50.3, I50.4, I50.8, I50.9
Peripheral vascular disease	I70, I70.0, I70.1, I70.2, I70.8, I70.9, I71, I71.0, I71.1, I71.2, I71.3, I71.4, I71.5, I71.6, I71.8, I71.9, I72, I72.0, I72.1, I72.2, I72.3, I72.4, I72.8, I72.9, I73.0, I73.1, I73.8, I73.9, I74, I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9, I77, I77.0, I77.1, I77.2, I77.3, I77.4, I77.5, I77.6, I77.8, I77.9
Cerebral accident	I60, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.7, I61.8, I61.9, I62, I62.0, I62.1, I62.9, I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6,I63.8, I63.9, I64, I64.0, I64.1, I64.2, I64.3, I64.4, I64.5, I64.6, I64.8, I64.9, G45, G45.0, G45.1, G45.2, G45.3, G45.4, G45.8, G45.9, G46, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8
Hemiplegia	G81, G81.0, G81.1, G81.9, G82, G82.0, G82.1, G82.2, G82.3, G82.4, G82.5

Dementia	F00, F00.0, F00.1, F00.2, F00.39, F01, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, F02, F02.0, F02.1, F02.2, F02.3, F02.4, F02.8, F03, F05, F05.0, F05.1, F05.8, F05.9, G30, G30.0, G30.1, G30.8, G30.9
Chronic lung disease	J40, J41, J41.0, J41.1, J41.8, J42, J43, J43.0, J43.1, J43.2, J43.8, J43.9, J44, J44.0, J44.1, J44.8, J44.9, J45, J45.0, J45.1, J45.8, J45.9, J46, J47, J60, J61, J62, J62.0, J62.8, J63, J63.0, J63.1, J63.2, J63.3, J63.4, J63.5, J63.8, J64, J65, J66, J66.0, J66.1, J66.2, J66.8, J67, J67.0, J67.1, J67.2, J67.3, J67.4, J67.5, J67.6, J67.7, J67.8, J67.9, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	D86, D86.0, D86.1, D86.2, D86.3, D86.8, D86.9, M05, M05.0, M05.1, M05.2, M05.3, M05.8, M05.9, M06, M06.0, M06.1, M06.2, M06.3, M06.4, M06.8, M06.9, M08, M08.0, M08.1, M08.2, M08.3, M08.4, M08.8, M08.9, M09, M09.0, M09.1, M09.2, M09.8, M30, M30.0, M30.1, M30.2, M30.3, M30.8, M31, M31.0, M31.1, M31.2, M31.3, M31.4, M31.5, M31.6, M31.7, M31.8, M31.9, M32, M32.0, M32.1, M32.2, M32.8, M32.9, M33, M33.0, M33.1, M33.8, M33.9, M34, M34.0, M34.1, M34.2, M34.8, M34.9, M35, M35.0, M35.1, M35.2, M35.3, M35.4, M35.5, M35.6, M35.7, M35.8, M35.9, M36, M36.0, M36.1, M36.2, M36.3, M36.4, M36.8
Peptic ulcer disease	K22.1, K25, K25.0, K25.1, K25.2, K25.3, K25.4, K25.5, K25.6, K25.7, K25.9, K26, K26.0, K26.1, K26.2, K26.3, K26.4, K26.5, K26.6, K26.7, K26.9, K27, K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9, K28, K28.0, K28.1, K28.2, K28.3, K28.4, K28.5, K28.6, K28.7, K28.9
Mild liver disease	B18, B18.0, B18.1, B18.2, B18.8, B18.9, K70.0, K70.1, K70.2, 70.3, K70.9, K71, K71.0, K71.1, K71.2, K71.3, K71.4, K71.5, K71.6, K71.7, K71.8, K71.9, K73, K73.0, K73.1, K73.2, K73.8, K73.9, K74, K74.0, K74.1, K74.2, K74.3, K74.4, K74.5, K74.6, K76.1, K76.2, K76.3, K76.4, K76.8, K76.9
Moderate or severe	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K72.0, K72.1,

liver disease	K72.9, K76.6, I85, I85.0, I85.9, I86.4, I98.2
Moderate or severe renal disease	I12, I12.0, I12.9, I13, I13.0, I13.1, I13.2, I13.9, N00, N00.0, N00.1, N00.2, N00.3, N00.4, N00.5, N00.6, N00.7, N00.8, N00.9, N1, N01.0, N01.1, N01.2, N01.3, N01.4, N01.5, N01.6, N01.7, N01.8, N01.9, N02, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N03, N03.0, N03.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9, N04, N04.0, N04.1, N04.2, N04.3, N04.4, N04.5, N04.6, N04.7, N04.8, N04.9, N05, N05.0, N05.1, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9, N07, N07.0, N07.1, N07.2, N07.3, N07.4, N07.5, N07.6, N07.7, N07.8, N07.9, N11, N11.0, N11.1, N11.8, N11.9, N14, N14.0, N14.1, N14.2, N14.3, N14.4, N17, N17.0, N17.1, N17.2, N17.8, N17.9, N18, N18.0, N18.8, N18.9, N19, Q61, Q61.0, Q61.1, Q61.2, Q61.3, Q61.4, Q61.5, Q61.8, Q61.9
Diabetes mellitus without signs of end-organ damage	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
Diabetes mellitus with end-organ damage	E10.2, E10.3, E10.4, E10.5, E10.6, E10.7, E10.8, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8
Tumor	C00-C75, C81-C85, C88, C90-C96
Metastasis	C76-C80
HIV/AIDS	B20, B20.0, B20.1, B20.2, B20.3, B20.4, B20.5, B20.6, B20.7, B20.8, B20.9, B21, B21.0, B21.1, B21.2, B21.3, B21.7, B21.8, B21.9, B22, B22.0, B22.1, B22.2, B22.7, B23, B23.0, B23.1, B23.2, B23.8, B24
Hypertension	I10, I11, I11.0, I11.9, I12, I12.0, I12.9, I13, I13.0, I13.1, I13.2, I13.9, I15, I15.0, I15.1, I15.2, I15.8, I15.9
Bleeding or coagulation disorders	D65, D66, D67, D68.0, D68.1, D68.2, D68.3, D68.4, D68.5, D68.6, D68.8, D68.9, D69.1, D69.3, D69.4, D69.5, D69.6
End-stage renal disease	N18.5, N18.6
Mitral stenosis	I05.0, I34.2

Table 3: ATC codes for concomitant drug use

Drug class	ATC codes
Antihistamines	A02BA
Antiplatelets	B01AC
Corticosteroids	H02AB
NSAIDs	M01A
PPIs	A02BC
SSRIs	N06AB
Statins	C10AA
Antihypertensive medications	
Alpha-adrenergic blockers	C02A, C02B, C02C
Beta-blockers	C07A, C07B
Calcium channel blockers	C08, C09BB, C09DB, C07FB
Medications affecting the RAAS	C09
Thiazides	C03A, C09BA, C09DA, C07B, C07D, C08G
Other diuretics	C02L, C03B, C03D, C03EA, C03X, C07C, C07D
Vasodilators	C02D, C04, C05, C07E

3.8 Calculation of medication adherence

Medication adherence was estimated using the PDC, i.e., how many days the patient was estimated to have taken his medication during his follow-up period. In Iceland, 70-75% of warfarin treatment is monitored by the Landspitali Anticoagulation Management Center in Reykjavik. Using the DAWN database, which contains information on all dose adjustments for these patients during the follow-up period, we calculated the weighted mean daily dose for each patient (in mg). This allowed us to estimate the total amount of warfarin (in mg) that the patient would have to have filled in order to comply with his dosing regimen. Subsequently, the PDC was estimated by dividing the total amount of warfarin receiving (in mg) by the expected amount needed during the follow-up period.

Similarly, the PDC for DOACs was calculated as the total number of tablets received during the study period divided by the expected amount needed during the follow-up period. This accounted for patients being switched from a standard dose to reduced dosing or vice versa. Patients receiving rivaroxaban due to VTE were estimated to have received 15 mg twice daily for 3 weeks, followed by 20 mg once daily as per the product monograph. Similarly, the dosing regimen for apixaban due to VTE was estimated to be 10 mg twice daily for 1 week, followed by 5 mg twice daily. All other dosing regimens were estimated to be twice daily for apixaban and dabigatran, and once daily for rivaroxaban.

3.9 Statistical analysis

For all 5 papers, inverse probability weighting (IPW) was used to yield balanced study groups. IPW includes the whole study population, calculates propensity scores from potential confounders, and assigns weights to patients based on the inverse of the probability of receiving the observed exposure, thus creating balanced pseudopopulations. The propensity score was calculated with gradient boosted logistic regression using the average treatment effect as an estimand. The following variables were included in the IPW model: age, sex, all variables in the Charlson score (except AIDS which was too sporadic), hypertension, bleeding or coagulation disorders, prior history of VTE events, prior GIB, prior epistaxis event requiring hospital admission (only included in paper IV), treatment indication, region of residence, and concomitant use of antihistamines, antihypertensives, antiplatelets, corticosteroids, NSAIDs, proton pump inhibitors, selective serotonin receptor inhibitors, and statins. Standardized mean difference

(SMD) was used to estimate balance between study groups after weighting. An SMD below 0.1 was considered ideal, while an SMD below 0.2 was considered acceptable (Goldstone, Chiu et al. 2017, Zakrison, Austin et al. 2018). For papers I-II, an acceptable balance was achieved between all study groups. For papers III-V, an acceptable balance was achieved for all variables except for treatment indication and prior history of VTE (a highly correlated variable). To account for this, a sensitivity analysis limited to patients with AF as treatment indication was performed. Additionally, for paper III, a Cox regression that adjusted for all variables with SMD>0.1 was performed when comparing GIB rates between OACs.

Categorical variables of small sample sizes were compared using the Fisher's exact test, while the $\chi 2$ test was used for larger sample sizes. Continuous variables, estimated to follow the normal distribution, were compared using the analysis of variance. Otherwise, the Kruskal-Wallis test was used. Bleeding and thromboembolic event rates were compared using Cox regression and the data were visualized using propensity score-weighted Kaplan-Meier graphs. For papers II-III, the proportional causes of upper and lower GIB between groups were compared using Fisher's exact test. For paper IV, no patient receiving dabigatran had an epistaxis event. Therefore, differences in epistaxis rates between dabigatran and other OACs were estimated using log-rank test only.

For paper V, nonadherence was compared using logistic regression that accounted for length of follow-up. To identify factors associated with nonadherence, univariate analysis was performed. This analysis compared 32 variables. Therefore, using Bonferroni correction for multiple testing, a P value of less than 0.001 was considered significant. Multivariable analysis was performed including variables from the univariate analysis with significant association with nonadherence. Finally, rates of major bleeding and thromboembolic events were compared between adherent and nonadherent users using Cox regression that accounted for the type of OAC received.

Finally, to assess the effect of potentially unmeasured confounders, the E-value of the primary study outcomes was calculated in papers I-II. The E-value is defined as “the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment–outcome association, conditional on the measured covariates” (VanderWeele and Ding 2017).

All statistical analysis was performed in R (R Foundation for Statistical Computing, Austria) using RStudio (RStudio Inc., Boston, MA). All statistical tests were two-tailed and a p-value of less than 0.05 was considered statistically significant.

3.10 Sensitivity analysis

Various sensitivity analyses were performed for the 5 papers. All the papers included a sensitivity analysis that was limited to patients with AF only. Additionally, for paper II, a second analysis was performed that was limited to patients with AF living in the capital area and with GIB events limited to those identified at Landspitali University Hospital, the only hospital in the capital area. For paper III, a subanalysis was performed that compared GIB rates between warfarin patients monitored by the novel Fiix-measurement test or conventional INR measurements. This analysis included new users only and follow-up was censored if a patient was switched to Fiix-monitoring. Lastly, for paper V, a sensitivity analysis was performed that included all patients receiving DOACs irrespective of area of residence.

4 Results

This thesis is based on 5 papers evaluating the safety, efficacy, and adherence of OACs. In Paper I, the rates of thromboembolism and major bleeding were compared between patients receiving apixaban, dabigatran, and rivaroxaban. Similarly, in paper II, GIB rates were compared in the same population. In paper III, the rates of GIB between patients receiving warfarin and DOACs were compared. Specifically, it examined potential differences in upper and lower GIB rates between patients receiving the different drugs. In Paper IV, the rates of epistaxis were compared between patients receiving apixaban, dabigatran, rivaroxaban, and warfarin. Additionally, it compared differences in the presentation, treatment, and outcomes of epistaxis events between patients receiving these 4 types of drugs. Lastly, in paper V nonadherence rates were compared between different OACs. Additionally, factors associated with nonadherence were estimated and rates of thromboembolism and major bleeding were compared between adherent and nonadherent patients.

4.1 Paper I – Comparison of major bleeding and thromboembolic events between different direct oral anticoagulants

In total, 8,892 patients filled a prescription for DOACs during the study period. Of those, 2,819 patients were excluded as they filled an OAC prescription within 12 months of their eligibility in the study. Additionally, 205 patients were excluded for other reasons as depicted in Figure 3. The final study population included 2,157 patients receiving apixaban, 494 patients receiving dabigatran, and 3,217 patients receiving rivaroxaban. The IPW model yielded balanced study groups (Table 4). The weighted mean follow-up was 1.2 years, 1.8 years, and 1.7 years for patients receiving apixaban, dabigatran, and rivaroxaban respectively.

4.1.1 Thromboembolism rates

Overall, 141 thromboembolic events were identified during the follow-up period, including 68 MI events (48%), 53 ischemic stroke or TIA events (38%), 16 VTE events 11%), and 3 arterial thromboembolic events (2%). Overall, 117 thromboembolic events (83%) were identified using ICD-10 codes, 17 (12%) by searching the national death registry, and 1 by reviewing

diagnostic imaging. Finally, 6 events (4%) were identified during chart review of another diagnosis.

Dabigatran was associated with higher rates of thromboembolism compared to rivaroxaban. This was largely due to twofold higher rates of MI for dabigatran compared to rivaroxaban (Figure 4A and Table 5). Dabigatran also had approximately twofold higher rates of MI compared to apixaban, but the confidence intervals (CIs) were wide and included the possibility of a null effect for this comparison. Composite rates of ischemic stroke or TIA were similar between the three drugs. Rates of VTE and arterial thromboembolism were too low to make meaningful comparisons between the drugs (Table 5).

Compared to our robust searching algorithm, the traditional method of using only a few specific ICD-10 codes to identify cases had a sensitivity of 48.2% for any thromboembolism and 98.9% specificity. The PPV for any thromboembolism was 43.9% and the NPV was 99.5% (Table 6). The PPV ranged from 14.3% for VTE to 72.4% for MI.

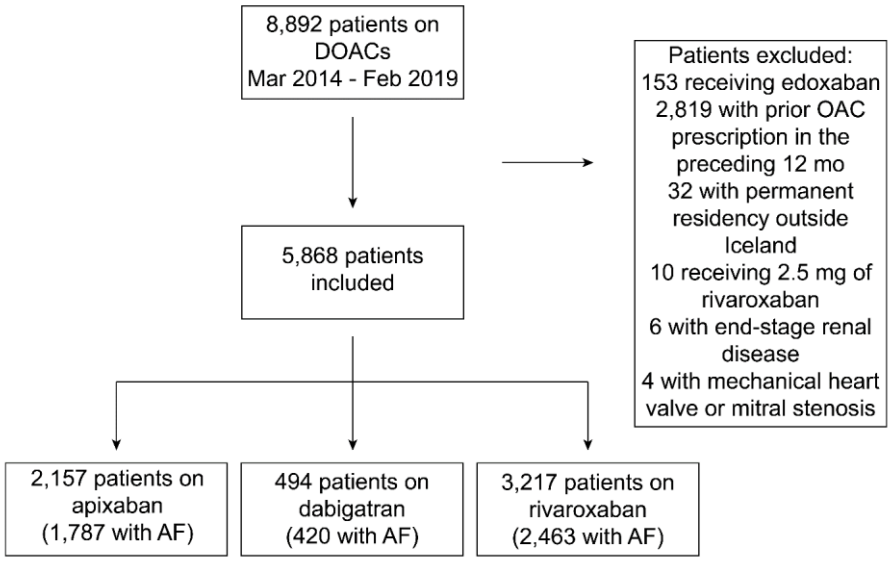

Figure 3: Flowchart for patient selection in papers I and II.

4.1.2 Major bleeding rates

In total, 212 major bleeding events were identified during the follow-up period, including 149 GIB events (70%), 35 intracranial hemorrhages (17%), and 28 other major bleeding events (13%). These events were identified by

using ICD-10 codes 177 (83%), reviewing endoscopic procedure codes – 26 (12%), searching the national death registry – 6 (3%), and reviewing diagnostic imaging – 1 (0.5%). Additionally, 2 events (1%) were identified during chart review of another diagnosis.

Rivaroxaban was associated with higher rates of major bleeding compared to both apixaban and dabigatran, although the second comparison included the possibility of a null effect (Figure 4A and Table 7). Rates of intracranial hemorrhage were similar across all three drugs. Compared to apixaban, rivaroxaban was associated with higher rates of both major GIB and major bleeding from other locations (Table 7).

Compared to our robust searching algorithm, the traditional method of using only a few specific ICD-10 codes to identify cases had a sensitivity of 32.5% for major bleeding events and 98.9% specificity. The PPV for major bleeding was 78.4% and the NPV was 98.7% (Table 6).

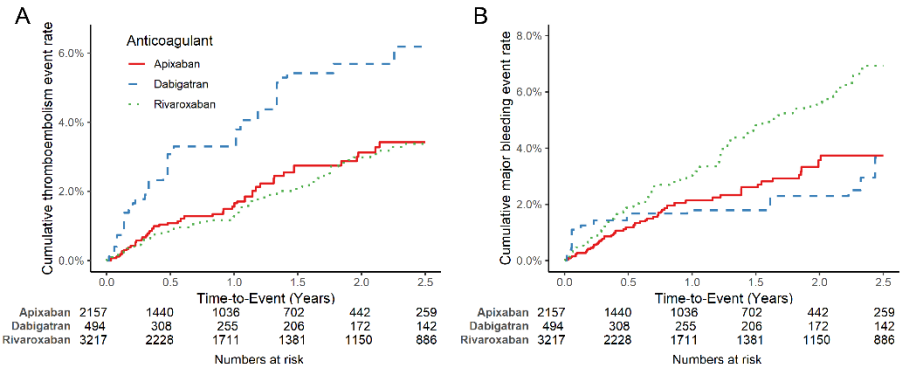

Figure 4: Propensity score-weighted Kaplan-Meier curves comparing rates of A) major bleeding and B) any thromboembolism between new users of apixaban, dabigatran, and rivaroxaban.

4.1.3 Mortality and stroke rates

All-cause mortality was similar across all three DOACs (Table 8). Interestingly, dabigatran was associated with twofold higher rates of vascular death compared to apixaban and rivaroxaban users. However, this must be interpreted in the context of wide CIs that included the possibility of null effect in both instances. The number of all-cause stroke, ischemic stroke, and hemorrhagic stroke did not differ between the three drugs (Table 8).

4.1.4 Estimation of the effect of potential confounders

The E-value for the comparison of any major bleeding for apixaban and rivaroxaban users was 2.72 for the point estimate and 1.63 for the lower limit of the CI. This means that an unmeasured confounder, unrelated to the potential confounders included in the IPW model, would have to be 172% more common in the rivaroxaban group and increase the risk for major bleeding by 172% to explain away the observed difference, or be 63% more common in the rivaroxaban group and increase the risk for major bleeding by 63%, for the CI to include the possibility of a null effect. The E-value for the point estimate was 2.66 for the comparison between dabigatran and rivaroxaban users.

The E-value for the comparison of any thromboembolism between apixaban and rivaroxaban users was 2.98 for the point estimate and 1.04 for the lower limit of the CI. Similarly, the E-value for the comparison of MI between apixaban and rivaroxaban users was 3.94 for the point estimate and 1.41 for the lower limit of the CI.

4.1.5 Sensitivity analysis

A sensitivity analysis limited to patients with AF only was performed. Baseline characteristics for this population are provided in Table 9. This analysis included 1,787 patients receiving apixaban, 420 receiving dabigatran, and 2,463 patients receiving rivaroxaban. Differences in any thromboembolism rates between dabigatran users and patients receiving apixaban and dabigatran were less pronounced than in the primary analysis (Table 10). As in the primary analysis, the rates of MI were twice higher for dabigatran users compared to both apixaban and rivaroxaban users, although the CIs were wide and included the possibility of a null effect for former comparison. Rivaroxaban was associated with higher rates of major bleeding compared to both apixaban and dabigatran (Table 11). Rivaroxaban was associated with higher rates of major GIB compared to both apixaban and dabigatran, although the former comparison included the possibility of a null effect. Additionally, rivaroxaban users had higher rates of other major bleeding compared to apixaban users. The rates of stroke and all-cause mortality were similar between the three drugs (Table 12).

Table 4: Baseline characteristics of the study population of papers I and II

	Apixaban (n=2,157)	Dabigatran (n=474)	Rivaroxaban (n=3,217)	SMD† Before	After
Age	72.4 (13.4)	70.0 (13.6)	68.6 (13.0)	0.191	0.046
Sex (% male)	1153 (53.5)	279 (56.5)	1905 (59.2)	0.078	0.076
CHA_2DS_2-VASc score	2.8 (1.6)	2.6 (1.5)	2.3 (1.5)	0.224	0.050
Charlson comorbidity index	0.9 (1.4)	0.7 (1.2)	0.6 (1.1)	0.154	0.060
Ischemic heart disease	162 (7.5)	38 (7.7)	224 (7.0)	0.019	0.005
Congestive heart failure	176 (8.2)	40 (8.1)	184 (5.7)	0.064	0.012
Peripheral vascular disease	96 (4.5)	24 (4.9)	108 (3.4)	0.051	0.025
Cerebrovascular disease	272 (12.6)	37 (7.5)	169 (5.3)	0.174	0.035
Hemiplegia	22 (1.0)	4 (0.8)	16 (0.5)	0.040	0.049
Diabetes mellitus	102 (4.7)	22 (4.5)	101 (3.1)	0.055	0.016
Diabetes mellitus with end-organ damage	64 (3.0)	12 (2.4)	68 (2.1)	0.036	0.018
Chronic lung disease	125 (5.8)	25 (5.1)	122 (3.8)	0.063	0.033
Moderate/severe renal disease	74 (3.4)	11 (2.2)	72 (2.2)	0.048	0.060
Liver disease	17 (0.8)	2 (0.4)	17 (0.5)	0.033	0.037
Peptic ulcer disease	48 (2.2)	11 (2.2)	36 (1.1)	0.058	0.020
Connective tissue disease	49 (2.3)	8 (1.6)	58 (1.8)	0.032	0.057
Dementia	54 (2.5)	6 (1.2)	37 (1.2)	0.068	0.085
Any tumor	255 (11.8)	51 (10.3)	279 (8.7)	0.069	0.038
Metastatic solid tumor	11 (0.5)	1 (0.2)	24 (0.7)	0.054	0.062
Hypertension	1415 (65.6)	326 (66.0)	1898 (59.0)	0.097	0.030
Bleeding disease	14 (0.6)	1 (0.2)	15 (0.5)	0.046	0.049
Prior GIB	97 (4.5)	24 (4.9)	86 (2.7)	0.077	0.029
Prior VTE	265 (12.3)	46 (9.3)	672 (20.9)	0.219	0.142
Dosing (low dose)	458 (21.2)	225 (45.5)	616 (19.1)	0.391	0.044
Concomitant drug use					
Antihistamines	12 (0.6)	5 (1.0)	18 (0.6)	0.034	0.013

Antiplatelets	584 (27.1)	134 (27.1)	643 (20.0)	0.113	0.024
Corticosteroids	444 (20.6)	98 (19.8)	625 (19.4)	0.019	0.045
NSAIDs	482 (22.3)	102 (20.6)	823 (25.6)	0.078	0.086
PPIs	885 (41.0)	186 (37.7)	1190 (37.0)	0.055	0.011
SSRIs	402 (18.6)	58 (11.7)	464 (14.4)	0.129	0.121
Statins	964 (44.7)	223 (45.1)	1289 (40.1)	0.068	0.022
Treatment indication				0.239	0.147
AF	1787 (82.8)	420 (85.0)	2463 (76.6)		
VTE	236 (10.9)	41 (8.3)	605 (18.8)		
Ischemic stroke	75 (3.5)	13 (2.6)	38 (1.2)		
Other	51 (2.4)	17 (3.4)	93 (2.9)		
Unknown	8 (0.4)	3 (0.6)	18 (0.6)		
Area of residence				0.316	0.126
Capital Area	1512 (70.1)	310 (62.8)	1960 (60.9)		
Eastern	73 (3.4)	17 (3.4)	90 (2.8)		
Northern	144 (6.7)	55 (11.1)	495 (15.4)		
Southern	267 (12.4)	99 (20.0)	438 (13.6)		
Western	116 (5.4)	12 (2.4)	179 (5.6)		
Westfjords	45 (2.1)	1 (0.2)	55 (1.7)		

AF = Atrial fibrillation, GIB = Gastrointestinal bleeding, NSAID = Nonsteroidal anti-inflammatory drug, PPI = Proton pump inhibitor, SMD = standardized mean difference, SSRI = Selective serotonin receptor inhibitor, VTE = Venous thromboembolism. *Data is represented as either mean (standard deviation) or n (%). †SMD below 0.1 was considered ideal balance, while SMD below 0.2 was considered acceptable balance.

Table 5: Comparison of thromboembolic rates between direct oral anticoagulants: All patients

Oral anti-coagulant	Events per 100 person-years	HR (95% CI) compared to apixaban	HR (95% CI) compared to dabigatran	HR (95% CI) compared to rivaroxaban
Any thromboembolism				
Apixaban	1.8	-	0.63 (0.33-1.18)	1.12 (0.75-1.67)
Dabigatran	2.4	1.60 (0.84-3.03)	-	1.79 (1.00-3.21)
Rivaroxaban	1.4	0.89 (0.60-1.33)	0.56 (0.31-1.00)	-
Ischemic stroke or transient ischemic attack				
Apixaban	0.9	-	1.21 (0.38-3.83)	1.42 (0.76-2.65)
Dabigatran	0.6	0.83 (0.26-2.61)	-	1.18 (0.38-3.65)
Rivaroxaban	0.5	0.70 (0.38-1.31)	0.85 (0.27-2.65)	-
Myocardial infarct				
Apixaban	0.8	-	0.49 (0.21-1.14)	1.11 (0.61-2.04)
Dabigatran	1.4	2.03 (0.88-4.70)	-	2.26 (1.09-4.66)
Rivaroxaban	0.6	0.90 (0.49-1.65)	0.44 (0.21-0.92)	-
Venous thromboembolism				
Apixaban	0.2	-	0.31 (0.04-2.58)	0.72 (0.22-2.38)
Dabigatran	0.4	3.23 (0.39-26.89)	-	2.34 (0.36-15.25)
Rivaroxaban	0.2	1.38 (0.42-4.54)	0.43 (0.07-2.79)	-
Arterial thromboembolism				
Apixaban	0	-	n/a	n/a
Dabigatran	0.05	n/a	-	1.44 (0.13-16.49)
Rivaroxaban	0.04	n/a	0.69 (0.06-7.92)	-

95% CI = 95% confidence interval, HR = hazard ratio.

Table 6: Sensitivity, specificity, and predictive values of conventional ICD-10 code searches compared to our robust searching algorithm

Outcome	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Only primary discharge diagnoses				
Major bleeding	32.5	98.9	78.4	98.7
Gastrointestinal bleeding	19.0	99.9	91.8	96.7
Intracranial hemorrhage	50.0	100	100	99.7
Other bleeding	35.7	99.7	37.0	99.7
Any thromboembolism	48.2	98.9	51.1	98.7
Ischemic stroke or transient ischemic attack	44.6	99.4	43.9	99.5
Myocardial infarct	79.7	99.6	72.4	99.8
Venous thromboembolism	29.4	99.5	14.3	99.8
Arterial thromboembolism	66.7	~100	66.7	~100
All hospital discharge codes and codes from emergency department visits				
Major bleeding	66.5	96.7	43.4	98.7
Gastrointestinal bleeding	53.7	99.1	66.1	98.8
Intracranial hemorrhage	86.1	99.9	88.6	99.9
Other bleeding	89.3	97.5	18.5	99.9
Any thromboembolism	83.0	96.6	37.4	99.6
Ischemic stroke or transient ischemic attack	89.3	98.6	37.6	99.9
Myocardial infarct	79.7	99.6	72.4	99.8
Venous thromboembolism	82.4	98.2	12.0	99.9
Arterial thromboembolism	66.7	99.9	40.0	~100

Table 7: Comparison of major bleeding rates between direct oral anticoagulants: All patients

Oral anti-coagulant	Events per 100 person-years	HR (95% CI) compared to apixaban	HR (95% CI) compared to dabigatran	HR (95% CI) compared to rivaroxaban
Major bleeding				
Apixaban	1.8	-	0.98 (0.50-1.93)	0.60 (0.42-0.85)
Dabigatran	1.8	1.02 (0.52-1.99)	-	0.61 (0.33-1.12)
Rivaroxaban	2.9	1.67 (1.18-2.36)	1.64 (0.89-3.01)	-
Intracranial hemorrhage				
Apixaban	0.4	-	1.36 (0.42-4.44)	0.95 (0.41-2.18)
Dabigatran	0.3	0.74 (0.23-2.40)	-	0.70 (0.21-2.27)
Rivaroxaban	0.4	1.06 (0.46-2.43)	1.43 (0.44-4.67)	-
Major gastrointestinal bleeding				
Apixaban	1.4	-	1.06 (0.46-2.46)	0.67 (0.45-1.00)
Dabigatran	1.3	0.95 (0.41-2.19)	-	0.63 (0.29-1.36)
Rivaroxaban	2.0	1.50 (1.00-2.24)	1.58 (0.74-3.40)	-
Other major bleeding				
Apixaban	0.02	-	0.09 (0.01-1.09)	0.04 (0.01-0.31)
Dabigatran	0.2	10.78 (0.91-127.21)	-	0.44 (0.09-2.07)
Rivaroxaban	0.5	24.34 (3.27-181.39)	2.26 (0.48-10.54)	-

95% CI = 95% confidence interval, HR = hazard ratio.

Table 8: Comparison of stroke and mortality rates between direct oral anticoagulants: All patients

Oral anti-coagulant	Events per 100 person-years	HR (95% CI) compared to apixaban	HR (95% CI) compared to dabigatran	HR (95% CI) compared to rivaroxaban
Any stroke				
Apixaban	0.7	-	1.07 (0.39-2.95)	1.35 (0.72-2.56)
Dabigatran	0.7	0.94 (0.34-2.59)	-	1.27 (0.47-3.39)
Rivaroxaban	0.5	0.74 (0.39-1.39)	0.79 (0.29-2.11)	-
Ischemic stroke				
Apixaban	0.6	-	1.38 (0.32-5.96)	1.39 (0.69-2.79)
Dabigatran	0.3	0.72 (0.17-3.12)	-	1.00 (0.24-4.24)
Rivaroxaban	0.4	0.72 (0.36-1.45)	1.00 (0.24-4.21)	-
Hemorrhagic stroke				
Apixaban	0.1	-	0.58 (0.13-2.54)	1.10 (0.28-4.25)
Dabigatran	0.3	1.71 (0.39-7.45)	-	1.88 (0.48-7.30)
Rivaroxaban	0.1	0.91 (0.24-3.53)	0.53 (0.14-2.06)	-
All-cause mortality				
Apixaban	3.6	-	1.29 (0.79-2.09)	1.06 (0.81-1.37)
Dabigatran	2.8	0.78 (0.48-1.27)	-	0.82 (0.51-1.32)
Rivaroxaban	3.4	0.95 (0.73-1.23)	1.22 (0.76-1.95)	-
Vascular mortality				
Apixaban	0.5	-	0.50 (0.20-1.28)	1.01 (0.53-1.89)
Dabigatran	0.9	1.98 (0.78-5.02)	-	1.99 (0.84-4.74)
Rivaroxaban	0.5	0.99 (0.53-1.87)	0.50 (0.21-1.19)	-

95% CI = 95% confidence interval, HR = hazard ratio.

Table 9: Baseline characteristics of the sensitivity analysis for papers I and II, including patients with atrial fibrillation only*

	Apixaban (n=1,787)	Dabigatran (n=420)	Rivaroxaban (n=2,463)	SMD† Before	After
Age	73.8 (12.0)	71.3 (12.0)	70.7 (11.4)	0.175	0.074
Sex (% male)	976 (54.6)	245 (58.3)	1526 (62.0)	0.099	0.089
CHA_2DS_2-VASc score	2.8 (1.6)	2.6 (1.5)	2.4 (1.5)	0.202	0.082
Charlson comorbidity index	0.9 (1.4)	0.7 (1.1)	0.6 (1.1)	0.156	0.082
Ischemic heart disease	142 (7.9)	34 (8.1)	187 (7.6)	0.012	0.013
Congestive heart failure	158 (8.8)	34 (8.1)	156 (6.3)	0.063	0.025
Peripheral vascular disease	81 (4.5)	16 (3.8)	91 (3.7)	0.028	0.024
Cerebrovascular disease	207 (11.6)	25 (6.0)	125 (5.1)	0.159	0.038
Hemiplegia	15 (0.8)	2 (0.5)	8 (0.3)	0.046	0.020
Diabetes mellitus	84 (4.7)	22 (5.2)	84 (3.4)	0.060	0.033
Diabetes mellitus with end-organ damage	50 (2.8)	12 (2.9)	57 (2.3)	0.023	0.043
Chronic lung disease	105 (5.9)	20 (4.8)	90 (3.7)	0.070	0.030
Moderate/severe renal disease	61 (3.4)	9 (2.1)	59 (2.4)	0.052	0.066
Liver disease	17 (1.0)	0 (0.0)	13 (0.5)	0.097	0.084
Peptic ulcer disease	42 (2.4)	9 (2.1)	27 (1.1)	0.064	0.013
Connective tissue disease	35 (2.0)	8 (1.9)	45 (1.8)	0.006	0.028
Dementia	45 (2.5)	6 (1.4)	25 (1.0)	0.077	0.060
Any tumor	207 (11.6)	38 (9.0)	191 (7.8)	0.087	0.055
Metastatic solid tumor	8 (0.4)	1 (0.2)	12 (0.5)	0.028	0.032
Hypertension	1245 (69.7)	298 (71.0)	1613 (65.5)	0.078	0.023
Bleeding disease	13 (0.7)	1 (0.2)	10 (0.4)	0.048	0.044
Prior GIB	80 (4.5)	19 (4.5)	68 (2.8)	0.063	0.039
Prior VTE	27 (1.5)	4 (1.0)	59 (2.4)	0.076	0.028
Dosing (low dose)	394 (22.0)	190 (45.2)	515 (20.9)	0.356	0.040
Concomitant drug use					

Antihistamines	9 (0.5)	5 (1.2)	16 (0.6)	0.050	0.019
Antiplatelets	488 (27.3)	114 (27.1)	532 (21.6)	0.089	0.021
Corticosteroids	356 (19.9)	82 (19.5)	455 (18.5)	0.025	0.031
NSAIDs	384 (21.5)	87 (20.7)	586 (23.8)	0.049	0.045
PPIs	735 (41.1)	158 (37.6)	882 (35.8)	0.073	0.024
SSRIs	313 (17.5)	46 (11.0)	322 (13.1)	0.126	0.131
Statins	829 (46.4)	198 (47.1)	1088 (44.2)	0.040	0.021
Area of residence				0.319	0.129
Capital Area	1269 (71.0)	258 (61.4)	1529 (62.1)		
Eastern	58 (3.2)	15 (3.6)	58 (2.4)		
Northern	120 (6.7)	46 (11.0)	361 (14.7)		
Southern	220 (12.3)	90 (21.4)	335 (13.6)		
Western	87 (4.9)	10 (2.4)	135 (5.5)		
Westfjords	33 (1.8)	1 (0.2)	45 (1.8)		

AF = Atrial fibrillation, GIB = Gastrointestinal bleeding, NSAID = Nonsteroidal anti-inflammatory drug, PPI = Proton pump inhibitor, SMD = standardized mean difference, SSRI = Selective serotonin receptor inhibitor, VTE = Venous thromboembolism. *Data is represented as either mean (standard deviation) or n (%). †SMD below 0.1 was considered ideal balance, while SMD below 0.2 was considered acceptable balance.

Table 10: Comparison of thromboembolic rates between direct oral anticoagulants: Patients with atrial fibrillation only

Oral anti-coagulant	Events per 100 person-years	HR (95% CI) compared to apixaban	HR (95% CI) compared to dabigatran	HR (95% CI) compared to rivaroxaban
Any thromboembolism				
Apixaban	1.7	-	0.82 (0.40-1.72)	1.13 (0.73-1.75)
Dabigatran	1.8	1.21 (0.58-2.52)	-	1.37 (0.70-2.68)
Rivaroxaban	1.4	0.88 (0.57-1.37)	0.73 (0.37-1.43)	-
Ischemic stroke or transient ischemic attack				
Apixaban	0.8	-	2.12 (0.44-10.12)	1.34 (0.68-2.63)
Dabigatran	0.3	0.47 (0.10-2.26)	-	0.63 (0.14-2.89)
Rivaroxaban	0.5	0.75 (0.38-1.46)	1.58 (0.35-7.19)	-
Myocardial infarct				
Apixaban	0.7	-	0.44 (0.18-1.11)	0.98 (0.51-1.89)
Dabigatran	1.4	2.26 (0.90-5.67)	-	2.21 (1.00-4.90)
Rivaroxaban	0.7	1.02 (0.53-1.96)	0.45 (0.20-1.00)	-
Venous thromboembolism				
Apixaban	0.2	-	4.81 (0.45-51.05)	1.87 (0.51-6.86)
Dabigatran	0.04	0.21 (0.02-2.20)	-	0.39 (0.04-3.48)
Rivaroxaban	0.1	0.54 (0.15-1.97)	2.58 (0.29-23.12)	-
Arterial thromboembolism				
Apixaban	0	-	n/a	n/a
Dabigatran	0	n/a	-	n/a
Rivaroxaban	0.03	n/a	n/a	-

95% CI = 95% confidence interval, HR = hazard ratio.

Table 11: Comparison of major bleeding rates between direct oral anticoagulants: Patients with atrial fibrillation only

Oral anti-coagulant	Events per 100 person-years	HR (95% CI) compared to apixaban	HR (95% CI) compared to dabigatran	HR (95% CI) compared to rivaroxaban
Major bleeding				
Apixaban	1.8	-	1.33 (0.72-2.48)	0.61 (0.42-0.89)
Dabigatran	1.4	0.75 (0.40-1.40)	-	0.46 (0.25-0.83)
Rivaroxaban	2.9	1.64 (1.13-2.37)	2.18 (1.21-3.93)	-
Intracranial hemorrhage				
Apixaban	0.3	-	1.82 (0.50-6.62)	1.09 (0.42-2.84)
Dabigatran	0.3	0.55 (0.15-1.99)	-	0.60 (0.15-2.43)
Rivaroxaban	0.4	0.92 (0.35-2.39)	1.67 (0.41-6.81)	-
Major gastrointestinal bleeding				
Apixaban	1.4	-	1.57 (0.75-3.29)	0.66 (0.43-1.02)
Dabigatran	0.9	0.64 (0.30-1.34)	-	0.42 (0.21-0.87)
Rivaroxaban	2.1	1.51 (0.98-2.30)	2.36 (1.15-4.83)	-
Other major bleeding				
Apixaban	0.02	-	0.09 (0.01-1.09)	0.05 (0.01-0.34)
Dabigatran	0.2	10.97 (0.91-131.71)	-	0.50 (0.11-2.31)
Rivaroxaban	0.5	22.09 (2.98-163.50)	2.01 (0.43-9.38)	-

95% CI = 95% confidence interval, HR = hazard ratio.

Table 12: Comparison of stroke and mortality rates between direct oral anticoagulants: Patients with atrial fibrillation only

Oral anti-coagulant	Events per 100 person-years	HR (95% CI) compared to apixaban	HR (95% CI) compared to dabigatran	HR (95% CI) compared to rivaroxaban
Any stroke				
Apixaban	0.7	-	1.93 (0.60-6.27)	1.29 (0.63-2.64)
Dabigatran	0.4	0.52 (0.16-1.68)	-	0.67 (0.20-2.22)
Rivaroxaban	0.5	0.77 (0.38-1.58)	1.49 (0.45-4.96)	-
Ischemic stroke				
Apixaban	0.5	-	3.44 (0.41-29.22)	1.17 (0.55-2.50)
Dabigatran	0.1	0.29 (0.03-2.46)	-	0.34 (0.04-2.73)
Rivaroxaban	0.4	0.85 (0.40-1.82)	2.94 (0.37-23.60)	-
Hemorrhagic stroke				
Apixaban	0.1	-	0.90 (0.20-4.06)	1.44 (0.31-6.81)
Dabigatran	0.3	1.11 (0.25-5.00)	-	1.60 (0.33-7.69)
Rivaroxaban	0.1	0.69 (0.15-3.26)	0.62 (0.13-2.99)	-
All-cause mortality				
Apixaban	3.3	-	1.36 (0.79-2.34)	1.05 (0.79-1.39)
Dabigatran	2.5	0.74 (0.43-1.27)	-	0.77 (0.46-1.30)
Rivaroxaban	3.2	0.95 (0.72-1.27)	1.30 (0.77-2.18)	-
Vascular mortality				
Apixaban	0.6	-	0.56 (0.20-1.58)	1.20 (0.62-2.35)
Dabigatran	1.0	1.80 (0.63-5.12)	-	2.17 (0.80-5.85)
Rivaroxaban	0.5	0.83 (0.43-1.62)	0.46 (0.17-1.25)	-

95% CI = 95% confidence interval, HR = hazard ratio.

4.2 Paper II – Comparison of gastrointestinal bleeding rates between different direct oral anticoagulants

This paper was based on the same population as paper I (Figure 3 and Table 4).

In total, 241 clinically relevant GIB events were identified during the follow-up period. Of those, 135 (56%) were classified as lower GIB, 72 (30%) as upper GIB, and 34 (14%) could not be classified. These events were identified using a thorough ICD-10 codes search – 190 (79%), by reviewing endoscopic procedures – 49 (20%), and by searching the national death registry – 2 (1%).

When only previously validated ICD-10 codes were used to identify cases and without manual verification, 130 GIB events were identified. This method had 52.7% sensitivity, 99.9% specificity, 97.7% PPV, and 98.0% NPV compared to our searching algorithm.

4.2.1 Gastrointestinal bleeding rates

Rivaroxaban was associated with higher rates of any clinically relevant GIB compared to both apixaban and dabigatran, although the latter comparison did not reject the null hypothesis (Figure 5A and Table 13). Interestingly, dabigatran was associated with approximately threefold lower rates of upper GIB compared to both apixaban and rivaroxaban, although this must be interpreted in the context of wide CIs (Table 13). Lower GIB rates were higher for rivaroxaban compared to apixaban (Table 13).

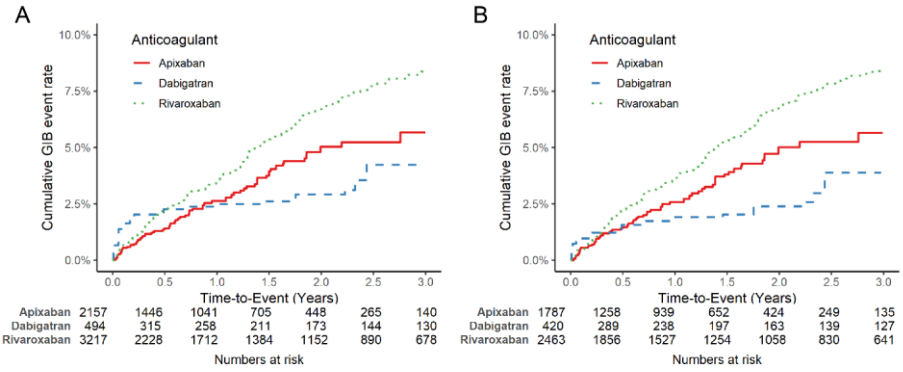

Figure 5: Propensity score-weighted Kaplan-Meier curves comparing rates of any clinically relevant gastrointestinal bleeding between new users of apixaban, dabigatran, and rivaroxaban in A) all patients and b) patients with atrial fibrillation only.

4.2.2 Estimation of the effect of potential confounders

The E-value for the comparison of any clinically relevant GIB between apixaban and rivaroxaban users was 2.19 for the point estimate and 1.26 for the lower limit of the CI. The E-value for the point estimate was 2.64 for the comparison between dabigatran and rivaroxaban users.

4.2.3 Sensitivity analysis

A sensitivity analysis that included patients with AF only demonstrated similar results (Table 14). Rivaroxaban was associated with higher overall rates of GIB compared to both apixaban and dabigatran (Figure 5B). Similarly, upper GIB rates were higher for rivaroxaban than dabigatran. Consistently, a second analysis restricted to patients with AF living in the capital area and with GIB events limited to those identified and Landspitali University Hospital demonstrated similar results (Table 15).

Table 13: Comparison of GIB rates between patients receiving rivaroxaban, apixaban, or dabigatran for all patients

Oral anti-coagulant	GIB events per 100 py	HR [95% CI] compared to apixaban	HR [95% CI] compared to dabigatran	HR [95% CI] compared to rivaroxaban
Overall GIB				
Apixaban	2.5	-	1.15 [0.61-2.17]	0.71 [0.52-0.96]
Dabigatran	1.9	0.87 [0.46-1.65]	-	0.61 [0.34-1.10]
Rivaroxaban	3.2	1.42 [1.04-1.93]	1.63 [0.91-2.92]	-
Major GIB				
Apixaban	1.4	-	0.93 [0.42-2.08]	0.67 [0.45-1.00]
Dabigatran	1.4	1.08 [0.48-2.40]	-	0.72 [0.35-1.48]
Rivaroxaban	1.9	1.50 [1.00-2.24]	1.39 [0.67-2.88]	-
Upper GIB				
Apixaban	0.8	-	2.90 [0.98-8.55]	0.77 [0.44-1.35]
Dabigatran	0.3	0.35 [0.12-1.02]	-	0.27 [0.09-0.76]
Rivaroxaban	1.0	1.30 [0.74-2.27]	3.75 [1.32-10.71]	-
Lower GIB				
Apixaban	1.2	-	0.65 [0.31-1.39]	0.65 [0.43-1.00]
Dabigatran	1.7	1.53 [0.72-3.24]	-	1.00 [0.51-1.95]
Rivaroxaban	1.7	1.53 [1.00-2.33]	1.00 [0.51-1.96]	-

AF = Atrial fibrillation, CI = Confidence interval, GIB = Gastrointestinal bleeding, HR = Hazard ratio, py = Person-years. *Upper and lower GIB rates do not equate to the overall GIB rate, as some GIB events could not be classified as either upper or lower.

Table 14: Comparison of GIB rates between patients receiving rivaroxaban, apixaban, or dabigatran for patients with atrial fibrillation only

Oral anti-coagulant	GIB events per 100 py	HR [95% CI] compared to apixaban	HR [95% CI] compared to dabigatran	HR [95% CI] compared to rivaroxaban
Overall GIB				
Apixaban	2.4	-	1.46 [0.80-2.64]	0.71 [0.52-0.99]
Dabigatran	1.6	0.69 [0.38-1.24]	-	0.49 [0.28-0.86]
Rivaroxaban	3.2	1.40 [1.01-1.94]	2.04 [1.17-3.55]	-
Major GIB				
Apixaban	1.4	-	1.31 [0.66-2.58]	0.67 [0.44-1.02]
Dabigatran	1.1	0.77 [0.39-1.51]	-	0.51 [0.27-0.98]
Rivaroxaban	2.0	1.49 [0.98-2.28]	1.95 [1.02-3.73]	-
Upper GIB				
Apixaban	0.8	-	2.19 [0.72-6.63]	0.77 [0.43-1.36]
Dabigatran	0.4	0.46 [0.15-1.39]	-	0.35 [0.12-0.99]
Rivaroxaban	1.0	1.30 [0.73-2.32]	2.85 [1.01-8.04]	-
Lower GIB				
Apixaban	1.3	-	1.04 [0.51-2.12]	0.78 [0.50-1.21]
Dabigatran	1.2	0.96 [0.47-1.95]	-	0.75 [0.39-1.44]
Rivaroxaban	1.6	1.28 [0.83-1.99]	1.34 [0.69-2.59]	-

AF = Atrial fibrillation, CI = Confidence interval, GIB = Gastrointestinal bleeding, HR = Hazard ratio, py = Person-years. *Upper and lower GIB rates do not equate to the overall GIB rate, as some GIB events could not be classified as either upper or lower.

Table 15: Comparison of GIB rates between patients receiving rivaroxaban, apixaban, or dabigatran for patients with atrial fibrillation and living in the greater capital area only

Oral anti-coagulant	GIB events per 100 py	HR [95% CI] compared to apixaban	HR [95% CI] compared to dabigatran	HR [95% CI] compared to rivaroxaban
Overall GIB				
Apixaban	2.7	-	1.44 [0.73-2.84]	0.76 [0.52-1.10]
Dabigatran	1.9	0.69 [0.35-1.36]	-	0.52 [0.28-0.99]
Rivaroxaban	3.4	1.32 [0.91-1.92]	1.91 [1.01-3.63]	-
Major GIB				
Apixaban	1.7	-	1.42 [0.67-3.01]	0.73 [0.46-1.17]
Dabigatran	1.3	0.70 [0.33-1.49]	-	0.51 [0.25-1.07]
Rivaroxaban	2.3	1.36 [0.85-2.18]	1.94 [0.93-4.04]	-
Upper GIB				
Apixaban	1.0	-	1.83 [0.59-5.68]	0.81 [0.43-1.53]
Dabigatran	0.6	0.55 [0.18-1.70]	-	0.44 [0.15-1.28]
Rivaroxaban	1.2	1.23 [0.65-2.33]	2.26 [0.78-6.49]	-
Lower GIB				
Apixaban	1.5	-	1.16 [0.50-2.69]	0.90 [0.54-1.49]
Dabigatran	1.3	0.87 [0.37-2.02]	-	0.78 [0.35-1.74]
Rivaroxaban	1.6	1.12 [0.67-1.86]	1.29 [0.57-2.90]	-

AF = Atrial fibrillation, CI = Confidence interval, GIB = Gastrointestinal bleeding, HR = Hazard ratio, py = Person-years. *Upper and lower GIB rates do not equate to the overall GIB rate, as some GIB events could not be classified as either upper or lower.

4.3 Paper III – Comparison of gastrointestinal bleeding rates between warfarin and direct oral anticoagulants

In total, 14,611 patients filled an OAC prescription during the study period. Of those, 6,967 had received an OAC prescription within 12 months of their eligibility in the study and were excluded. Additionally, 563 patients were excluded for other reasons as depicted in Figure 6. The final study population included 7,081 patients; including 2,098 patients receiving apixaban, 474 receiving dabigatran, 3,106 receiving rivaroxaban, and 1,403 receiving warfarin (Table 16). The mean weighted follow-up period was 1.1 years for patients receiving apixaban, 1.7 years for patients receiving dabigatran, 1.6 years for patients receiving rivaroxaban, and 1.5 years for patients receiving warfarin.

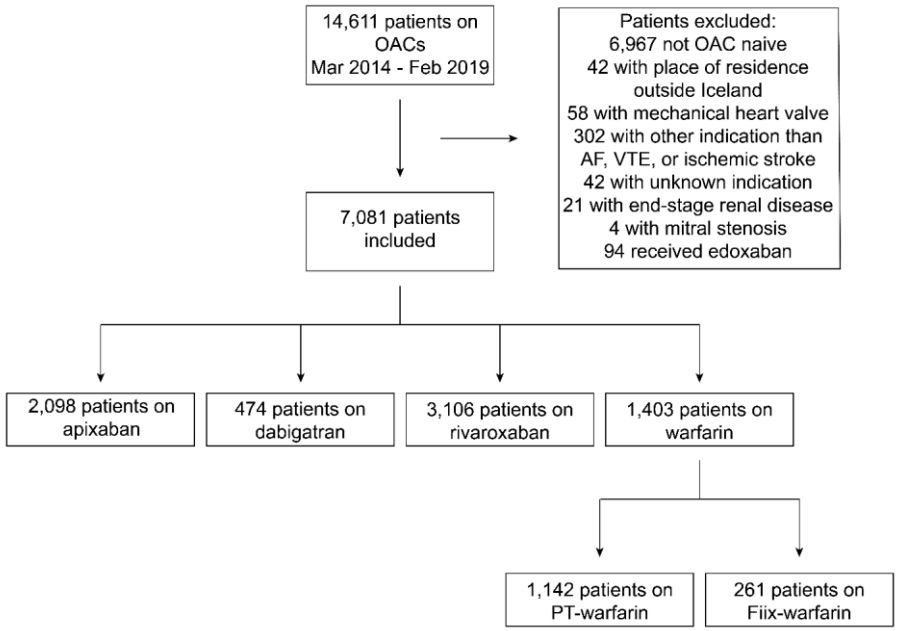

Figure 6: Flowchart for patient selection in papers III-IV.

4.3.1 Gastrointestinal bleeding rates

In total, 295 GIB events were identified during the follow-up of the final study population; 105 events (36%) were classified as upper GIB, 150 events (51%) as lower GIB, and 40 GIB events (14%) had an unknown location. Overall, 5 patients had fatal GIB events; including 3 patients on warfarin. The other 2 were treated with apixaban and rivaroxaban.

Warfarin was associated with similar rates of any clinically relevant GIB and major GIB compared to DOACs (Figure 7-8). When warfarin was compared to individual DOACs, it was associated with higher rates of major GIB compared to apixaban (2.3 events/100-py vs. 1.5 events/100-py, HR 1.79, 95% CI 1.06-3.05). Otherwise, rates of overall and major GIB were not markedly different between warfarin and individual DOACs.

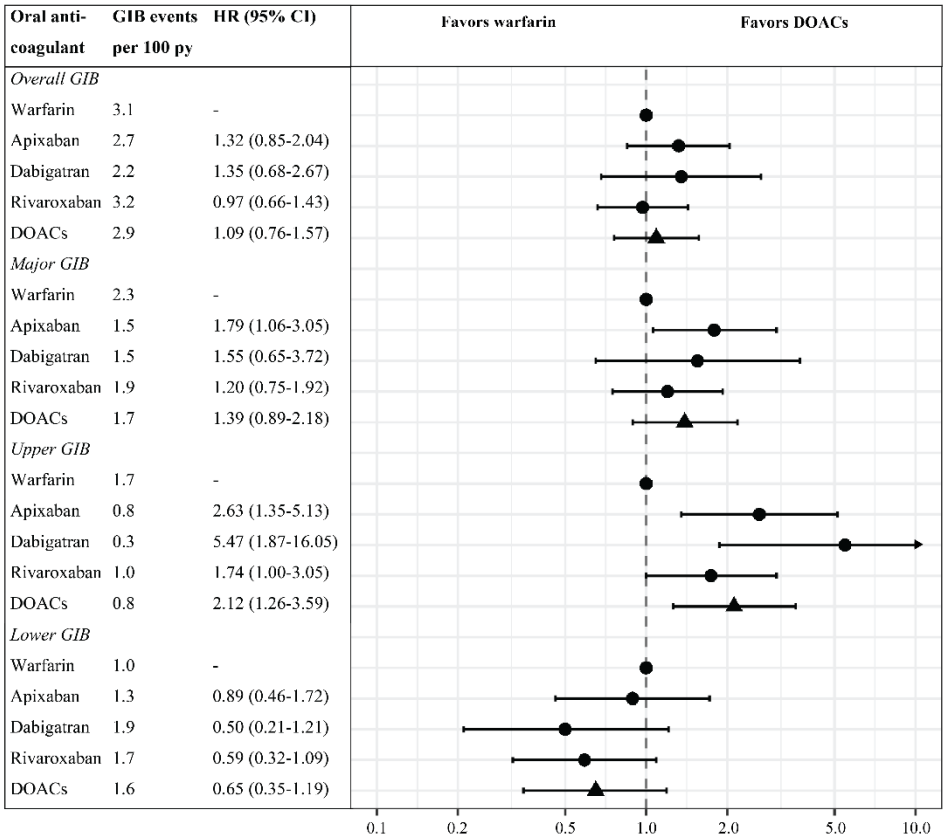

Figure 7: Comparison of propensity score-weighted incidence rates and hazard ratios of gastrointestinal bleeding (GIB) for patients receiving warfarin and direct oral anticoagulants (DOACs) in the primary analysis.

Warfarin was associated with higher rates of upper GIB (1.7 events/100-py vs. 0.8 events/100-py, HR 2.12, 95% CI 1.26-3.59), while lower GIB rates were not markedly different between the groups (1.0 events/100-py vs. 1.6 events/100-py, HR 0.65, 95% CI 0.35-1.19). These results were consistent when warfarin was compared to individual DOACs (Figure 7 and 9).

Interestingly, compared to DOACs, differences in upper GIB rates were more pronounced in male warfarin users (1.8 events/py-100 vs. 0.7 events/100-py, HR 2.52, 95% CI 1.22-5.21) than female users (1.4 events/100-py vs. 1.0 events/100-py, HR 1.66, 95% CI 0.74-3.71). Lower GIB rates were similar for warfarin and DOACs for both sexes.

Peptic ulcer disease was proportionally less common cause of upper GIB for warfarin compared to DOACs (18% vs. 39%, odds ratio 0.33, 95% CI 0.10-0.96) (Table 17). However, propensity-weighted absolute rates of GIB due to peptic ulcer disease were similar between warfarin and DOAC users (0.3 events/100-py vs. 0.3 events/100-py, HR 1.18, 95% CI 0.39-3.52).

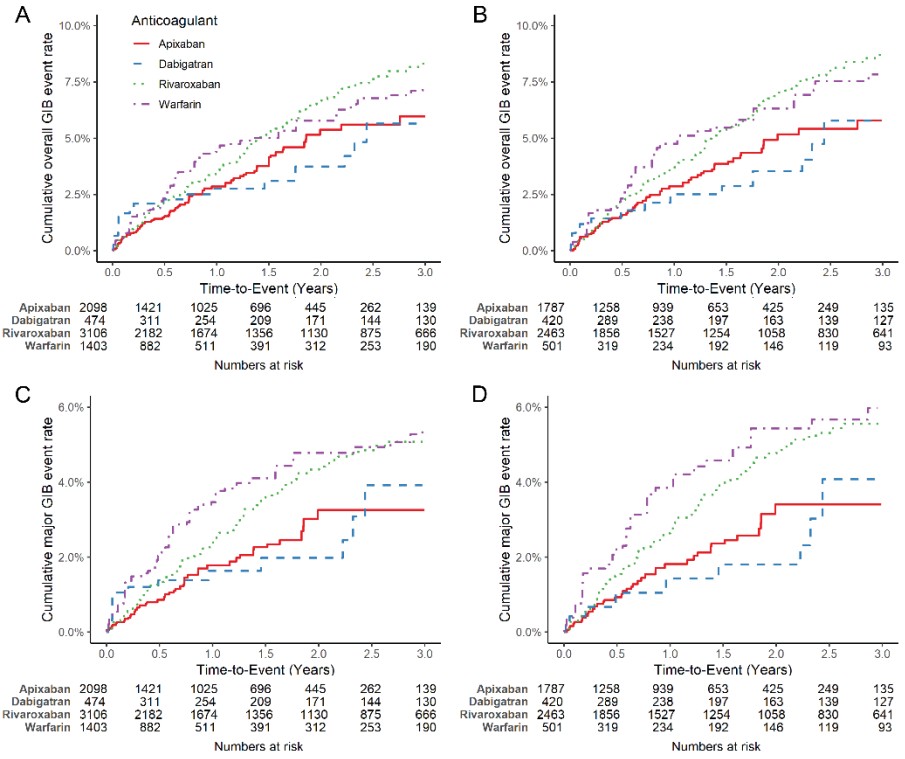

Figure 8: Propensity score-weighted Kaplan-Meier graphs comparing rates of any clinically relevant and major gastrointestinal bleeding (GIB) between warfarin and direct oral anticoagulants. A-B) demonstrates rates of any clinically relevant GIB for all patients and patients with atrial fibrillation only. C-D) demonstrates rates of major GIB for all patients and patients with atrial fibrillation only.

4.3.2 Sensitivity analysis

A sensitivity analysis of patients with AF only was performed. The IPW model yielded acceptable balance between all study groups (Table 18). In total, 1,787 patients received apixaban, 420 dabigatran, 2,463 rivaroxaban, and 501 warfarin. The average weighted follow-up period was 1.3 years for apixaban, 1.9 years for dabigatran, 1.8 years for rivaroxaban, and 1.6 years for warfarin. The results of this analysis were similar to the primary analysis (Figure 8-10).

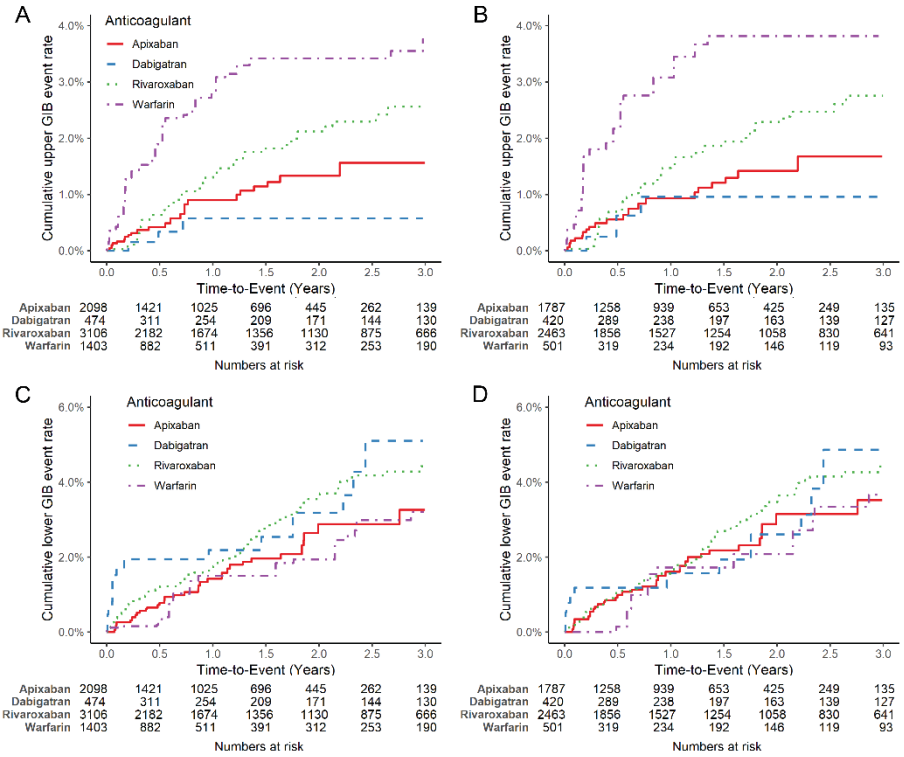

Figure 9: Propensity score-weighted Kaplan-Meier graphs comparing rates of upper and lower gastrointestinal bleeding (GIB) between warfarin and direct oral anticoagulants. A-B) demonstrates rates of upper GIB for all patients and patients with atrial fibrillation only. C-D) demonstrates rates of lower GIB for all patients and patients with atrial fibrillation only.

4.3.3 In-group comparison of warfarin by anticoagulation monitoring

Warfarin treatment monitored by the novel Fiix-measurement was associated with similar rates of any clinically relevant GIB (HR 0.85, 95% CI 0.34-2.11), major GIB (HR 0.82, 95% CI 0.26-2.55), upper GIB (HR 1.08, 95% CI 0.36-3.25), and lower GIB (HR 0.82, 95% CI 0.17-4.05) compared to conventional INR monitoring.

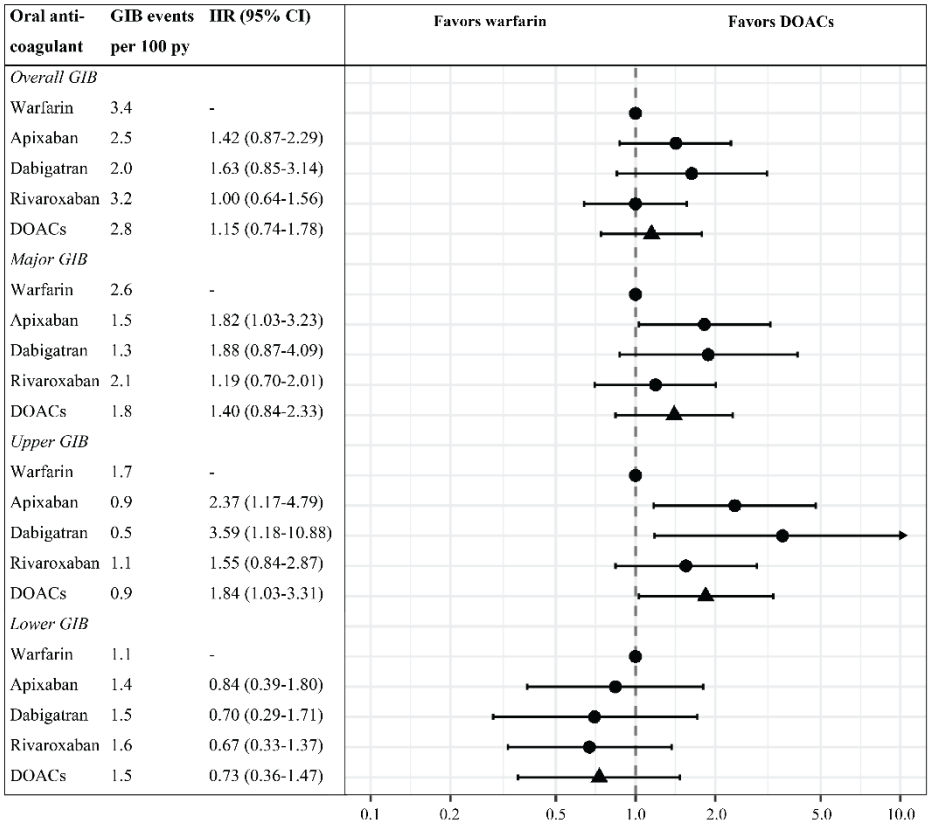

Figure 10: Comparison of propensity score-weighted incidence rates and hazard ratios of gastrointestinal bleeding (GIB) for patients receiving warfarin and direct oral anticoagulants (DOACs) in the sensitivity analysis.

Table 16: Baseline characteristics of the study population of papers III and IV

	Apixaban (n=2,098)	Dabigatran (n=474)	Rivaroxaban (n=3,106)	Warfarin (n=1,403)	SMD* Before	After
Age	72.7 (13.2)	70.1 (13.6)	68.7 (13.0)	66.8 (16.8)	0.221	0.041
Sex (% male)	1119 (53.3)	270 (57.0)	1844 (59.4)	746 (53.2)	0.075	0.065
CHA_2DS_2-VASc score	2.8 (1.6)	2.6 (1.5)	2.3 (1.5)	2.5 (1.7)	0.175	0.055
Charlson comorbidity index	0.9 (1.4)	0.7 (1.1)	0.6 (1.1)	1.0 (1.5)	0.167	0.059
Ischemic heart disease	155 (7.4)	36 (7.6)	208 (6.7)	91 (6.5)	0.026	0.032
Congestive heart failure	173 (8.2)	38 (8.0)	173 (5.6)	114 (8.1)	0.054	0.020
Peripheral vascular disease	94 (4.5)	19 (4.0)	107 (3.4)	61 (4.3)	0.029	0.020
Cerebrovascular disease	266 (12.7)	35 (7.4)	164 (5.3)	114 (8.1)	0.136	0.031
Hemiplegia	22 (1.0)	4 (0.8)	13 (0.4)	13 (0.9)	0.039	0.082
Diabetes mellitus	99 (4.7)	22 (4.6)	97 (3.1)	58 (4.1)	0.045	0.028
Diabetes mellitus with end-organ damage	63 (3.0)	12 (2.5)	64 (2.1)	40 (2.9)	0.033	0.029
Chronic lung disease	124 (5.9)	24 (5.1)	120 (3.9)	95 (6.8)	0.071	0.023
Moderate/severe renal disease	73 (3.5)	10 (2.1)	69 (2.2)	74 (5.3)	0.097	0.049
Liver disease	17 (0.8)	1 (0.2)	17 (0.5)	11 (0.8)	0.047	0.038
Peptic ulcer disease	47 (2.2)	10 (2.1)	36 (1.2)	39 (2.8)	0.060	0.026
Connective tissue disease	48 (2.3)	8 (1.7)	58 (1.9)	38 (2.7)	0.040	0.052
Dementia	53 (2.5)	6 (1.3)	37 (1.2)	36 (2.6)	0.066	0.063
Any tumor	251 (12.0)	48 (10.1)	268 (8.6)	207 (14.8)	0.106	0.040
Metastatic solid tumor	11 (0.5)	1 (0.2)	23 (0.7)	18 (1.3)	0.069	0.071
Hypertension	1387 (66.1)	314 (66.2)	1836 (59.1)	704 (50.2)	0.189	0.063
Bleeding disease	14 (0.7)	1 (0.2)	14 (0.5)	9 (0.6)	0.039	0.053

Prior GIB	93 (4.4)	23 (4.9)	85 (2.7)	68 (4.8)	0.059	0.030
Prior VTE	263 (12.5)	45 (9.5)	664 (21.4)	919 (65.5)	0.729	0.250
Concomitant drug use						
Antihistamines	11 (0.5)	5 (1.1)	18 (0.6)	11 (0.8)	0.034	0.037
Antiplatelets	566 (27.0)	126 (26.6)	604 (19.4)	300 (21.4)	0.110	0.070
Corticosteroids	436 (20.8)	94 (19.8)	612 (19.7)	373 (26.6)	0.086	0.049
NSAIDs	463 (22.1)	97 (20.5)	790 (25.4)	345 (24.6)	0.069	0.073
PPIs	860 (41.0)	179 (37.8)	1150 (37.0)	601 (42.8)	0.070	0.066
SSRIs	395 (18.8)	56 (11.8)	446 (14.4)	271 (19.3)	0.124	0.095
Statins	940 (44.8)	210 (44.3)	1237 (39.8)	439 (31.3)	0.155	0.077
Treatment indication					0.716	0.230
AF	1787 (85.2)	420 (88.6)	2463 (79.3)	501 (35.7)		
VTE	236 (11.2)	41 (8.6)	605 (19.5)	875 (62.4)		
Ischemic stroke	75 (3.6)	13 (2.7)	38 (1.2)	27 (1.9)		
Area of residence					0.258	0.129
Capital Area	1471 (70.1)	295 (62.2)	1891 (60.9)	934 (66.6)		
Eastern	70 (3.3)	17 (3.6)	85 (2.7)	57 (4.1)		
Northern	139 (6.6)	52 (11.0)	476 (15.3)	134 (9.6)		
Southern	262 (12.5)	97 (20.5)	424 (13.7)	191 (13.6)		
Western	111 (5.3)	12 (2.5)	175 (5.6)	64 (4.6)		
Westfjords	45 (2.1)	1 (0.2)	55 (1.8)	23 (1.6)		

*Maximal standardized mean difference (SMD) before and after inverse probability weighing. SMD below 0.1 was considered ideal. Variables with SMD greater than 0.1 were adjusted for using Cox regression when comparing outcome rates.

GIB = Gastrointestinal bleeding, NSAID = Nonsteroidal anti-inflammatory drug, PPI = Proton pump inhibitor, SMD = Standardized mean difference, SSRI = Selective serotonin receptor inhibitor, VTE = Venous thromboembolism.

Table 17: Comparison of the causes of upper and lower gastrointestinal bleeding for warfarin and DOACs

	Warfarin n (%)	DOACs n (%)	OR [95% CI]
Upper GIB			
Peptic ulcer	6 (17.6)	28 (39.4)	0.33 [0.10-0.96]
Mucosal erosion	10 (29.4)	18 (25.4)	1.22 [0.44-3.31]
Angiodysplasia	7 (20.6)	16 (22.5)	0.89 [0.28-2.64]
Esophageal ulcer	1 (2.9)	3 (4.2)	0.69 (0.01-8.96)
Esophageal varices	2 (5.9)	0	∞ (0.40-∞)
Esophagitis	2 (5.9)	0	∞ (0.40-∞)
Mallory-Weiss tear	2 (5.9)	0	∞ (0.40-∞)
Other*	1 (2.9)	1 (1.4)	2.10 [0.03-168.61]
Unexplained	3 (8.8)	5 (7.0)	1.27 [0.19-7.04]
Lower GIB			
Diverticulosis	5 (23.8)	29 (22.5)	1.08 [0.28-3.43]
Hemorrhoid	0 (0)	19 (14.7)	0 [0-1.24]
Colorectal cancer	4 (19.0)	18 (14.0)	1.45 [0.32-5.18]
Polyp	0 (0)	12 (9.3)	0 [0-2.20]
Angiodysplasia	1 (4.8)	15 (11.6)	0.38 [0.01-2.77]
Colitis	2 (9.5)	3 (2.3)	4.35 [0.34-40.70]
Rectal ulcer	1 (4.8)	7 (5.4)	0.87 [0.02-7.41]
Bowel ulcer	2 (9.5)	3 (2.3)	4.35 [0.34-40.70]
Postop bleeding	0 (0)	3 (2.3)	0 [0-15.23]
Ischemic colitis	0 (0.0)	2 (1.6)	0 (0-33.23)
Other**	1 (4.8)	1 (0.8)	6.27 [0.08-503.88]
Unexplained	5 (23.8)	17 (13.2)	2.05 [0.52-6.91]

*Other upper GIB causes included: Polyp (2 cases), post-papillotomy bleeding, and Mallory-Weiss tear.

CI = Confidence interval, GIB = Gastrointestinal bleeding, OR = Odds ratio.

Table 18: Baseline characteristics for the sensitivity analysis of papers III and IV

	Apixaban (n=1,787)	Dabigatran (n=420)	Rivaroxaban (n=2,463)	Warfarin (n=501)	SMD* Before	After
Age	73.8 (12.0)	71.3 (12.0)	70.7 (11.4)	75.9 (10.4)	0.269	0.078
Sex (% male)	976 (54.6)	245 (58.3)	1526 (62.0)	301 (60.1)	0.081	0.076
CHA_2DS_2-VASc score	2.8 (1.6)	2.6 (1.5)	2.4 (1.5)	3.2 (1.6)	0.287	0.073
Charlson comorbidity index	0.9 (1.4)	0.7 (1.1)	0.6 (1.1)	1.3 (1.6)	0.275	0.067
Ischemic heart disease	142 (7.9)	34 (8.1)	187 (7.6)	58 (11.6)	0.069	0.032
Congestive heart failure	158 (8.8)	34 (8.1)	156 (6.3)	77 (15.4)	0.152	0.034
Peripheral vascular disease	81 (4.5)	16 (3.8)	91 (3.7)	36 (7.2)	0.083	0.044
Cerebrovascular disease	207 (11.6)	25 (6.0)	125 (5.1)	68 (13.6)	0.182	0.067
Hemiplegia	15 (0.8)	2 (0.5)	8 (0.3)	4 (0.8)	0.041	0.076
Diabetes mellitus	84 (4.7)	22 (5.2)	84 (3.4)	29 (5.8)	0.061	0.058
Diabetes mellitus with end-organ damage	50 (2.8)	12 (2.9)	57 (2.3)	24 (4.8)	0.068	0.021
Chronic lung disease	105 (5.9)	20 (4.8)	90 (3.7)	34 (6.8)	0.079	0.015
Moderate/severe renal disease	61 (3.4)	9 (2.1)	59 (2.4)	45 (9.0)	0.163	0.059
Liver disease	17 (1.0)	0 (0.0)	13 (0.5)	3 (0.6)	0.075	0.096
Peptic ulcer disease	42 (2.4)	9 (2.1)	27 (1.1)	22 (4.4)	0.106	0.021
Connective tissue disease	35 (2.0)	8 (1.9)	45 (1.8)	14 (2.8)	0.033	0.034
Dementia	45 (2.5)	6 (1.4)	25 (1.0)	15 (3.0)	0.085	0.063
Any tumor	207 (11.6)	38 (9.0)	191 (7.8)	73 (14.6)	0.123	0.047
Metastatic solid	8 (0.4)	1 (0.2)	12 (0.5)	4 (0.8)	0.041	0.046

tumor						
Hypertension	1245 (69.7)	298 (71.0)	1613 (65.5)	367 (73.3)	0.089	0.109
Bleeding disease	13 (0.7)	1 (0.2)	10 (0.4)	2 (0.4)	0.036	0.068
Prior GIB	80 (4.5)	19 (4.5)	68 (2.8)	36 (7.2)	0.104	0.011
Prior VTE	27 (1.5)	4 (1.0)	59 (2.4)	44 (8.8)	0.202	0.096
Concomitant drug use						
Antihistamines	9 (0.5)	5 (1.2)	16 (0.6)	8 (1.6)	0.064	0.036
Antiplatelets	488 (27.3)	114 (27.1)	532 (21.6)	194 (38.7)	0.19	0.046
Corticosteroids	356 (19.9)	82 (19.5)	455 (18.5)	128 (25.5)	0.087	0.008
NSAIDs	384 (21.5)	87 (20.7)	586 (23.8)	82 (16.4)	0.096	0.083
PPIs	735 (41.1)	158 (37.6)	882 (35.8)	242 (48.3)	0.139	0.076
SSRIs	313 (17.5)	46 (11.0)	322 (13.1)	89 (17.8)	0.118	0.092
Statins	829 (46.4)	198 (47.1)	1088 (44.2)	237 (47.3)	0.034	0.083
Area of residence					0.287	0.108
Capital Area	1269 (71.0)	258 (61.4)	1529 (62.1)	306 (61.1)		
Eastern	58 (3.2)	15 (3.6)	58 (2.4)	31 (6.2)		
Northern	120 (6.7)	46 (11.0)	361 (14.7)	48 (9.6)		
Southern	220 (12.3)	90 (21.4)	335 (13.6)	80 (16.0)		
Western	87 (4.9)	10 (2.4)	135 (5.5)	28 (5.6)		
Westfjords	33 (1.8)	1 (0.2)	45 (1.8)	8 (1.6)		

4.4 Paper IV – Comparison of epistaxis rates between oral anticoagulants

This paper was based on the same population as paper III (Figure 6 and Table 16).

4.4.1 Characteristics of epistaxis events

Overall, 93 patients presented with clinically relevant epistaxis during the study period. Of those, 11 (12%) events fulfilled the criteria of major bleeding, including 1 fatal event. Interestingly, of the 77 patients who continued their anticoagulation treatment after a nonmajor epistaxis event, 7 patients (9%) later presented with major bleeding during the follow-up period. Of those, 3 bleeding events originated in the gastrointestinal tract while 4 events were intracranial hemorrhages.

Patients receiving warfarin were more likely to have a CBC drawn compared to apixaban (79% vs. 39%, odds ratio [OR] 5.51, 95% CI 1.31-26.20) and rivaroxaban (79% vs. 51%, OR 3.46, 95% CI 1.10-12.38). Otherwise, no difference was noted in the presentation, treatment, and outcomes of epistaxis events between individual drugs (Table 19).

4.4.2 Epistaxis event rates

Warfarin was associated with higher rates of epistaxis compared to apixaban (2.2 events/100-py vs. 0.6 events/100-py, HR 4.22, 95% CI 2.08-8.59), rivaroxaban (2.2 events/100-py vs. 1.0 events/100-py, HR 2.26, 95% CI 1.28-4.01), and dabigatran (2.2 events/100-py vs. no events, HR n/a, $p<0.001$) (Figure 11A). Additionally, rivaroxaban was associated with higher epistaxis rates compared to apixaban (1.0 events/100-py vs. 0.6 events/100-py, HR 1.87, 95% CI 1.05-3.30) and dabigatran (1.0 events/100-py vs. no events, HR n/a, $p=0.006$) (Table 20).

Apixaban trended towards lower major epistaxis event rates compared to both warfarin (0.02 events/100-py vs. 0.16 events/100-py, HR 0.11, 95% CI 0.01-1.11 and rivaroxaban (0.02 events/100-py vs. 0.12 events/100-py, HR 0.15, 95% CI 0.02-1.22), although the results included the possibility of null effect in both instances.

A sensitivity analysis including patients with AF only demonstrated similar results (Figure 11B and Table 20). Furthermore, epistaxis rates were similar for standard and reduced dose DOACs (Table 21).

Additionally, epistaxis rates were similar between patients monitored using the novel Fiix-test and the conventional INR measurements (1.5 events/100-py vs. 1.6 events/100-py, HR 0.89, 95% CI 0.28-2.81).

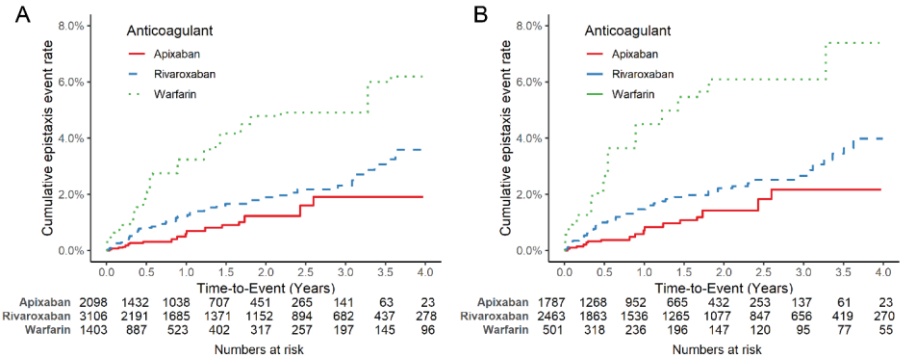

Figure 11: Propensity score-weighted Kaplan-Meier graphs comparing epistaxis event rates between oral anticoagulants for A) all patients and B) patients with AF.

Table 19: Epistaxis characteristics

	All patients	Warfarin	Apixaban	Rivaroxaban	P-value
Total epistaxis events	93	28	18	47	
Major epistaxis	11 (12)	4 (14)	1 (6)	6 (13)	
Sent from a referring physician	15 (16)	5 (18)	3 (17)	7 (15)	0.93
Location					0.22
Anterior	74 (80)	21 (75)	17 (94)	36 (77)	
Posterior	19 (20)	7 (25)	1 (6)	11 (23)	
Work-up					
CBC	53 (57)	22 (79)	7 (39)	24 (51)	0.01
Hb drop (g/dL)	0.9 (0.0-1.7)	0.7 (0.0-1.8)	1.2 (0.5-1.6)	0.6 (0.0-1.6)	0.88
INR[a]		2.5 (2.1-3.4)			
INR>3		9 (32)			
Nasal endoscopy	5 (5)	2 (7)	1 (6)	2 (4)	0.84
ENT consulted	43 (46)	15 (52)	9 (50)	18 (38)	0.30
Treatment[b]					
Cauterization	56 (60)	15 (54)	11 (61)	30 (64)	0.72
Nasal packing	37 (40)	13 (46)	5 (28)	19 (40)	0.60
Surgery[c]	1 (1)	1 (4)	0	0	0.49
Conservative	17 (18)	7 (25)	3 (17)	7 (15)	0.59
Transfusion	3 (3)	2 (7)	0	1 (2)	0.43
Hospitalization	10 (11)	5 (18)	0	5 (11)	0.16
Length of stay	2 (1-3)	3 (1-6)		2 (2-2)	0.59
Treatment discontinuation	7 (8)	4 (14)	1 (6)	2 (4)	0.33
Recurrence of epistaxis	12 (13)	3 (11)	3 (17)	6 (13)	0.84

Data is presented as n (%) or median (quartiles). Abbreviations: CBC = Complete blood count, ENT = Ear-nose-throat physician, Hb = Hemoglobin, INR = International normalized ratio.

[a]All warfarin patients had an INR measurement, except one. [b]The sum does not equal 100% as some patients received more than one type of treatment. [c]No patient underwent embolization.

Table 20: Comparison of epistaxis rates between warfarin and direct oral anticoagulants

Oral anti-coagulant[a]	Epistaxis events per 100 py	HR (95% CI) compared to warfarin	HR (95% CI) compared to apixaban	HR (95% CI) compared to rivaroxaban
Any clinically relevant epistaxis				
Whole cohort				
Warfarin	2.2	-	4.22 (2.08-8.59)	2.26 (1.28-4.01)
Apixaban	0.6	0.24 (0.12-0.48)	-	0.54 (0.30-0.95)
Rivaroxaban	1.0	0.44 (0.25-0.78)	1.87 (1.05-3.30)	-
Patients with AF only				
Warfarin	2.7	-	4.48 (2.06-9.76)	2.39 (1.26-4.54)
Apixaban	0.7	0.22 (0.10-0.49)	-	0.53 (0.30-0.95)
Rivaroxaban	1.1	0.41 (0.22-0.80)	1.87 (1.05-3.34)	-
Major epistaxis				
Whole cohort				
Warfarin	0.16	-	8.31 (0.84-82.17)	1.30 (0.32-5.34)
Apixaban	0.02	0.12 (0.01-1.19)	-	0.16 (0.02-1.28)
Rivaroxaban	0.12	0.77 (0.19-3.14)	6.37 (0.78-52.12)	-
Patients with AF only				
Warfarin	0.15	-	6.82 (0.53-87.99)	1.03 (0.18-5.80)
Apixaban	0.02	0.15 (0.01-1.89)	-	0.15 (0.02-1.23)
Rivaroxaban	0.14	0.97 (0.17-5.49)	6.63 (0.81-54.01)	-

Abbreviations: CI = confidence interval, HR = hazard ratio, py = person-years.

[a]Dabigatran is not included as it had no epistaxis events during the period. However, log-rank test demonstrated significantly higher epistaxis rates for warfarin compared to dabigatran for all patients ($p>0.001$) and patients with atrial fibrillation only ($p>0.001$), while major epistaxis rates were not statistically different between the drugs.

Table 21: Comparison of epistaxis rates between warfarin and standard dose or reduced dose direct oral anticoagulants

Oral anti-coagulant[a]	Epistaxis events per 100 py	HR (95% CI) compared to warfarin	HR (95% CI) compared to apixaban	HR (95% CI) compared to rivaroxaban
Standard dose DOACs				
Whole cohort				
Warfarin	2.3	-	4.38 (1.94-9.87)	2.42 (1.27-4.61)
Apixaban	0.6	0.23 (0.10-0.51)	-	0.55 (0.28-1.07)
Rivaroxaban	0.9	0.41 (0.22-0.79)	1.81 (0.93-3.52)	-
Patients with AF only				
Warfarin	2.6	-	4.56 (1.86-11.20)	2.28 (1.10-4.74)
Apixaban	0.7	0.22 (0.09-0.54)	-	0.50 (0.25-0.92)
Rivaroxaban	1.1	0.44 (0.21-0.91)	2.00 (1.01-3.96)	-
Reduced dose DOACs				
Whole cohort				
Warfarin	1.8	-	3.25 (1.13-9.34)	1.77 (0.83-3.75)
Apixaban	0.6	0.31 (0.11-0.88)	-	0.54 (0.18-1.67)
Rivaroxaban	1.0	0.57 (0.27-1.20)	1.84 (0.60-5.65)	-
Patients with AF only				
Warfarin	2.2	-	4.10 (1.34-12.54)	1.85 (0.79-4.29)
Apixaban	0.6	0.24 (0.08-0.75)	-	0.45 (0.15-1.36)
Rivaroxaban	1.1	0.54 (0.23-1.26)	2.22 (0.73-6.70)	-

Abbreviations: CI = confidence interval, HR = hazard ratio, py = person-years.

[a]Dabigatran is not included as it had no epistaxis events during the period. However, log-rank test demonstrated higher epistaxis rates for warfarin compared to standard dose dabigatran for all patients (p=0.006) and patients with atrial fibrillation only (p=0.005). Similarly, warfarin was associated with higher epistaxis rates than reduced dose dabigatran for all patients (p=0.05) and patients with atrial fibrillation only (p=0.01).

4.5 Paper V – Comparison of medication nonadherence between oral anticoagulants

This analysis was limited to patients receiving apixaban, dabigatran, rivaroxaban, and warfarin; living in the capital area; and having AF, VTE, or cryptogenic stroke. Overall, this analysis included 3,847 patients, including 1,266 patients receiving apixaban, 247 receiving dabigatran, 1,566 receiving rivaroxaban, and 768 receiving warfarin. The flowchart for selection of the study cohort is provided in Figure 12. The average follow-up period was 1.4 years for patients receiving apixaban, 2.1 years for dabigatran, 2.0 years for rivaroxaban, and 1.3 years for warfarin. Baseline characteristics of the study population are provided in Table 22.

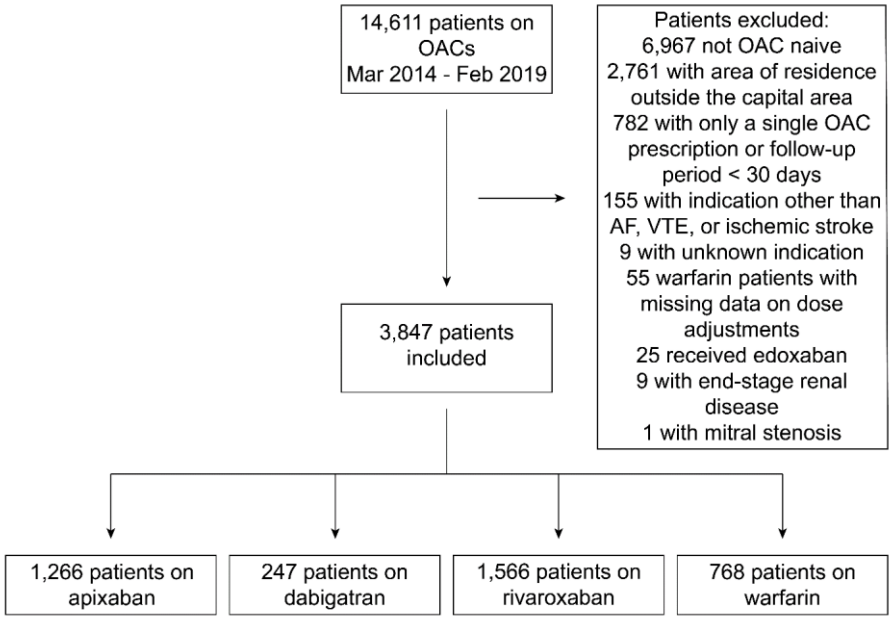

Figure 12: Flowchart for selection of the study cohort for paper V.

4.5.1 Medication nonadherence

The medication adherence of the total cohort was very good overall, with the majority of patients with perfect adherence (i.e., PDC of 100%) (Figure 13). The median PDC was 100% for patients receiving apixaban (Interquartile range [IQR] 94.3%-100%), 99.7% for patients receiving dabigatran (IQR 90.8%-100%), 100% for patients receiving rivaroxaban (IQR 95.2%-100%), and 97.0% for patients receiving warfarin (IQR 85.4%-100%) (Figure 14).

The crude nonadherence was 16.7% for warfarin users (95% CI 14.0%-19.3%), 16.2% for dabigatran users (95% CI 11.6%-20.8%), 12.4% for rivaroxaban users (95% CI 10.8%-14.0%), and 10.5% for apixaban users (95% CI 8.8%-12.2%) (Figure 15A). After accounting for baseline covariates using propensity score-weighting, dabigatran was associated with significantly higher odds of nonadherence compared to apixaban (15.5% vs. 11.9%, OR 1.57, 95% CI 1.21-2.04, p<0.001), rivaroxaban (15.5% vs. 11.3%, OR 1.45, 95% CI 1.12-1.89, p=0.005), and warfarin (15.5% vs. 11.1%, OR 1.63, 95% CI 1.23-2.15, p<0.001). Meanwhile, nonadherence was similar between apixaban, rivaroxaban, and warfarin users (Figure 15B).

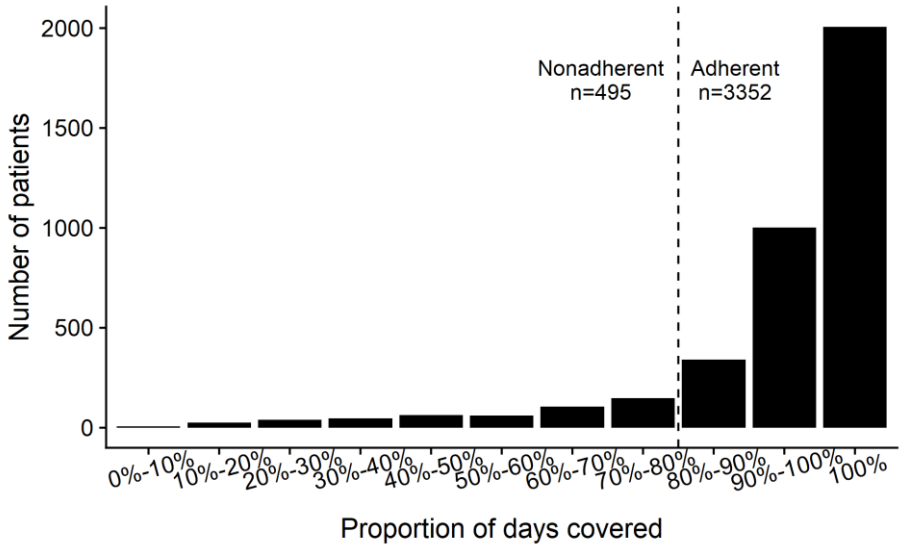

Figure 13: Bar graph demonstrating the distribution of medication adherence for the study population, using proportion of days covered.

4.5.2 Patient factors associated with nonadherence

Nonadherent patients were younger, more commonly male, and had lower CHA_2DS_2-VASc score compared to adherent patients (Table 23). Additionally, nonadherent patients were less likely to have hypertension, history of cerebrovascular accident, or to have received concomitant statin treatment.

After multivariable logistic model adjustment, dabigatran usage and male gender were both associated with higher odds of nonadherence (Table 24). Meanwhile, hypertension, history of cerebrovascular accident, and concomitant use of statins were all independently associated with lower odds of nonadherence.

4.5.3 Comparison of treatment outcomes between adherent and nonadherent patients

Rates of thromboembolism (1.9 events/100-py vs. 2.1 events/100-py, HR 0.86, 95% CI 0.31-2.37) and major bleeding (2.8 events per 100 person-years (events/100-py) vs. 2.3 events/100-py, hazard ratio [HR] 0.97, 95% CI 0.55-1.73) were similar between adherent and nonadherent patients.

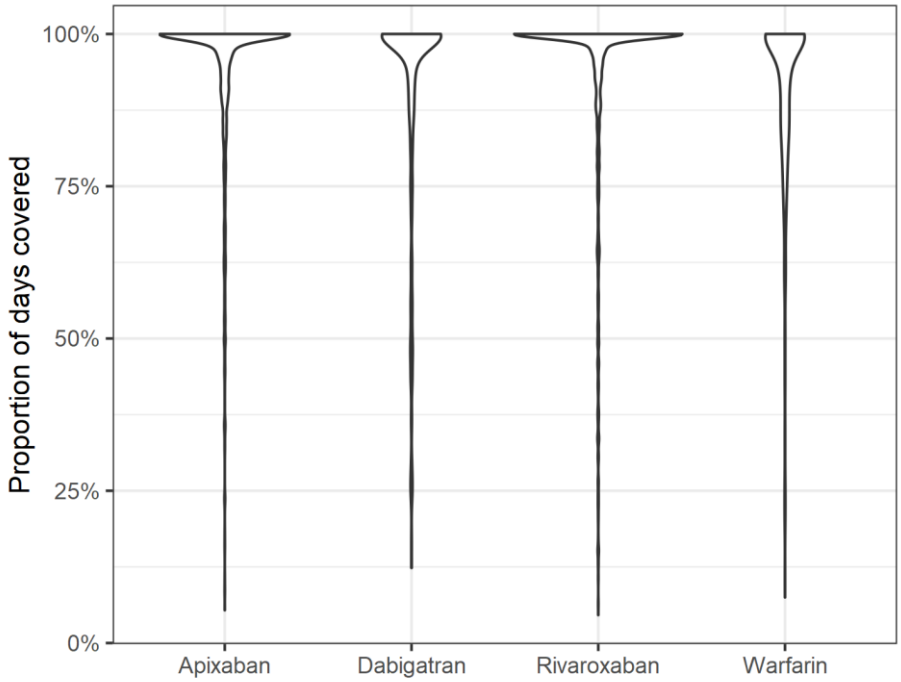

Figure 14: A violin plot comparing the distribution of medication adherence between patients receiving different oral anticoagulants.

4.5.4 Sensitivity analysis

A sensitivity analysis including patients with AF only was performed, which included 1,104 patients receiving apixaban, 223 receiving dabigatran, 1,307 receiving rivaroxaban, and 229 receiving warfarin. The average follow-up period was 1.5 years for apixaban, 2.2 years for dabigatran, 2.2 years for rivaroxaban, and 1.6 years for warfarin. Comparison of baseline characteristics is provided in Table 25.

Before accounting for propensity scores, 9.9% of apixaban users were nonadherent compared to 13.4%, 13.5%, and 16.6% of rivaroxaban, warfarin, and dabigatran users respectively (Fig 16A). After propensity score-

weighting, dabigatran was associated with higher odds of nonadherence compared to apixaban (16.2% vs. 10.5%, OR 2.05, 95% CI 1.51-2.81, p<0.001), rivaroxaban (16.2% vs. 12.5%, OR 1.34, 95% CI 1.00-1.80, p=0.05), and warfarin (16.2% vs. 7.6%, OR 2.75, 95% CI 1.63-3.37, p<0.001). Additionally, rivaroxaban was associated with higher odds of nonadherence compared to apixaban (OR 1.53, 95% CI 1.11-2.12, p=0.009) and warfarin (OR 2.05, 95% CI 1.41-2.01, p<0.001) (Fig 16B).

Another sensitivity analysis including patients receiving DOACs and living anywhere in the country was performed to account for potential differences due to area of residence (Table 26). As in the primary analysis, dabigatran was associated with higher odds of nonadherence compared to apixaban (16.3% vs. 11.5%, OR 1.81, 95% CI 1.47-2.23, p<0.001) and rivaroxaban (16.3% vs. 11.6%, OR 1.53, 95% CI 1.25-1.88, p<0.001), while no differences were noted between apixaban and rivaroxaban. Importantly, the odds of nonadherence were similar between patients who lived in the capital area and those who did not (OR 1.05, 95% CI 0.87-1.27).

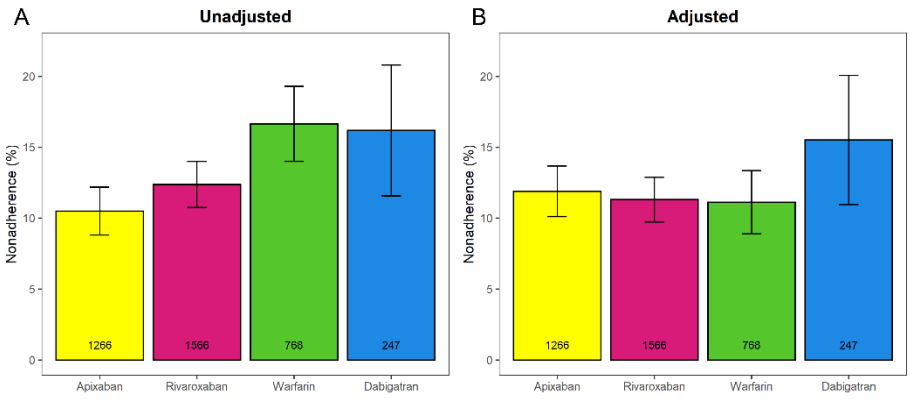

Figure 15: Bar graphs comparing the rates of nonadherence between patients receiving different oral anticoagulants in an A) unadjusted cohort and B) propensity score-weighted cohort.

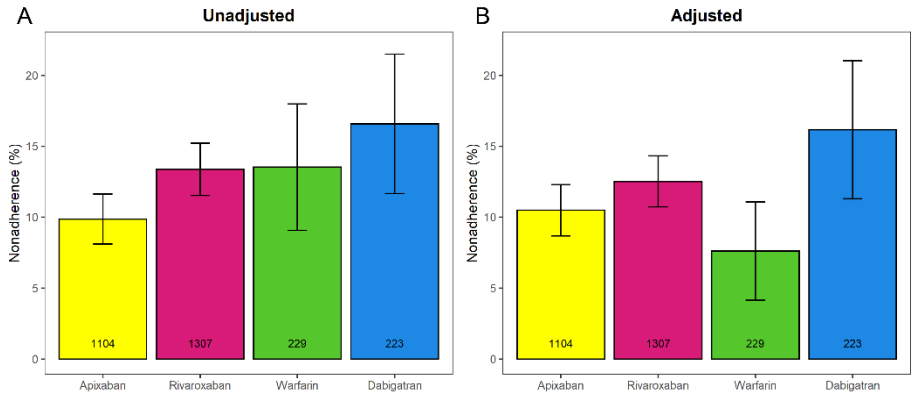

Figure 16: Bar graphs comparing the rates of nonadherence between patients receiving different oral anticoagulants in an A) unadjusted cohort and B) propensity score-weighted cohort.

Table 22: Baseline characteristics of the study population

Variables	Apixaban n=1266	Dabigatran n=247	Rivaroxaban n=1566	Warfarin n=768	SMD Before IPW	SMD After IPW
Age	73.6 (12.8)	71.2 (13.1)	69.4 (12.5)	65.3 (16.7)	0.313	0.060
Sex (male)	668 (52.8)	126 (51.0)	938 (59.9)	390 (50.8)	0.098	0.136
CHA_2DS_2-VASC score	3.0 (1.7)	2.7 (1.5)	2.4 (1.5)	2.4 (1.7)	0.200	0.050
Charlson comorbidity index	1.0 (1.4)	0.7 (1.2)	0.7 (1.2)	1.0 (1.4)	0.143	0.067
Ischemic heart disease	95 (7.5)	14 (5.7)	103 (6.6)	43 (5.6)	0.045	0.034
Heart failure	125 (9.9)	18 (7.3)	110 (7.0)	62 (8.1)	0.056	0.048
Peripheral vascular disease	62 (4.9)	8 (3.2)	58 (3.7)	33 (4.3)	0.047	0.059
Cerebrovascular disease	190 (15.0)	26 (10.5)	104 (6.6)	61 (7.9)	0.151	0.040
Dementia	40 (3.2)	4 (1.6)	26 (1.7)	14 (1.8)	0.053	0.082
Chronic lung disease	85 (6.7)	14 (5.7)	75 (4.8)	61 (7.9)	0.072	0.028
Connective tissue disease	39 (3.1)	4 (1.6)	37 (2.4)	20 (2.6)	0.051	0.062
Peptic ulcer disease	36 (2.8)	7 (2.8)	24 (1.5)	21 (2.7)	0.046	0.069
Diabetes mellitus	70 (5.5)	6 (2.4)	60 (3.8)	33 (4.3)	0.084	0.134
Diabetes mellitus with end-organ damage	43 (3.4)	5 (2.0)	40 (2.6)	23 (3.0)	0.047	0.064
Hemiplegia	15 (1.2)	1 (0.4)	8 (0.5)	11 (1.4)	0.067	0.048
Moderate/severe renal disease	49 (3.9)	8 (3.2)	46 (2.9)	46 (6.0)	0.080	0.011
Any tumor	166 (13.1)	28 (11.3)	160 (10.2)	120 (15.6)	0.090	0.033
Metastatic	7 (0.6)	1 (0.4)	15 (1.0)	6 (0.8)	0.039	0.061

cancer						
Hypertension	861 (68.0)	174 (70.4)	972 (62.1)	359 (46.7)	0.267	0.059
Bleeding or coagulation disorder	10 (0.8)	1 (0.4)	9 (0.6)	8 (1.0)	0.042	0.042
Liver disease	12 (0.9)	1 (0.4)	14 (0.9)	7 (0.9)	0.034	0.028
History of gastro-intestinal bleeding	74 (5.8)	14 (5.7)	58 (3.7)	36 (4.7)	0.058	0.063
History of VTE	135 (10.7)	23 (9.3)	284 (18.1)	553 (72.0)	0.843	0.288
Concomitant drug use						
Antihistamine	7 (0.6)	1 (0.4)	6 (0.4)	6 (0.8)	0.030	0.023
Antiplatelet	343 (27.1)	65 (26.3)	322 (20.6)	143 (18.6)	0.124	0.098
NSAID	246 (19.4)	53 (21.5)	353 (22.5)	179 (23.3)	0.052	0.081
PPI	528 (41.7)	89 (36.0)	569 (36.3)	316 (41.1)	0.075	0.083
SSRI	257 (20.3)	28 (11.3)	226 (14.4)	157 (20.4)	0.151	0.147
Statin	588 (46.4)	109 (44.1)	678 (43.3)	219 (28.5)	0.191	0.094
Steroid	252 (19.9)	45 (18.2)	297 (19.0)	187 (24.3)	0.079	0.057
Treatment indication					0.845	0.258
AF	1104 (87.2)	223 (90.3)	1307 (83.5)	229 (29.8)		
Ischemic stroke	47 (3.7)	2 (0.8)	13 (0.8)	16 (2.1)		
VTE	115 (9.1)	22 (8.9)	246 (15.7)	523 (68.1)		

AF = atrial fibrillation, IPW = Inverse probability weighting, NSAID = Nonsteroidal anti-inflammatory drug, PPI = Proton pump inhibitor, SMD = Standardized mean difference, SSRI = Selective serotonin receptor inhibitor, VTE = Venous thromboembolism.

Table 23: Univariate analysis comparing factors associated with nonadherence

	Adherent n= 3352	Nonadherent n=495	P-value
Age	70.6 (13.7)	66.5 (14.8)	<0.001
Sex (male)	1811 (54.0)	311 (62.8)	<0.001
CHA_2DS_2-VASC score	2.7 (1.6)	2.1 (1.6)	<0.001
Charlson comorbidity index	0.9 (1.4)	0.8 (1.2)	0.09
Ischemic heart disease	224 (6.7)	31 (6.3)	0.80
Heart failure	282 (8.4)	33 (6.7)	0.22
Peripheral vascular disease	144 (4.3)	17 (3.4)	0.44
Cerebrovascular disease	357 (10.7)	24 (4.8)	<0.001
Dementia	77 (2.3)	7 (1.4)	0.28
Chronic lung disease	203 (6.1)	32 (6.5)	0.80
Connective tissue disease	90 (2.7)	10 (2.0)	0.47
Peptic ulcer disease	75 (2.2)	13 (2.6)	0.71
Diabetes mellitus	155 (4.6)	14 (2.8)	0.09
Diabetes mellitus with end-organ damage	102 (3.0)	9 (1.8)	0.17
Hemiplegia	31 (0.9)	4 (0.8)	1.00
Moderate/severe renal disease	129 (3.8)	20 (4.0)	0.94
Any tumor	411 (12.3)	63 (12.7)	0.83
Metastatic cancer	25 (0.7)	4 (0.8)	1.00
Hypertension	2113 (63.0)	253 (51.1)	<0.001
Bleeding or coagulation disorder	21 (0.6)	7 (1.4)	0.10
Liver disease	27 (0.8)	7 (1.4)	0.27
History of gastrointestinal bleeding	160 (4.8)	22 (4.4)	0.84
History of VTE	847 (25.3)	148 (29.9)	0.03
Concomitant drug use			
Antihistamine	16 (0.5)	4 (0.8)	0.54
Antiplatelet	786 (23.4)	87 (17.6)	0.004
NSAID	715 (21.3)	116 (23.4)	0.32
PPI	1319 (39.3)	183 (37.0)	0.34
SSRI	597 (17.8)	71 (14.3)	0.07
Statin	1431 (42.7)	163 (32.9)	<0.001
Steroid	684 (20.4)	97 (19.6)	0.72
Treatment indication			0.14
AF	2511 (74.9)	352 (71.1)	
Cryptogenic stroke	69 (2.1)	9 (1.8)	
VTE	772 (23.0)	134 (27.1)	

P < 0.001 was considered significant.

AF = atrial fibrillation, NSAID = Nonsteroidal anti-inflammatory drug, PPI = Proton pump inhibitor, SMD = Standardized mean difference, SSRI = Selective serotonin receptor inhibitor, VTE = Venous thromboembolism.

Table 24: Logistic regression estimating factors associated with nonadherence

Variable	Odds ratio	95% confidence intervals	P-value
Oral anticoagulant			
Not Dabigatran	1 (Ref)	N/A	N/A
Dabigatran	1.44	1.00-2.04	0.046
Age	0.99	0.98-1.00	0.07
Sex (male)	1.34	1.05-1.72	0.02
CHA_2DS_2-VASc score	0.95	0.84-1.08	0.43
Cerebrovascular disease	0.56	0.33-0.90	0.02
Hypertension	0.76	0.60-0.97	0.03
Statin usage	0.77	0.62-0.95	0.02

Table 25: Baseline characteristics of the sensitivity analysis of patients with atrial fibrillation

Variables	Apixaban n=1104	Dabigatran n=223	Rivaroxaban n=1307	Warfarin n=229	SMD Before IPW	SMD After IPW
Age	74.3 (11.8)	71.8 (11.8)	70.9 (11.1)	75.6 (10.1)	0.253	0.056
Sex (male)	589 (53.4)	116 (52.0)	813 (62.2)	132 (57.6)	0.118	0.145
CHA_2DS_2-VASC score	2.9 (1.6)	2.7 (1.5)	2.5 (1.5)	3.3 (1.7)	0.278	0.064
Charlson comorbidity index	1.0 (1.4)	0.7 (1.2)	0.7 (1.2)	1.4 (1.7)	0.291	0.092
Ischemic heart disease	88 (8.0)	12 (5.4)	96 (7.3)	27 (11.8)	0.120	0.069
Heart failure	113 (10.2)	15 (6.7)	99 (7.6)	39 (17.0)	0.178	0.090
Peripheral vascular disease	54 (4.9)	8 (3.6)	52 (4.0)	19 (8.3)	0.108	0.049
Cerebrovascular disease	150 (13.6)	21 (9.4)	86 (6.6)	31 (13.5)	0.139	0.044
Dementia	34 (3.1)	4 (1.8)	16 (1.2)	4 (1.7)	0.065	0.106
Chronic lung disease	74 (6.7)	12 (5.4)	60 (4.6)	21 (9.2)	0.100	0.046
Connective tissue disease	29 (2.6)	4 (1.8)	31 (2.4)	6 (2.6)	0.031	0.040
Peptic ulcer disease	32 (2.9)	6 (2.7)	19 (1.5)	13 (5.7)	0.119	0.049
Diabetes mellitus	58 (5.3)	6 (2.7)	55 (4.2)	14 (6.1)	0.092	0.093
Diabetes mellitus with end-organ damage	33 (3.0)	5 (2.2)	37 (2.8)	13 (5.7)	0.091	0.028
Hemiplegia	11 (1.0)	0 (0.0)	6 (0.5)	3 (1.3)	0.097	0.106
Moderate/severe renal disease	42 (3.8)	7 (3.1)	38 (2.9)	30 (13.1)	0.199	0.032
Any tumor	141 (12.8)	25 (11.2)	120 (9.2)	36 (15.7)	0.108	0.045
Metastatic	6 (0.5)	1 (0.4)	8 (0.6)	0 (0.0)	0.059	0.090

cancer						
Hypertension	776 (70.3)	166 (74.4)	881 (67.4)	165 (72.1)	0.084	0.126
Bleeding or coagulation disorder	10 (0.9)	1 (0.4)	8 (0.6)	2 (0.9)	0.033	0.064
Liver disease	12 (1.1)	0 (0.0)	11 (0.8)	2 (0.9)	0.077	0.169
History of gastro-intestinal bleeding	63 (5.7)	10 (4.5)	47 (3.6)	21 (9.2)	0.125	0.022
History of VTE	20 (1.8)	1 (0.4)	38 (2.9)	30 (13.1)	0.289	0.126
Concomitant drug use						
Antihistamine	5 (0.5)	1 (0.4)	6 (0.5)	3 (1.3)	0.046	0.025
Antiplatelet	302 (27.4)	58 (26.0)	293 (22.4)	88 (38.4)	0.181	0.041
NSAID	208 (18.8)	48 (21.5)	287 (22.0)	28 (12.2)	0.142	0.135
PPI	458 (41.5)	81 (36.3)	453 (34.7)	109 (47.6)	0.150	0.055
SSRI	202 (18.3)	23 (10.3)	170 (13.0)	47 (20.5)	0.167	0.136
Statin	528 (47.8)	105 (47.1)	621 (47.5)	102 (44.5)	0.034	0.101
Steroid	215 (19.5)	39 (17.5)	230 (17.6)	47 (20.5)	0.047	0.109

AF = atrial fibrillation, NSAID = Nonsteroidal anti-inflammatory drug, PPI = Proton pump inhibitor, SMD = Standardized mean difference, SSRI = Selective serotonin receptor inhibitor, VTE = Venous thromboembolism.

Table 26: Baseline characteristics of the sensitivity analysis of patients receiving direct oral anticoagulants and living in all regions of Iceland

Variables	Apixaban n=1805	Dabigatran n=386	Rivaroxaban n=2608	SMD Before IPW	SMD After IPW
Age	73.4 (12.6)	71.3 (12.9)	69.4 (12.6)	0.210	0.035
Sex (male)	956 (53.0)	212 (54.9)	1534 (58.8)	0.079	0.053
CHA_2DS_2-VASC score	2.9 (1.6)	2.7 (1.4)	2.4 (1.5)	0.247	0.048
Charlson comorbidity index	0.9 (1.4)	0.7 (1.1)	0.6 (1.1)	0.167	0.025
Ischemic heart disease	130 (7.2)	33 (8.5)	167 (6.4)	0.054	0.023
Heart failure	152 (8.4)	33 (8.5)	149 (5.7)	0.074	0.012
Peripheral vascular disease	84 (4.7)	13 (3.4)	88 (3.4)	0.044	0.028
Cerebrovascular disease	249 (13.8)	32 (8.3)	144 (5.5)	0.190	0.038
Dementia	47 (2.6)	5 (1.3)	30 (1.2)	0.072	0.058
Chronic lung disease	102 (5.7)	19 (4.9)	98 (3.8)	0.060	0.019
Connective tissue disease	43 (2.4)	6 (1.6)	48 (1.8)	0.040	0.036
Peptic ulcer disease	40 (2.2)	10 (2.6)	31 (1.2)	0.069	0.020
Diabetes mellitus	91 (5.0)	18 (4.7)	82 (3.1)	0.064	0.018
Diabetes mellitus with end-organ damage	56 (3.1)	9 (2.3)	53 (2.0)	0.045	0.027
Hemiplegia	20 (1.1)	3 (0.8)	11 (0.4)	0.053	0.089
Moderate/severe renal disease	61 (3.4)	8 (2.1)	58 (2.2)	0.054	0.037
Any tumor	214 (11.9)	39 (10.1)	230 (8.8)	0.067	0.030
Metastatic cancer	9 (0.5)	1 (0.3)	21 (0.8)	0.051	0.062
Hypertension	1241 (68.8)	272 (70.5)	1595 (61.2)	0.131	0.049
Bleeding or coagulation disorder	11 (0.6)	1 (0.3)	12 (0.5)	0.036	0.041

Liver disease	14 (0.8)	1 (0.3)	14 (0.5)	0.049	0.014
History of gastro-intestinal bleeding	81 (4.5)	19 (4.9)	74 (2.8)	0.072	0.029
History of VTE	201 (11.1)	29 (7.5)	507 (19.4)	0.237	0.151
Concomitant drug use					
Antihistamine	10 (0.6)	3 (0.8)	15 (0.6)	0.018	0.065
Antiplatelet	499 (27.6)	108 (28.0)	531 (20.4)	0.119	0.080
NSAID	392 (21.7)	81 (21.0)	669 (25.7)	0.074	0.063
PPI	754 (41.8)	140 (36.3)	978 (37.5)	0.075	0.059
SSRI	352 (19.5)	47 (12.2)	375 (14.4)	0.134	0.065
Statin	850 (47.1)	180 (46.6)	1087 (41.7)	0.073	0.021
Steroid	373 (20.7)	75 (19.4)	518 (19.9)	0.021	0.020
Treatment indication				0.246	0.126
AF	1561 (86.5)	351 (90.9)	2118 (81.2)		
Ischemic stroke	68 (3.8)	8 (2.1)	35 (1.3)		
VTE	176 (9.8)	27 (7.0)	455 (17.4)		
Area of residence				0.325	0.111
Capital Area	1266 (70.1)	247 (64.0)	1566 (60.0)		
Eastern	64 (3.5)	10 (2.6)	74 (2.8)		
Northern	119 (6.6)	41 (10.6)	419 (16.1)		
Southern	220 (12.2)	77 (19.9)	352 (13.5)		
Western	97 (5.4)	10 (2.6)	150 (5.8)		
Westfjords	39 (2.2)	1 (0.3)	47 (1.8)		

AF = atrial fibrillation, NSAID = Nonsteroidal anti-inflammatory drug, PPI = Proton pump inhibitor, SMD = Standardized mean difference, SSRI = Selective serotonin receptor inhibitor, VTE = Venous thromboembolism.

5 Discussion

In this doctoral thesis, dabigatran was associated with higher rates of any thromboembolism compared to rivaroxaban. This was mostly driven by higher rates of MI, but dabigatran was associated with twofold higher rates of MI compared to other DOACs. Rivaroxaban was associated with higher rates of GIB and overall major bleeding compared to apixaban and dabigatran. Warfarin was associated with higher rates of upper GIB and epistaxis compared to DOACs. Dabigatran was associated with higher nonadherence compared to warfarin, apixaban, and rivaroxaban but otherwise adherence was similar between different OACs.

5.1 Comparison of thromboembolic outcomes between direct oral anticoagulants

Rivaroxaban was associated with lower rates of any thromboembolism compared to dabigatran, which was mostly driven by higher MI rates for patients receiving dabigatran. Otherwise, rates of ischemic stroke; hemorrhage stroke; all-cause stroke; and composite of ischemic stroke and TIA, were similar between the three drugs. The incidence of venous and arterial thromboembolisms was too low to make any meaningful comparisons.

The similar rates of stroke among patients receiving different DOACs reported in this thesis are consistent with results from previous studies from Denmark, Taiwan, and the UK (Chan, Kuo et al. 2016, Andersson, Svanstrom et al. 2018, Vinogradova, Coupland et al. 2018, Mueller, Alvarez-Madrazo et al. 2019). However, they are in contrast to a previous study from USA that found significantly higher rates of ischemic stroke or arterial embolism in patients receiving rivaroxaban compared to those receiving apixaban (Fralick, Colacci et al. 2020). The US study was based on the Optum insurance database that is mostly limited to privately insured patients (Fralick, Colacci et al. 2020). These results may therefore potentially be affected by selection bias.

5.2 Dabigatran is associated with higher rates of myocardial infarction compared to other oral anticoagulants

Our results demonstrated that MI rates were twofold higher for dabigatran compared to apixaban and rivaroxaban, although the CIs were wide and included the possibility of a null effect for the former comparison. This is in contrast to previous observational studies but consistent with findings from RCTs. A registry study from the US found similar MI rates between dabigatran and rivaroxaban (Graham, Reichman et al. 2016). This study was limited to patients over the age of 64 years receiving public health insurance through the Medicare insurance coverage. Therefore, these patients may not be representative of the general population. Additionally, the study only assessed comorbid conditions using relevant ICD-9 codes within 6 months of cohort entry. This is likely to lead to missed diagnoses of important baseline covariates. A study from France demonstrated similar results (Blin, Dureau-Pournin et al. 2019). This study was limited to the first year after marketing, which, due to the increased usage of DOACs in recent years, may not be representative of today's DOAC population. A study from Taiwan found similar MI rates between dabigatran and rivaroxaban (Chan, Kuo et al. 2016). This study was based on a population that was likely at reduced risk of MI compared to patients in the current study. For example, only 3% of their study cohort had a prior history of MI compared to over 7% in our cohort. Additionally, 41-45% of dabigatran and rivaroxaban users were receiving concomitant antiplatelet therapy, as opposed to 20-27% of dabigatran and rivaroxaban users in our cohort. Consistently, MI rates were twice as common in our cohort compared to the one from Taiwan. The differences between our results and previous observational studies may therefore be explained by differences in study design. In addition to the above-mentioned, previous observational studies have likely suffered from low sensitivity, but our searching algorithm identified 66% more MI events compared to using ICD-10 codes only (68 events vs. 41 events).

A similar discrepancy has been noted between RCTs and observational studies comparing MI rates between dabigatran and warfarin users. A meta-analysis of 14 RCTs demonstrated that dabigatran was associated with higher MI rates compared to warfarin (Douxfils, Buckinx et al. 2014), while a meta-analysis of observational studies demonstrated similar MI rates between users of the two drugs (Carmo, Moscoso Costa et al. 2016). The increased MI risk of dabigatran has been hypothesized to be due to platelet activation. An RCT demonstrated that dabigatran increased thromboxane excretion in a non-dose-dependent manner while warfarin usage did not

affect thromboxane excretion (Ezekowitz, Reilly et al. 2007). This is interesting as thromboxane is a marker of platelet activation. Additionally, three studies have demonstrated increased platelet aggregation in patients receiving dabigatran but not in patients receiving rivaroxaban or warfarin (Olivier, Weik et al. 2016, Petzold, Thienel et al. 2016, Achilles, Mohring et al. 2017). Furthermore, these results were replicated in a mouse arterial injury model using intravital microscopy and in a human atherosclerotic plaque homogenate model (Petzold, Thienel et al. 2016). The increased MI risk associated with dabigatran might also, at least partly, be due to less intense anticoagulant effect, but a small study using samples from 46 dabigatran users and 28 warfarin users demonstrated that warfarin was associated with greater reduction in thrombin generation compared to dabigatran (Dale, Eikelboom et al. 2013). Supporting this, a RCT comparing dabigatran and warfarin treatment in patients with mechanical heart valves was discontinued prematurely due to higher rates of ischemic stroke and pericardial bleeding in patients receiving dabigatran (Eikelboom, Connolly et al. 2013). Additionally, our results demonstrate that dabigatran was associated with lower medication adherence than other OACs. Although our results did not find significantly higher rates of thromboembolism in nonadherent patients, previous studies with higher statistical power found higher rates of thromboembolism in nonadherent patients (Shore, Carey et al. 2014, Yao, Abraham et al. 2016). A previous study from USA using the Optum database demonstrated that among patients with a CHA_2DS_2-VASc score of 2 or higher, poor adherence was associated with higher rates of the composite outcome of ischemic stroke, systemic embolism, and all-cause mortality (Yao, Abraham et al. 2016). Another study from USA based on data from Veteran Administration Health hospitals demonstrated that poor adherence to dabigatran was associated with higher likelihood of all-cause mortality and stroke (Shore, Carey et al. 2014).

5.3 Warfarin is associated with higher overall bleeding risk than direct oral anticoagulants

In the RCTs of patients with AF, warfarin was associated with higher rates of major bleeding compared to apixaban, edoxaban, and low-dose dabigatran (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Giugliano, Ruff et al. 2013). Meanwhile, major bleeding rates were similar in patients receiving warfarin and patients receiving rivaroxaban and high-dose dabigatran (Connolly, Ezekowitz et al. 2009, Patel, Mahaffey et al. 2011). However, warfarin was associated with lower rates of major GIB compared to

both rivaroxaban and high-dose dabigatran (Connolly, Ezekowitz et al. 2009, Patel, Mahaffey et al. 2011). When analyzing major non-GI bleeding, warfarin was associated with higher bleeding rates compared to all DOACs (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011, Giugliano, Ruff et al. 2013).

The higher overall GIB risk of DOACs compared to warfarin has been suggested to be due to local anticoagulative effects (Desai, Kolb et al. 2013, Cheung and Leung 2017). As opposed to warfarin which is administered in a biologically inactive form, apixaban, edoxaban, and rivaroxaban are all administered in an anticoagulant active form. Dabigatran is administered as a prodrug, but a significant proportion is cleaved intraluminally to its active form in the GI tract (Desai, Kolb et al. 2013). Additionally, dabigatran, which contains tartaric acid, has been hypothesized to cause direct caustic effects on the GI tract (Cheung and Leung 2017). Furthermore, only 6% of dabigatran, 50% of apixaban, and 80% of rivaroxaban are absorbed in the GI tract (Desai, Kolb et al. 2013). This might explain why DOACs have proportionally more effect on the lower GI tract compared to warfarin. In the current thesis, we demonstrated that warfarin was associated with higher rates of upper GIB compared to DOACs. It is thus conceivable that warfarin has higher overall bleeding risk, which is masked in the lower GI tract due to the local anticoagulative effects of DOACs in the lower GI tract. Supporting this our results also demonstrate higher epistaxis rates for warfarin users compared to patients receiving DOACs.

The higher upper GIB risk of warfarin observed in this thesis is consistent with findings from RCTs (Eikelboom, Wallentin et al. 2011, Hori, Matsumoto et al. 2012, Bahit, Lopes et al. 2017). However, it is inconsistent with previous observational studies (Abraham, Singh et al. 2015, Vinogradova, Coupland et al. 2018). A previous study from the US found similar rates of upper GIB rates between warfarin users and patients receiving dabigatran and rivaroxaban (Abraham, Singh et al. 2015), while a study from the UK found that warfarin was associated with higher upper GIB rates compared to rivaroxaban but lower rates compared to apixaban. Neither of these two studies manually verified GIB events, which likely explains their different results compared to those in the current thesis, but without manual verification of GIB events, differentiation between upper and lower GIB can be very difficult.

Intriguingly, our results suggest that the risk of upper GIB in warfarin users is more pronounced in males than females. The cause of this is unknown but

may be linked to a higher overall risk of upper GIB in males compared to females (Button, Roberts et al. 2011).

The interpretation of our results is complicated by the fact that warfarin was monitored using two different INR measurements during the study period; conventional PT-test and the novel Fiix-test. However, rates of clinically relevant GIB, upper GIB, lower GIB, and major GIB were similar between patients monitored by the two different tests. Similarly, epistaxis rates were similar between patients monitored using Fiix- or PT measurements. This was expected as previous studies have demonstrated that Fiix-monitoring reduces the risk of thromboembolism compared to conventional PT measurements, while major bleeding rates have been found to be similar for patients monitored using the two different measurements (Onundarson, Francis et al. 2015, Oskarsdottir, Gudmundsdottir et al. 2021).

5.4 Rivaroxaban is associated with higher bleeding rates than other direct oral anticoagulants

In the current thesis, rivaroxaban was associated with higher rates of major bleeding and clinically relevant GIB compared to other DOACs. This is in line with previous observational studies that have demonstrated that rivaroxaban users have higher rates of bleeding requiring hospitalization than other DOAC users (Chan, Kuo et al. 2016, Abraham, Noseworthy et al. 2017, Adeboyeje, Sylwestrzak et al. 2017, Hernandez, Zhang et al. 2017, Lai, Chen et al. 2017, Vinogradova, Coupland et al. 2018, Mueller, Alvarez-Madrazo et al. 2019, Fralick, Colacci et al. 2020). Additionally, rivaroxaban was associated with higher rates of clinically relevant epistaxis events compared to both apixaban and dabigatran.

The higher overall bleeding rates of rivaroxaban may be explained by differences in pharmacokinetics. While apixaban and dabigatran are both administered twice daily, rivaroxaban is given as a single daily dose. This may lead to a higher peak plasma concentration, making these patients more susceptible to bleeding. Supporting this, rivaroxaban has been shown to have about twice higher peak plasma concentration compared to apixaban in two crossover treatment studies (Frost, Song et al. 2014, Kreutz, Persson et al. 2017). Importantly, the anti-Xa activity was highly correlated to the plasma concentration, with rivaroxaban having both higher maximal anti-Xa activity and higher 24-hour AUC compared to apixaban (Frost, Song et al. 2014, Kreutz, Persson et al. 2017). Alternatively, the higher bleeding risk of rivaroxaban may be the result of higher medication adherence, since once-

daily dosing has been associated with higher adherence compared to two daily doses for chronic cardiovascular medications (Coleman, Roberts et al. 2012). Supporting this, our results demonstrated that dabigatran was associated with lower adherence compared to rivaroxaban. However, adherence was similar between patients receiving apixaban and rivaroxaban. Additionally, apixaban was associated with better adherence when only patients with AF were analyzed.

Table 27: Rates of major bleeding and thromboembolic events in the current thesis and in randomized controlled trials

	Current thesis			Randomized controlled trials		
Outcomes*	Apixaban	Dabigatran	Rivaroxaban	Apixaban	Dabigatran†	Rivaroxaban
Major bleeding	1.9	1.9	2.9	2.1	2.7-3.1	3.6
Intracranial hemorrhage	0.4	0.3	0.5	0.3	0.2-0.3	0.5
Gastro-intestinal bleeding	1.4	1.3	2.0	0.8	1.5	2.0
Myocardial infarct	0.8	1.3	0.6	0.5	0.7	0.9
All-cause stroke	0.7	0.7	0.6	1.2	1.0-1.4	1.7
Ischemic stroke	0.6	0.3	0.4	1.0‡	0.9‡	1.3
Hemorrhagic stroke	0.1	0.3	0.2	0.2	0.1	0.3

*All outcomes are presented as events per 100-years. †The values for dabigatran are presented as a range since they combine the results from both standard and low dose dabigatran treatments. ‡For the apixaban and dabigatran trials, this outcome included stroke of unspecified type as well.

5.5 Comparison of outcome rates compared to randomized controlled trials

In this thesis, rates of major bleeding ranged from 1.9-2.9 events/100-py, which is comparable to results of the initial RCTs for patients with AF (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011) (Table 27). Similarly, the rates of intracranial

hemorrhage, major GIB, and MI were similar in this thesis compared to the RCTs (Table 27). In contrast, the rates of all-cause stroke and ischemic stroke were lower in the current thesis compared to the RCTs, while rates of hemorrhagic stroke were similar in the current thesis and the RCTs. This might be explained by several factors. First, the RCTs included stroke of unspecified cause, while those were excluded in the current study. Second, the apixaban and dabigatran trials only included patients with $CHADS_2$ score of 1 or higher, while the rivaroxaban trial only included patients with a $CHADS_2$ score of 2 or higher. In contrast, the current thesis includes all patients irrespective of $CHADS_2$ scores. This is important as the risk of ischemic stroke has been demonstrated to increase by 50% for each 1-point increase in the $CHADS_2$ score (Gage, Waterman et al. 2001). Supporting this, the all-cause stroke rates for rivaroxaban users was 1.7 events/100-py compared to 1.2 events/100-py and 1.0 events/100-py for apixaban and high-dose dabigatran users respectively (Connolly, Ezekowitz et al. 2009, Granger, Alexander et al. 2011, Patel, Mahaffey et al. 2011). This also emphasizes the limitations of performing indirect comparisons of DOACs using results from RCTs.

5.6 Comparison of adherence to different oral anticoagulants

The lower adherence of dabigatran demonstrated in the current study is consistent with previous observational studies (McHorney, Crivera et al. 2015, Forslund, Wettermark et al. 2016, Johnson, Lefevre et al. 2016, Yao, Abraham et al. 2016, Collings, Lefevre et al. 2017, Lamberts, Staerk et al. 2017, Rodriguez-Bernal, Peiro et al. 2018, Banerjee, Benedetto et al. 2020, Salmasi, Loewen et al. 2020). This may be related to the frequent dyspepsia side effects of dabigatran treatment. In the RE-LY study, 12% of patients receiving dabigatran reported dyspepsia compared to 4% of warfarin users (Connolly, Ezekowitz et al. 2009). Additionally, more than 3 times as many patients discontinued their treatment due to non-bleeding-related gastrointestinal symptoms compared to warfarin (Connolly, Ezekowitz et al. 2009).

Conversely, adherence was similar between apixaban, rivaroxaban, and warfarin. This is interesting as previous studies have yielded conflicting reports when comparing the adherence of warfarin and DOACs (Yao, Abraham et al. 2016, Sorensen, Jamie Nielsen et al. 2017, Briasoulis, Inampudi et al. 2018, Banerjee, Benedetto et al. 2020). The major limitation of previous adherence studies is that they don't account for dose adjustments

between drug prescriptions (Yao, Abraham et al. 2016, Sorensen, Jamie Nielsen et al. 2017, Briasoulis, Inampudi et al. 2018, Banerjee, Benedetto et al. 2020). As warfarin dosing is continuously being modified according to INR values, this may make their data unreliable. Indeed, in a previous study from Sweden comparing the adherence and persistence of OACs, patients receiving warfarin were excluded when comparing adherence as “the proportion of days covered could not be calculated for warfarin treatment due to the highly variable dosage regimens” (Forslund, Wettermark et al. 2016).

In this thesis, female gender, hypertension, history of cerebrovascular accident, and concomitant statin use were all associated with lower odds of nonadherence. This suggests that patients with higher comorbidity were associated with lower odds of nonadherence. This is reassuring as these patients are likely at higher risk of both thromboembolic and major bleeding events.

In our cohort, 10.5-16.7% of OAC users were nonadherent. This is consistent with previous studies from Scandinavia which have demonstrated nonadherence ranging from 4.3% to 23.2% (Gorst-Rasmussen, Skjoth et al. 2015, Forslund, Wettermark et al. 2016). However, nonadherence has been reported to be much higher in studies from USA (Shore, Carey et al. 2014, Crivera, Nelson et al. 2015, McHorney, Crivera et al. 2015, Zhou, Chang et al. 2015, Brown, Shewale et al. 2016, Yao, Abraham et al. 2016, Banerjee, Benedetto et al. 2020). A study based on a large US insurance database found that nonadherence to rivaroxaban was 24.6%, 29.4% to apixaban, and 32.4% to dabigatran (Crivera, Nelson et al. 2015). In comparison, other studies have reported nonadherence as high as 52.5% for DOACs and 59.8% for warfarin (Yao, Abraham et al. 2016). The differences between Scandinavian and US studies may be explained by different study designs. Most studies from USA have gathered data on drug prescriptions from either Veteran Health Administration pharmacies (Shore, Carey et al. 2014) or insurance claims (Crivera, Nelson et al. 2015, McHorney, Crivera et al. 2015, Zhou, Chang et al. 2015, Brown, Shewale et al. 2016, Yao, Abraham et al. 2016) which may be more likely to miss prescriptions compared to the centralized nationwide prescription database used in Scandinavian studies such as ours. In addition, this difference may, at least partly, be due to the increased social disparity in the American population, as patients with low socioeconomic status may not afford to fill their drug prescriptions on time.

In the current study, thromboembolic and major bleeding rates were similar between adherent and nonadherent patients after accounting for

baseline characteristics. In comparison, a previous study demonstrated that among patients with a CHA_2DS_2-VASc score of 2 or higher, poor adherence was associated with higher rates of the composite outcome of ischemic stroke, systemic embolism, and all-cause mortality (Yao, Abraham et al. 2016). Additionally, poor adherence was associated with lower rates of major bleeding (Yao, Abraham et al. 2016). Another study limited to patients receiving dabigatran demonstrated that nonadherence was associated with higher likelihood of all-cause mortality and stroke, but not MI or major bleeding (Shore, Carey et al. 2014). The reason for the differences between previous studies and the current one, is likely due to the fact that our study was based on an "on-treatment" analysis, where all thromboembolic and major bleeding events were manually verified and events excluded if the patients had not been receiving OACs in the preceding 2 days. Previous studies have not manually verified outcome events and are therefore more representative of an "intention-to-treat" analysis (Shore, Carey et al. 2014, Yao, Abraham et al. 2016). Additionally, the current thesis had lower statistical power compared to the above-mentioned studies. Overall, our cohort included 495 nonadherent patients compared to 36,735 and 1,494 patients in the other two studies respectively (Shore, Carey et al. 2014, Yao, Abraham et al. 2016).

5.7 Severity of epistaxis events in patients receiving oral anticoagulants

Overall, 12% of all clinically relevant epistaxis events fulfilled the ISTH criteria for major bleeding and one event was fatal. Interestingly, 9% of all patients who continued their anticoagulation after an initial nonmajor epistaxis event later presented with major bleeding during the study period. These were either major GIB or intracranial hemorrhage. This raises the question whether an epistaxis episode, severe enough for a patient to seek the emergency department or to be admitted, may serve as a marker of increased risk of major bleeding in patients on OACs.

5.8 Strengths and limitations

The current thesis has several strengths. It was both nationwide and population-based, using a centralized national drug prescription database to include all patients in Iceland receiving OACs over a 5-year study period. The data gathering process was extremely robust, including data from all the major hospitals in Iceland, and with manual verification of each major bleeding or thromboembolic event. By manually reviewing patient charts, we

were able to identify the treatment indication for over 99% of the study cohort, greatly increasing the accuracy of the data. Additionally, a thorough searching algorithm was included to identify events, but events were identified using ICD-10 codes, by reviewing the results of endoscopic procedures and diagnostic imaging, and by searching the national death registry. This method had much higher accuracy compared to the traditional method of using only a few specific ICD-10 codes to identify events and without manually verifying events.

Our results must also be interpreted in the context of several limitations. First, although a robust propensity score-weighting method was used to account for indication bias, we cannot exclude that some unmeasured confounding exists. In this context, our database lacked data on important socioeconomic and lifestyle factors, such as alcohol consumption, smoking, education, household income, employment, and obesity. However, as Iceland has a universal health insurance coverage with reimbursement of all DOACs, differences in OAC treatment due to socioeconomic status is probably minimal, or at least less common than in many other populations. Second, our database did not include data on baseline laboratory values, such as hemoglobin or creatinine values. However, we did account for prior history of bleeding and moderate to severe renal disease in our IPW model. Third, our database did not include data on over-the-counter usage of medications, such as NSAIDs, proton pump inhibitors, or antiplatelets. This is important as over-the-counter usage of these drugs is rather common in Iceland. Fifth, although our study period was 5 years, the mean follow-up period was only 1.1-2.2 years, in large part due to a high number of patients starting OAC treatment at the tail-end of the study period. Sixth, the dabigatran and warfarin groups were relatively small compared to previous registry studies, especially when only patients with AF were included. Lastly, there are a number of factors that complicate the comparison of patients receiving warfarin and DOACs. For example, the population that receives warfarin and DOACs are different in many ways; patients receiving warfarin were more commonly being treated due to VTE and a significantly higher proportion of warfarin users were OAC experienced at the start of our study period. As DOACs are currently recommended as the first line of treatment for AF and VTE (January, Wann et al. 2019, Konstantinides, Meyer et al. 2020, Hindricks, Potpara et al. 2021, Stevens, Woller et al. 2021), the number of patients initiating warfarin treatment has been declining in recent years. Therefore, more patients were initiated on warfarin treatment during the first half of the study period compared to the latter half. Additionally, two different

measurement tests were used to monitor warfarin treatment during the study period. While this had limited consequences when comparing bleeding rates between the drugs, Fiix-measurements have been demonstrated to reduce the rates of thromboembolism by approximately 50% (Onundarson, Francis et al. 2015, Oskarsdottir, Gudmundsdottir et al. 2021). This makes any generalization of thromboembolic rates between warfarin and DOACs in our study cohort difficult. These data are therefore not included in this thesis. However, the next step will be to compare study outcomes between DOACs and Fiix- or PT-monitored warfarin treatment in an OAC experienced cohort, which offers a much higher statistical power compared to using an OAC naïve cohort only.

6 Conclusions

In this OAC naïve cohort, rivaroxaban was associated with lower rates of any thromboembolism and MI compared to dabigatran. Apixaban was associated with lower rates of MI compared to dabigatran, although this comparison did not reject the null hypothesis. Rivaroxaban was associated with higher rates of any major bleeding, any clinically relevant GIB, and any clinically relevant epistaxis compared to apixaban and dabigatran. Rates of stroke and all-cause mortality were similar between all DOACs. Warfarin was associated with higher rates of upper but not lower or overall GIB compared to DOACs. Similarly, warfarin was associated with higher epistaxis rates compared to DOACs. Finally, dabigatran was associated with higher nonadherence compared to apixaban, rivaroxaban, and warfarin whereas nonadherence was similar between apixaban, rivaroxaban, and warfarin. Apart from OAC type, female gender, hypertension, history of cerebrovascular accident, and concomitant statin use were all associated with lower odds of nonadherence.

The results of the current thesis suggest that rivaroxaban has higher bleeding risk compared to other DOACs, while dabigatran has higher MI risk and higher odds of medication nonadherence. Therefore, rivaroxaban may not be suitable for patients at high risk of bleeding. Similarly, dabigatran may not be the optimal treatment for patients with high risk of MI, e.g., patients with known coronary artery disease or strong family history.

Our current study was limited to a rather small dabigatran study group. Therefore, population-based studies in a larger cohort with adequate follow-up and manual verification of events would be beneficial to confirm our findings. Additionally, our study did not compare thromboembolic event rates between warfarin and DOACs. While thromboembolic rates have been compared extensively between DOACs and conventional PT-monitored warfarin, other modes of warfarin monitoring have shown promise and may improve warfarin treatment. Previous studies comparing PT-monitored and Fiix-monitored warfarin have been largely limited to experienced warfarin users. Studies comparing Fiix-monitored warfarin and DOACs are currently missing. This comparison should ideally be performed using a new user-design. Unfortunately, our cohort was underpowered for this analysis.

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Original publications

Paper I

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