Effectiveness and safety of oral anticoagulants for atrial fibrillation in the era of NOACs

Studies using Norwegian nationwide registries

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To George Kenyon Rutherford

Acknowledgements

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1 Preface

The prevalence of atrial fibrillation, (AF), the most common sustained cardiac arrhythmia, is increasing rapidly.[1, 2] On average, it entails a two-fold increase in risk of all-cause mortality, and a five-fold increase in risk of stroke.[3] Oral anticoagulation reduces the risk of stroke by about two thirds, and is recommended for all patients at increased risk.[3]

Over the last decade, non-vitamin K antagonist oral anticoagulants (NOACs) have replaced vitamin K antagonists (e.g. warfarin) as the preferred class of drugs for stroke prevention in AF.[3-5] The NOACs dabigatran, rivaroxaban, apixaban and edoxaban were approved for use in AF after randomised controlled trials showed them to be non-inferior or superior to warfarin in terms of efficacy and safety.[6-9] However, several important questions emerge as a result of this therapeutic transition. Which are the most important risk factors for adverse events such as bleeding for patients on NOACs, and are they the same as for warfarin? How are the effectiveness and safety of these drugs compared to warfarin when used in clinical practice? Are there important individual differences in effectiveness and safety between the NOACs?

The Norwegian nationwide administrative health registries (the Norwegian Patient Registry (NPR) and the Norwegian Prescription database (NorPD)) contain data of very high quality on the AF population in Norway, and are ideally suited as data sources for observational studies.[10, 11] In this thesis, we have used data from the NPR and the NorPD to identify predictors of future bleeding events in patients with AF using NOACs. Furthermore, we have performed NOAC-warfarin as well as NOAC-NOAC comparisons for effectiveness and safety in real-world patients with AF.

2 List of papers

Paper I

Rutherford O-CW, Jonasson C, Ghanima W, Holst R, Halvorsen S. New score for assessing bleeding risk in patients with atrial fibrillation treated with NOACs. Open Heart 2018;5:e000931.

Paper II

Rutherford O-CW, Jonasson C, Ghanima W, Söderdahl F and Halvorsen S. Comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in atrial fibrillation: a nationwide cohort study. Eur Heart J Cardiovasc Pharmacother 2020;6:75-85.

Paper III

Rutherford O-CW, Jonasson C, Ghanima W, Söderdahl F, Halvorsen S. Effectiveness and safety of oral anticoagulants in elderly patients with atrial fibrillation. Heart. 2021 May 11;heartjnl-2020-318753.

3   Selected abbreviations

AF	Atrial fibrillation
ACC	American College of Cardiology
AHA	American Heart Association
B.i.d.	Bis in die, twice daily
CI	Confidence interval
CRNM	Clinically relevant non-major (used to describe bleeding)
DAG	Directed acyclic graph, causal diagram
E.G.	Exempli gratia
ESC	European society of cardiology
HF	Heart failure
HR	Hazard ratio
I.E.	Id est
INR	International normalised ratio (standardised prothrombin time)
NOAC	Non-vitamin K antagonist oral anticoagulant
NSAID	Non-steroidal anti-inflammatory drug
OAC	Oral anticoagulant
O.d.	Omne in die, once daily
PT	Prothrombin time
PTR	Prothrombin time ratio
SE	Systemic embolism
TIA	Transient ischaemic attack
VKA	Vitamin K antagonist

4 Introduction

4.1 Atrial fibrillation

4.1.1 Historical perspective

Atrial fibrillation (AF) has been recognised as a clinical entity for centuries. Still, the precise mechanism for the "irregularly irregular" ventricular rhythm characteristically observed was unknown until 1970 when Bootsma et al. described AF as "randomly spaced atrial impulses of random strength reaching the atrioventricular node from random directions."[12] Initially, AF was considered a trivial condition, but later became recognised as a risk factor for stroke, occurring more often in patients with increasing age and with comorbidities such as hypertension and cardiovascular disease.[13] Epidemiological studies based on the Framingham Heart Study, published in 1978, showed what an impact AF had on morbidity and mortality in affected patients.[14] In the absence of rheumatic heart disease, AF increased the risk of stroke five-fold. In the presence of rheumatic heart disease, the risk of stroke increased 17-fold.[14] Further analyses of data from the Framingham Heart Study published in 1991 showed that AF itself was an independent risk factor for stroke.[15]

Into the late 1980's and 1990's, awareness grew among clinicians and researchers of the thromboembolic nature of AF-related stroke.[16] Optimal stroke prophylaxis with antithrombotic drugs was studied extensively. By the end of the1990s, six randomised controlled trials (RCTs) had investigated the efficacy of warfarin vs placebo, five RCTs had investigated the efficacy of aspirin vs placebo, and five RCTs had investigated the efficacy of warfarin vs aspirin for prevention of thromboembolic events in AF.[17] A meta-analysis of these trials showed that warfarin was associated with a 62% (95% confidence interval (CI) 48% – 72%) relative risk reduction for ischaemic stroke of compared with placebo, and 46% (95% CI 27% – 60%) relative risk reduction compared with aspirin. [17]

In 2001, the first guidelines for management of patients with AF were published, as a joined effort from the American College of Cardiology (ACC), the American Heart Association (AHA) and the European Society of Cardiology (ESC).[18] After this, the issue of prevention and treatment of AF has gained enormous focus, with new ESC guidelines on management of AF published in 2010,[19] a focused update in 2012,[20] new guidelines in 2016,[21] and the latest

guidelines published in 2020.[3] The 'Atrial fibrillation Better Care' (ABC; A, Anti-coagulation/Avoid stroke; B, Better symptom management; C, Cardiovascular and Comorbidity optimisation) pathway outlining how care for AF patients should be integrated was introduced in the 2020 guidelines. This simple pathway highlights how stroke prevention with oral anticoagulants is the cornerstone of AF therapy.

For five decades, vitamin K antagonists were the only drugs available for oral anticoagulation in AF. Since the introduction of non-vitamin K antagonist oral anticoagulants (NOACs) in 2009, the range of therapeutic alternatives has increased. With several NOACs on the market in addition to warfarin, selecting the optimal drug has become somewhat complicated. In this thesis, we have sought to expand the present knowledge of the effectiveness and safety of NOACs, both as a class and as individual drugs.

4.1.2   Epidemiology and disease burden

AF is one of the major causes of stroke, sudden death, and cardiovascular morbidity in the world. It is the most common cardiac arrhythmia, and accounts for approximately one third of all arrhythmia-related hospitalisations.[22] The lifetime risk of developing AF is about 1 in 3,[23] and the incidence increases rapidly with advancing age.[24] The prevalence of AF differs markedly around the world, being more common in developed countries (Figure 1).
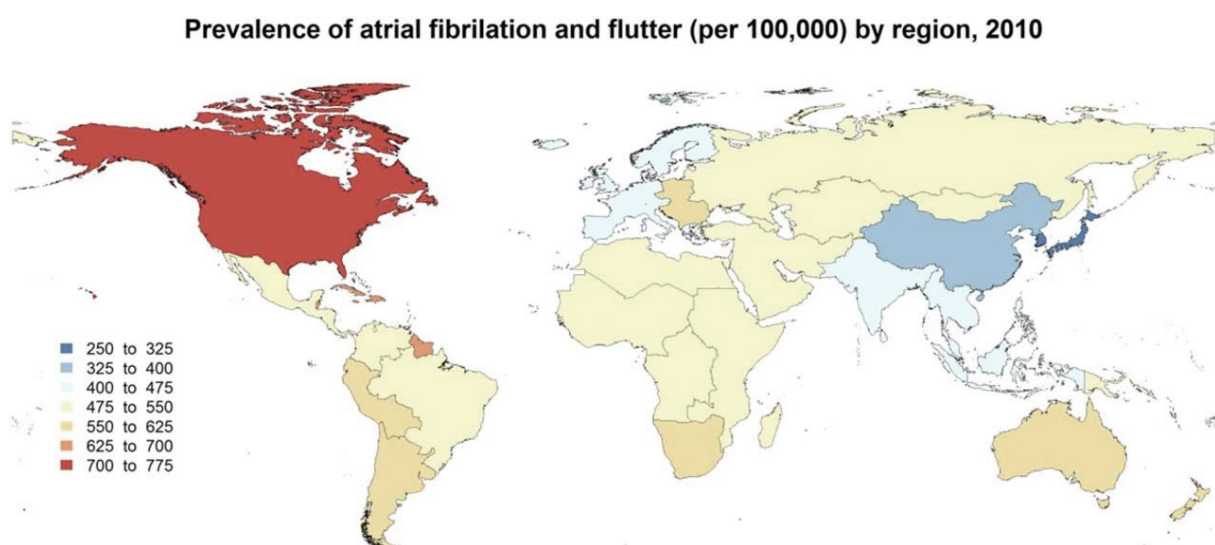
Figure 1. World map showing the age-adjusted prevalence rates (per 100 000 population) of atrial fibrillation in the 21 Global Burden of Disease regions, 2010. *Reproduced with permission from Chugh, et. al.[25].*

Higher life expectancy, older populations, and corresponding higher prevalence of AF-associated risk factors such as obesity and cardiovascular disease may partly explain this.[25] The region with the highest prevalence of AF is North America. Data from the Framingham Heart Study have shown that the age-adjusted prevalence of AF quadrupled from 1958-1967 to 1998-2007.[26] In 2010, the estimated numbers of women and men with AF worldwide were 12.6 million and 20.9 million, respectively.[25] The incidence and prevalence of AF are predicted to continue to rise in the coming decades.[21] This trend is explained by an ageing world population, along with increasing prevalence of AF risk-factors such as diabetes, obesity, heart failure, cardiovascular disease, and hypertension. Figure 2 shows the estimated change in prevalence of AF in the United Kingdom, suggesting a doubling in prevalence before 2050. In Norway this trend seems less dramatic with stable incidence rates in the period between 2004 and 2014, and an estimated prevalence of 3.4% in 2014.[27]
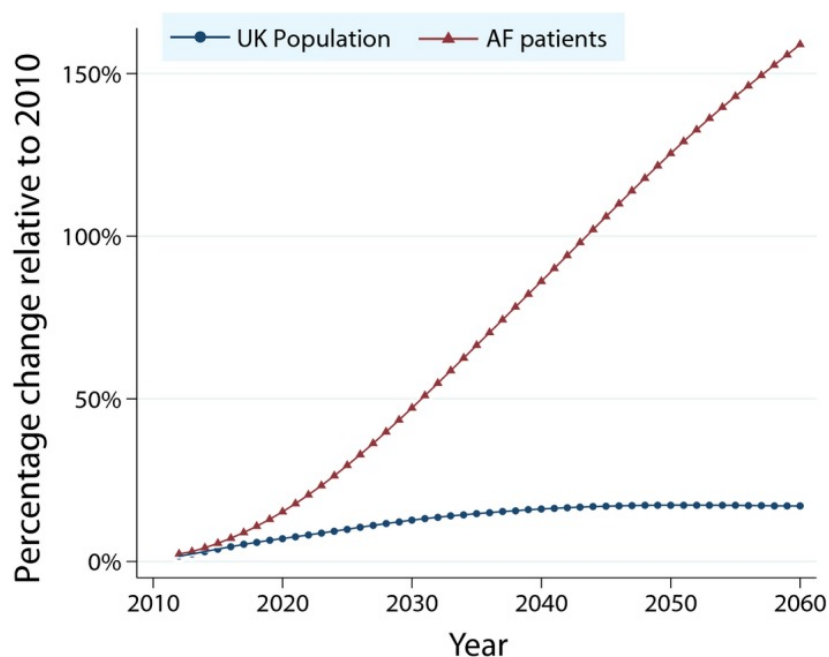
Figure 2. Estimated change from 2010 in the UK population and numbers of patients with AF in comparison to the predicted United Kingdom population, assuming increased incidence of AF. AF, atrial fibrillation. *Reproduced with permission from Lane, et. al..[24]*

AF is associated with a 1.5 to 3.5-fold increase in age-adjusted all-cause mortality,[3] an average 5-fold increase in risk of stroke or systemic embolism (SE),[21] and a 1.5-fold increase in cognitive decline/ vascular dementia.[28] Ischaemic strokes secondary to AF are more likely to involve occlusion of larger cerebral arteries than strokes not related to AF. Thus, AF-related

strokes are often more severe than strokes from other causes, with a higher likelihood of debilitation and death.[29] Patients with AF report significant reductions in quality of life,[30] and an increased risk of depression has been observed.[31, 32] Optimal management is thus of utmost importance.

4.1.3   Pathophysiology

AF is characterised by what seems like a state of electrical chaos in the atria, and may be precipitated by a number of factors. In addition to age, important triggers or conditions that increase the likelihood of developing AF are obesity, obstructive sleep apnoea, hypertension, diabetes, coronary heart disease, heart failure (HF) and chronic kidney disease.[33-37] Their common effect is that they convey physical changes to the atrial myocardium; a structural remodelling manifested by inflammation, enhanced connective tissue deposition, activation of fibroblasts and fibrosis.[38, 39] This structural remodelling in turn facilitates electrical focal triggering, and re-entry circuits by electrical dissociation of muscle bundles as well as heterogeneity in electrical conduction.[40] Once established, AF itself will perpetuate the structural changes in the atria, prolonging its own duration and increasing the likelihood of relapse.[41]

Structural changes, inflammation, expression of prothrombotic factors on the atrial endothelial surface and stasis of blood, especially in the left atrial appendage, establish a milieu in which thrombus formation is more likely to occur.[42] This explains the increased risk of thromboembolic events in patients with AF. Patients with AF also have a significantly higher risk of developing heart failure, seen in 20-30%.[3] Factors that increase the risk of heart failure are an accelerated ventricular rate, the irregularity of ventricular contractions in AF, loss of atrial systole, and often a worsening of mitral- and tricuspid regurgitation.[43] The increased risk of all-cause mortality associated with AF is probably a result of an increased age- and comorbidity-related risk of death, as well as thromboembolic events and heart failure related to AF.[44, 45]

There is a substantial genetic component in AF. More than 160 genes that are associated with the development of AF have been identified; many of which are involved in cardiac electrical and structural remodelling.[46, 47] Furthermore, it has been suggested that different types of atrial cardiomyopathies could lead to AF.[48, 49] This shift in the understanding of AF from merely an

electrical disorder to a disease at least partially triggered by genetic factors, characterised by physical changes including fibrosis in the atria, will likely give rise to new treatment strategies and new targets for future antiarrhythmic drugs. However, for the time being, it seems more important that focus among clinicians be directed toward the modifiable comorbidities that lead to AF.

4.2 Management of atrial fibrillation

The 2020 ESC guidelines for the diagnosis and management of AF emphasise the importance of a coordinated, patient-individualised, multidisciplinary approach to patient care.[3] Patient understanding of the importance of lifestyle interventions, risk factor modification, and adherence to therapy is of great importance. To achieve these goals, patient education and a shared decision-making process are recommended. The three pillars in care of AF patients are stroke prevention with oral anticoagulation, symptom control (rate- or rhythm control), and treatment of comorbidities and cardiovascular risk factors. Of relevance to this thesis is oral anticoagulation, which will be discussed in detail below.

4.2.1 Anticoagulation in atrial fibrillation

It is estimated that AF is the cause of about one third of ischaemic strokes, and use of oral anticoagulants (OACs) may reduce the risk of ischaemic stroke by about two thirds.[29] However, this resulting improvement in health and quality of life for AF patients comes at a cost of increased risk of bleeding. Major bleeding events occur in 3% to 4.5% of patients using OACs per year.[50]

In the 2001 ACC/AHA/ESC guidelines for the management of patients with AF, a detailed scheme to identify patients with indication for stroke prevention was proposed, based on risk factors such as age, heart failure, thyrotoxicosis, previous thromboembolism, rheumatic heart disease, persistent left atrial thrombus, coronary heart disease, diabetes, and hypertension.[18] Treatment recommendations depending on risk factor profiles were acetylsalicylic acid (325 mg daily) or oral anticoagulation with vitamin K antagonists (VKA, e.g. warfarin). Since then, guidelines for anticoagulation in AF have changed substantially.[3] Acetylsalicylic acid has been

shown to be inferior to anticoagulation for stroke prevention in AF,[17, 51] and vitamin K antagonists have to a large degree been replaced by NOACs. There are several reasons for this transition.

First, NOACs are non-inferior or superior to warfarin in terms of efficacy and safety. A meta-analysis of the pivotal RCTs comparing NOAC with warfarin showed that NOACs were associated with a similar risk of ischaemic stroke as warfarin, but a 19% reduction in risk of the combined outcome of stroke or SE, a 51% reduction in risk of haemorrhagic stroke, a 14% reduction in risk of major bleeding and a 10% reduction in risk of all-cause mortality.[52] Second, NOACs are more practical to use. They do not require the same close monitoring of effect (INR) by regular testing and frequent dose adjustments that accompany use of VKAs, nor do they require the same dietary restrictions. Below follows a more detailed description of OACs used in AF.

4.2.2   Vitamin K antagonists (warfarin)

Trying to solve the problem of the "Haemorrhagic sweet clover disease" that led to the death of so much cattle in the United States and Canada in the 1930's, Karl Paul Link and his research team isolated the coumarin "dicoumarol" from spoiled sweet-clover hay in 1939.[53] In 1945, Link and colleagues managed to produce a similar compound but with a higher bioavailability and longer half-life, named "warfarin" after the financier Wisconsin Alumni Research Foundation (WARF).

Coumarins inhibit the enzyme vitamin K epoxide reductase, diminishing available vitamin K for the synthesis of biologically active forms of the clotting factors II, VII, IX and X, as well as the regulatory factors protein C, protein S, and protein Z (Figure 3). Coumarins are thus collectively termed vitamin K antagonists (VKAs). Their anticoagulant effect needs to be measured regularly by determination of the international normalised ratio (INR), with the aim of achieving a high proportion of 'time in therapeutic range (TTR)' defined by an INR between 2.0 and 3.0. While there is no specific antidote to reverse the effects of VKAs, prothrombin complex concentrate ("PCC", complete reversal, within minutes), fresh frozen plasma ("FFP", partial reversal, within minutes), and oral or intravenous vitamin K (complete reversal, but needs several hours) will restore the blood's coagulative capability.[54]

By the end of the 1990s, 6 RCTs investigating the efficacy of oral anticoagulation with vitamin K antagonists for stroke prevention in AF had been published, and showed an average of 62% relative risk reduction for ischaemic stroke compared with placebo or no treatment.[16, 17] Furthermore, five RCTs had compared warfarin with aspirin, and found an average of 46% relative risk reduction in ischaemic stroke with warfarin compared with aspirin.[17] Despite the availability of NOACs, vitamin K antagonists still play an important role for stroke prevention in AF, being the only treatment established as safe and effective in rheumatic mitral valve disease and for patients with mechanical heart valves.[3]
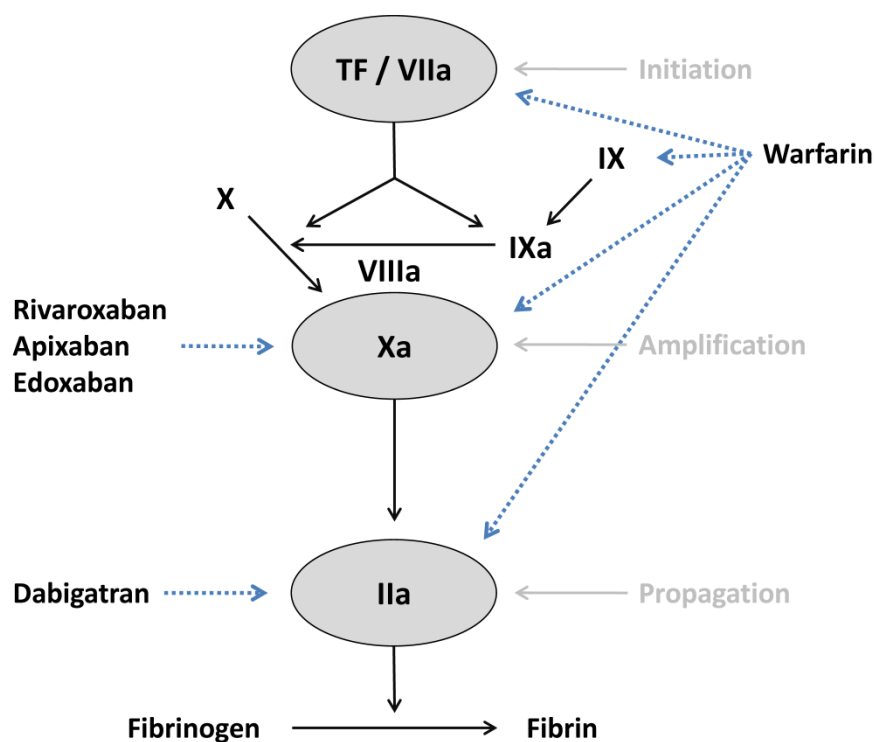
Figure 3, Oral anticoagulants and their targets in the coagulation cascade. TF, tissue factor; VIIa, activated factor VII; VIIIa, activated factor VIII; IX, factor IX; IXa, activated factor IX; factor X; Xa, activated factor X; IIa, activated factor II (thrombin). *Adapted from Weitz and Bates.* [55]

4.2.3   Non-vitamin K antagonist oral anticoagulants

For more than 50 years, VKAs were the only oral anticoagulants available. However, due to the need for regular monitoring of anticoagulation levels, as well as numerous drug-drug and drug-food interactions, great efforts were made to find more user-friendly and safer alternatives for VKAs.

- Dabigatran etexilate

Dabigatran etexilate was the first oral alternative to VKAs that became available on the market. Dabigatran etexilate is a prodrug which is hydrolysed in the liver to the active direct thrombin inhibitor dabigatran. It binds to the active site on thrombin (factor IIa), inhibiting thrombin-mediated activation of coagulation factors (figure 3). Dabigatran may also have an effect on thrombin-mediated platelet-aggregation. Additionally, it inhibits the activity of fibrin-bound thrombin, which would inhibit fibrinolysis in the absence of dabigatran. Thus, dabigatran may enhance fibrinolysis.[56] In 2009, the "Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate" (RE-LY) trial was published.[6] When published, it was the largest randomized controlled trial of antithrombotic therapy for stroke prevention ever performed. The RE-LY trial included a study population of 18 000 patients, and studied two separate doses of dabigatran etexilate (150 mg twice daily, and 110 mg twice daily) compared with warfarin in patients with AF and elevated risk of stroke. Relative to warfarin, dabigatran 110 mg twice daily was associated with a similar risk of stroke/SE (relative risk (RR) 0.91, 95% confidence interval (CI) 0.74–1.11), and a significantly lower risk of major bleeding (RR 0.80, 95% CI 0.69–0.93), as well as intracranial bleeding (RR 0.31, 95% CI 0.20–0.47). Dabigatran 150 mg twice daily significantly reduced the risk of stroke/SE (RR 0.66, 95% CI 0.53–0.82), as well as intracranial bleeding (RR 0.40, 95% CI 0.27–0.60), but there was a trend towards higher relative risk of major bleeding compared to warfarin (RR 1.16, 95% CI 1.00–1.34, p=0.052). For stroke prevention in AF, dabigatran received regulatory approval in Norway in August 2011. Later, an antidote to dabigatran was developed. Idarucizumab is a monoclonal antibody fragment that binds rapidly and specifically to dabigatran, reversing its anticoagulant activity.[57] Idarucizumab is available in Europe for use preoperatively before emergency surgery or in the case of life-threatening bleeding among patients using dabigatran.

- Rivaroxaban

The second NOAC on the market was rivaroxaban. Rivaroxaban is an oral factor Xa inhibitor that inhibits free factor Xa (figure 3) as well as clot-bound factor Xa or factor Xa incorporated into the prothrombinase-complex. This inhibition affects both the intrinsic and the extrinsic coagulation cascades. Rivaroxaban does not inhibit thrombin, and has no specific antiplatelet effect, but may reduce downstream platelet activation by reduction of thrombin formation.[58] The "Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation" (ROCKET AF

trial) was published in 2011, investigating the efficacy and safety of rivaroxaban compared with warfarin in patients with AF.[9] A total of 14 264 patients with AF and moderate-to-high risk of stroke (mean CHADS$_2$–score 3.5) were randomised to rivaroxaban 20 mg once daily, or dose-adjusted warfarin. Rivaroxaban was shown to be non-inferior to warfarin with respect to stroke (hazard ratio (HR) 0.88, 95% CI 0.75–1.03). There was no significant difference in risk of clinically relevant bleeding overall (HR 1.04, 95% CI 0.90–1.20), but rivaroxaban was associated with a significantly higher risk of gastrointestinal bleeding ($P<0.001$).

Rivaroxaban received regulatory approval for stroke prevention in AF in Norway in December, 2011.

- Apixaban

Apixaban is an oral factor Xa inhibitor (figure 3), with the same mechanism of action as rivaroxaban, but with a different dosing regimen, to be taken twice daily.[59] The "Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation" (ARISTOTLE) study was published in 2011.[8] In this study, 18 201 AF patients with at least one additional risk factor for stroke were randomised to taking apixaban (at a dose of 5 mg twice daily) or dose-adjusted warfarin. Compared with warfarin, apixaban significantly reduced the risk of stroke/SE (HR 0.79, 95% CI 0.66–0.95), major bleeding (HR 0.69, 95% CI 0.60–0.80), intracranial bleeding (HR 0.42, 95% CI 0.30–0.58), and all-cause mortality (HR 0.89, 95% CI 0.80–0.99). Apixaban received regulatory approval in Norway in November, 2012.

- Edoxaban

Edoxaban is a factor Xa inhibitor (figure 3), with a similar mechanism of action to that described for rivaroxaban.[60] Edoxaban was tested in the "Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48" (ENGAGE AF-TIMI 48) trial, published in 2013.[7] In the ENGAGE AF-TIMI 48 trial, 21 105 patients with AF and a CHADS2 score ≥2 were randomised to dose-adjusted warfarin, high-dose edoxaban (60 mg) or low-dose edoxaban (30 mg), all given once daily. Both dose regimens of edoxaban were shown to be non-inferior to warfarin with respect to risk of stroke/SE (HR 0.79, 97.5% CI 0.63–0.99 for edoxaban 60 mg., and HR 1.07, 97.5% CI 0.87–1.31 for edoxaban 30 mg.), and were associated with significantly lower rates of major bleeding (HR 0.8, 95% CI 0.71–0.91 for edoxaban 60 mg, and HR 0.47, 95% CI 0.41–0.55 for edoxaban 30 mg). Edoxaban received approval for AF in Norway in 2015 and was marketed from 2016.

- Antidote for factor Xa inhibitors

An antidote to factor Xa inhibitors has been developed. It is a modified recombinant inactive form of human factor Xa, "andexanet alfa", which binds and sequesters factor Xa inhibitor molecules, thereby neutralising them.[61] Andexanet alfa received a conditional marketing approval in the European Union on 26 April 2019, for the indication life-threatening or uncontrolled bleeding among patients using the factor Xa inhibitors rivaroxaban and apixaban.

Table 1 shows drug characteristics of the different OACs on the market in Norway. A summary of results from the RCTs leading to approval of the NOACs for AF is shown in Table 2.

Although the NOACs have been shown non-inferior or superior to warfarin in terms of efficacy and safety, there is still a knowledge gap with respect to which of the NOACs that confers the optimal efficacy and safety balance.

Table 1. Drug characteristics of dabigatran, rivaroxaban, apixaban and edoxaban

Drug characteristics	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Inhibits synthesis of factors[a]	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Bioavailability, (%)	>95	6	66 fasting, 80–100 with food	50	62
Time to peak levels, h	72–96	2	2–4	1–4	1–2
Half-life, h	20–60	12–17	5–13	9–14	10-14
Excretion	Renal (92%) Liver (8%)	Renal (80%) Liver (20%)	Liver (65%) Renal (35%)	Renal (25%) Liver (75%)	Renal (50%) Liver (50%)
Standard dose	O.d. Adjusted to INR 2.5 (±0.5)	2 × 150 mg / 2 × 110 mg	1 × 20 mg	2 × 5 mg	1 x 60 mg
Dose reduction (criteria)	O.d. Adjusted to INR 2.5 (±0.5)	2 × 110 mg if age ≥80 years, concomitant verapamil, increased risk of GI bleeding[b]	1 × 15 mg if CrCl ≤50 mL/min	2 × 2.5 mg if two out of three: Body weight ≤60 kg, age ≥80 years, serum creatinine ≥133 μmol/(1.5 mg/dL) [or if CrCl 15–29 mL/min]	1 × 30 mg if CrCl ≤50 mL/min, body weight ≤60 kg, or use of P-gp inhibitors[c]

a: factors II, VII, IX, X, protein C, protein S, protein Z; b: according to summary of product characteristics; c: ciclosporin, dronedarone, erythromycin, ketoconazole; CrCl: creatinine clearance; O.d. omne in die (once daily). *Adapted from Heidbuchel et al.,[62] and Steffel et al.[63]*

Table 2. Summary of the clinical trials comparing the NOACs dabigatran, rivaroxaban, apixaban and edoxaban with warfarin

Study characteristics	Dabigatran (RE-LY)[6]	Rivaroxaban (ROCKET AF)[9]	Apixaban (ARISTOTLE)[8]	Edoxaban (ENGAGE AF)[7]
Study design	PROBE design[a]	Randomised, double-blind, double-dummy	Randomised, double-blind, double-dummy	Randomised, double-blind, double-dummy
Number of patients	18 111	14 264	18 201	21 105
Follow-up period, years	2	1.9	1.8	2.8
Randomised groups	Dose-adjusted warfarin vs dabigatran 2 × 150 mg or 2 × 110 mg	Dose-adjusted warfarin vs rivaroxaban 1x 20 mg	Dose-adjusted warfarin vs apixaban 2 × 5 mg	Dose-adjusted warfarin vs edoxaban 1 x 60 or 1 x 30 mg

Baseline characteristics

Age, years	Mean 71.5 (SD 8,7)	Median 73 (IQR 65–78)	Median 70 (IQR 63–76)	Median 72 (IQR 64–78)
Male sex, %	63.6	61.3	64.5	61.9
CHADS$_2$ (mean)	2.1	3.5	2.1	2.8

Outcomes

	Warfarin	D150	D110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	E60	E30
Number of patients	6 022	6 076	6 015	7 133	7 131	9 081	9 120	7 036	7 035	7 034
Effect size statistic		(RR, 95% CI)			(HR, 95% CI)		(HR, 95% CI)		(HR, 95% CI)	
Stroke/SE										
%/yr	1.69	1.11	1.53	2.40	2.1	1.6	1.27	1.50	1.18	1.61
RR (95% CI) or		0.66	0.91		0.88		0.79		0.79	1.07
HR (95% CI)		(0.53-0.82)	(0.74-1.11)		(0.75-1.03)		(0.66-0.95)		(0.63-0.99)	(0.87-1.31)
Ischaemic stroke										
%/yr	1.2	0.92	1.34	1.42	1.34	1.05	0.97	1.25	1.25	1.77
RR (95% CI) or		0.76	1.11		0.94		0.92		1.00	1.41
HR (95% CI)		(0.60-0.98)	(0.89-1.40)		(0.75-1.17)		(0.74-1.13)		(0.83-1.19)	(1.19-1.67)
Major bleeding										
%/yr	3.36	3.11	2.71	3.4	3.6	3.09	2.13	3.43	2.75	1.61
RR (95% CI) or		0.93	0.80		1.04		0.69		0.80	0.47
HR (95% CI)		(0.81-1.07)	(0.69-0.93)		(0.90-1.20)		(0.60-0.80)		(0.71-0.91)	(0.41-0.55)
Intracranial bleeding										
%/yr	0.74	0.30	0.23	0.7	0.5	0.80	0.33	0.85	0.39	0.26
RR (95% CI) or		0.40	0.31		0.67		0.42		0.47	0.30
HR (95% CI)		(0.27-0.60)	(0.20-0.47)		(0.47-0.93)		(0.30-0.58)		(0.34-0.63)	(0.21-0.43)
Gastrointestinal bleeding										
%/yr	1.02	1.51	1.12	2.2	3.2	0.86	0.76	1.23	1.51	0.82
RR (95% CI) or		1.50	1.10		(P< 0.001)		0.89		1.23	0.67
HR (95% CI)		(1.19-1.89)	(0.86-1.41)				(0.70-1.15)		(1.02-1.50)	(0.53-0.83)
All-cause death										
%/yr	4.13	3.64	3.75	2.2	1.9	3.94	3.52	4.35	3.99	3.80
RR (95% CI) or		0.88 (0.77-1.00)	0.91 (0.80-1.03)		0.85		0.89		(P=0.082)	(P=0.006)
HR (95% CI)					(0.70-1.02)		(0.80-0.99)			

D 150, dabigatran 150 mg x 2; D 110, dabigatran 110 mg x 2; E60, edoxaban 60 mg x 1; E30, edoxaban 30 mg x 1; HR,hazard ratio; RR, relative risk. a: blinded evaluation of all outcomes. Two doses of dabigatran were compared with warfarin for stroke prevention in patients with NVAF and ≥1 risk factor for stroke, whereby the dose of dabigatran was blinded but not the warfarin regimen. *Adapted from Heidbuchel et al.* [62] *and Steffel et al.* [63]

4.3   Assessment of stroke risk in patients with AF

After the recognition of AF as a major independent risk factor for stroke,[14, 15] further investigations continued regarding which AF patients should be recommended oral anticoagulation, i.e. which AF patients had a stroke risk high enough to justify the bleeding risk associated with anticoagulation. The aim was to identify patients at particularly high risk of stroke, but also those at low risk. The Atrial Fibrillation Investigators (AFI) as well as the Stroke Prevention in AF (SPAF) trial investigators identified factors common for patients at truly low stroke risk (age < 65 years, no hypertension, previous stroke/transient ischaemic attack (TIA), or diabetes mellitus), and at elevated stroke risk (congestive heart failure, hypertension, and previous stroke/SE, combination of ≥ 75 years and female sex).[64, 65] In 2001, Gage and colleagues combined the findings from the AFI and SPAF investigators and validated the $CHADS_2$-score (Congestive heart failure, history of Hypertension, Age$\geq$ 75 years, Diabetes mellitus; Stroke or TIA) for estimation of stroke risk among patients with non-rheumatic AF not using an OAC.[66] The $CHADS_2$-score showed a better discriminative ability than either of the proposed AFI or SPAF–schemes. The original validation of the $CHADS_2$-score classified a $CHADS_2$ score of 0 as low risk, 1–2 as moderate risk, and >2 as high risk of stroke.

In 2010 Lip and colleagues proposed an expansion of the $CHADS_2$–score. The proposed new score included the 'major' risk factors previous stroke/TIA/SE and older age ($\geq$75 years), and the 'clinically relevant non-major' risk factors heart failure, hypertension, diabetes, female sex and vascular disease (specifically previous myocardial infarction, complex aortic plaques, and peripheral artery disease).[67] Instead of focusing on 'low', 'moderate' and 'high' stroke risk categories (with poor predictive abilities), stroke risk was more clearly recognised as a continuum.   The CHA_2DS_2-VASc score [congestive heart failure, hypertension, age $\geq$75, diabetes, stroke, vascular disease, age 65–74, and sex category (female)] (Table 3 and 4) was introduced in the 2010 European Society of Cardiology (ESC) guidelines for the management of atrial fibrillation.[19] The 2020 ESC guidelines for the diagnosis and management of AF still recommend estimating stroke risk for each individual patient using the CHA_2DS_2-VASc score, and the current consensus is that a CHA_2DS_2-VASc score of $\geq$2 for female patients and $\geq$1 for male patients warrants treatment with oral anticoagulation.[3]

During the last 10 years, several new stratification schemes for quantification of stroke risk in AF have been proposed. Among these are the Framingham stroke risk score,[68] the ATRIA

(Anticoagulation and Risk Factors in Atrial Fibrillation) stroke risk score,[69] the ABC (Age, Biomarkers, Clinical history) stroke risk score,[70] and the GARFIELD-AF (Global Anticoagulant Registry in the FIELD-Atrial Fibrillation) stroke risk score.[71] The risk factors presented are numerous, including geographical location (world region), demographics (race, age, gender), various clinical risk factors (heart failure, diabetes mellitus, chronic kidney disease), medical history (previous stroke/TIA), and biomarkers (natriuretic peptides, cardiac troponins). Furthermore, focus has shifted from a single risk assessment upon diagnosis of AF, and a consequent decision for or against oral anticoagulation, to recommending repeated stroke and bleeding risk assessments regularly and at least annually. Estimation of the 'delta' or ΔCHA_2DS_2-VASc score has been shown to out-perform the initial CHA_2DS_2-VASc in terms of predictive ability.[72]

4.4 Assessment of bleeding risk in patients with AF

Bleeding is the most serious and common complication to anticoagulation. Major bleeding events occur in 3% to 4.5% of patients using oral anticoagulation per year.[50] In 2010, Pisters and colleagues created the HAS-BLED score [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (65 years), Drugs/alcohol concomitantly] (table 3 and 4), based on investigations of the prospective Euro Heart Survey on AF.[73] Use of the HAS-BLED score was incorporated already in the 2010 ESC guidelines for management of AF, to identify patients with a high risk of bleeding in need of closer follow-up while on an OAC.[19]

Several other bleeding risk scores have been proposed, such as the HEMORR2HAGES (Hepatic or renal disease, Ethanol abuse, Malignancy, Older age (>75 years), Reduced platelet count or function, Re-bleeding (previous bleed), Hypertension, Anaemia, Genetic predisposition, Excessive fall risk, Stroke) bleeding risk score,[74] the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) bleeding risk score,[75] the ATRIA bleeding risk score,[76] the GARFIELD-AF bleeding risk score,[77] the Shireman bleeding risk score,[78] and the ABC bleeding risk score.[79, 80] The HAS-BLED score has been shown to be more accurate than the ATRIA and ORBIT scores.[81] [82] Deciding which score to use can be challenging; the ABC stroke- and the ABC bleeding risk scores have been shown superior to

the CHA_2DS_2-VASc and the HAS-BLED scores,[83] and the HAS-BLED score has been shown to be superior to the ABC bleeding risk score.[84]

All bleeding risk scores published to date have moderate predictive abilities, they are derived from very different patient populations, and include a wide variety of risk factors. As a consequence of their lack of precision, meaning that they do not accurately identify the true high-risk patients, some claim the bleeding risk scores may be more harmful than helpful and that all AF-patients could be regarded as high-risk.[80] Also, since the net clinical benefit of oral anticoagulation is maintained even in high-bleeding risk patients, bleeding risk scores should not be taken into consideration when deciding whether or not to recommend oral anticoagulation.

Tools for simpler and more reliable recognition of risk factors for modification or follow-up, and encouragement to initiate anticoagulation despite elevated risk are needed. [80, 85]

Table 3 and 4 show CHA_2DS_2-VASc and HAS-BLED schemes including increasing annual risk of stroke and bleeding with higher scores.

Table 3. CHA_2DS_2-VASc and HAS-BLED schemes

Stroke and bleeding risk stratification			
CHA_2DS_2-VASc (Stroke)	**Score**	**HAS-BLED (Major bleeding)**	**Score**
Congestive heart failure / LV dysfunction	1	Hypertension	1
Hypertension	1	Abnormal renal/liver function (1 pt. each)	1 or 2
Age ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding history or predisposition	1
Stroke/TIA	2	Labile INR	1
Vascular disease (prior MI, PAD, aortic plaque)	1	Elderly (age ≥65)	1
Age 65–74 years	1	Drugs (NSAIDs, antiplatelet drugs) or alcohol	1 or 2
Sex category (female)	1		
Maximum	9		9

TIA, transient ischaemic attack; LV, left ventricular; MI, myocardial infarction; PAD, peripheral arterial disease; NSAIDs, non-steroidal anti-inflammatory drugs; INR, international normalised ratio; CHA_2DS_2-VASc, [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female)]; HAS-BLED, [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (65 years), Drugs/alcohol concomitantly]. *Adapted from Camm et al,[19] and Pisters el al.[73]*

Table 4. Annual risk of stroke and bleeding with increasing CHA$_2$DS$_2$-VASc and HAS-BLED scores

Adjusted stroke and major bleeding rates according to CHA$_2$DS$_2$-VASc and HAS-BLED scores (%/year)			
CHA$_2$DS$_2$-VASc score (stroke)	**%/year**	**HAS-BLED score (major bleeding)**	**%/year**
0	0%	0	1.13%
1	1.3%	1	1.02%
2	2.2%	2	1.88%
3	3.2%	3	3.74%
4	4.0%	4	8,70%
5	6.7%	5	12.50%
6	9.8%	6	…
7	9.6%	7	…
8	6.7%	8	…
9	15.2%	9	…

CHA$_2$DS$_2$-VASc, [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female)]; HAS-BLED, [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (65 years), Drugs/alcohol concomitantly]. *Adapted from Camm et al.,[19] and Pisters et al.[73]*

4.5   Weighing stroke vs bleeding risk

Factors predicting stroke and bleeding in AF patients are often similar, as illustrated in table 3. In fact, the CHADS$_2$ and the CHA$_2$DS$_2$-VASc scores may both be used as bleeding risk scores, even though they were developed as stroke risk scores.[86] Similarly, the HAS-BLED score can be used to predict risk of stroke.[87] Apart from age which is immutable, risk factors such as diabetes, cardiovascular disease, chronic kidney disease and hypertension significantly increase the risk of both stroke and bleeding, and can be modified or treated. It is of particular importance to focus on treatment of these risk factors if possible, with lifestyle interventions, drug therapy and closer follow-up. Patients should also optimally be re-assessed for stroke risk and bleeding risk at each patient visit, keeping modifiable (hypertension, OAC adherence, labile INR, concurrent medication, and excess alcohol) and potentially modifiable (frailty, platelet count/function, anaemia, impaired renal function) risk factors in mind.[3, 88]

4.6 Risk of stroke and bleeding in Elderly patients

Age is a strong independent risk factor for the development of AF, but the large increase in prevalence with increasing age is also due to the fact that other risk factors (e.g. cardiovascular disease, hypertension, heart failure, diabetes) are also more prevalent in older patients.[67]

The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Study showed that warfarin compared with aspirin in elderly patients significantly reduced thromboembolic risk without increasing risk of bleeding complications.[89] Nevertheless, oral anticoagulation is still underused in the elderly population, likely due to fear of bleeding complications.[90, 91] It is of great importance to establish effective treatment strategies for the elderly, and to increase the proportion of elderly patients with AF that receive adequate anticoagulation.

Cognitive and functional impairment are both shown to significantly decrease adherence to OACs, which is especially relevant for elderly patients.[92] With NOACs there is no need for frequent INR controls or dietary adjustments. The need for frequent visits to a doctor's office may be especially challenging for the elderly, which makes NOACs easier to use for elderly patients. In the pivotal RCTs comparing NOACs with warfarin, the median age was just over 70 years, and only 30 to 40% of the patients were 75 years or older.[6-9] Subgroup analyses from these RCTs focusing on the patients ≥75 years have shown that NOACs were as effective as warfarin also in this population, but some of the NOACs seemed to be associated with a higher bleeding risk in the elderly.[93-96] The elderly patients included in these trials were carefully selected, and less is known about the effectiveness and safety of NOACs in the real world elderly population, bound to have a greater burden of fragility and comorbidity. More knowledge on how the NOACs perform in elderly patients with AF is needed.

4.7 The Norwegian nationwide health registries

In Norway as well as in the other Nordic countries, information from the entire health care sector (e.g. pharmacies and hospitals) nationwide is entered into administrative health registries. The flow of information from primary sources to the registries is mandatory and exempt from need of patient consent. These registries contain large quantities of medical information, and owing to unique personal identifiers for all citizens, data from different registries may be linked, making it possible to follow patients over time and across registries.[10,]

[97-99] Registry-based diagnosis codes in the Scandinavian countries have been validated in numerous studies, reporting positive predictive values of AF diagnosed in hospitals in the 89 – 93% range.[100, 101]

1.8 RCT vs observational studies

The gold standard for assessing and demonstrating the efficacy of an intervention or treatment is the RCT. Through randomization, equal distribution of known and unknown confounders is ensured. This enables researchers to study causal relationships between an intervention and an outcome. Nonetheless, RCTs are expensive, time-consuming, and prone to selection bias, which limits the generalisability of their results. Observational trials on the other hand, crucially lack the randomisation element, but may still offer advantages compared to RCTs. With less strict inclusion- and exclusion-criteria, and the possibility of including very large populations, they offer a closer approximation to the real-world treatment effect. This is especially advantageous if one is studying adverse events of an intervention or treatment.[102] Additionally, observational studies may offer insight into areas of research where RCTs are lacking. The fact that numerous recommendations in international cardiology guidelines are not based on RCTs, but rather on observational trials or expert consensus underscores their importance.[103] The biggest challenge for observational studies is the fact that without randomisation, unmeasured or unmeasurable confounders will invariably be present. Thus, observational studies most often describe associations rather than making causal inference. The saying by dr. Joseph Bavaria is very accurate; 'science tells us what we can do, trials tell us what we should do, and registries tell us what we are actually doing'. Nonetheless it is important to emphasise that observational studies typically reflect findings from RCTs. A 2014 Cochrane review found very little difference in effect estimates between RCTs and observational trials regardless of trial design or heterogeneity.[104]

When interpreting the results from observational studies, one should be aware of the difference between efficacy and effectiveness. Efficacy is the effect of an intervention under ideal circumstances, studied in RCTs. Effectiveness is the effect of an intervention in real life, assessed in observational studies.[105]

4.8 Rationale for the studies presented in this thesis

The usefulness of oral anticoagulation in AF has been confirmed beyond doubt, and NOACs have replaced vitamin K antagonists as the preferred class of OACs. Still, the risks of stroke and bleeding complications for patients on OACs remain high.

Bleeding risk is a dynamic entity, and frequent risk assessments followed by risk factor modification whenever possible is recommended. Most tools used for predicting bleeding events in patients on OACs were derived from cohorts of patients using VKAs, not NOACs. Also, they include many variables which are not readily available bedside. A simpler tool for repeated bleeding risk assessment would be useful.

Furthermore, the NOACs differ with respect to pharmacodynamic and pharmacokinetic characteristics, and performed differently compared with warfarin in the pivotal RCTs. There are reasons to assume that there might be important differences in effectiveness and safety between NOACs in clinical use. Owing to the lack of RCTs performing head-to head comparisons between the NOACs, evidence is still missing regarding which of the NOACs is optimal for different patient groups. Since elderly patients with their comorbidities make up the greater part of patients with AF, more information is particularly needed on effectiveness and safety of OACs in the elderly.

The Norwegian nationwide registries are well suited to identify important predictors of bleeding for patients with AF using NOACs, and to perform comparisons between OACs for effectiveness and safety.

5 Aims

5.1 General aims

The overall aim of this thesis was to identify independent predictors of bleeding for AF patients using NOACs, and to investigate potential differences in effectiveness and safety between OACs, in a real-world population of AF patients.

5.2 Specific aims

I. To identify independent risk factors for bleeding among patients with AF using NOACs (Paper I)

II. To develop a bleeding risk score specifically for users of NOACs (Paper I)

III. To study the comparative effectiveness and safety of dabigatran, rivaroxaban and apixaban in a nationwide population of patients with AF (Paper II)

IV. To assess the risks of stroke/SE and major bleeding associated with use of OACs in the subgroup of AF patients ≥75 years in clinical practice (Paper III)

6 Materials and methods

6.1 The Norwegian administrative health registries

6.1.1 The Norwegian Patient Registry

The Norwegian Patient Registry (NPR) holds diagnosis and procedure-codes for all hospital contacts (inpatient and outpatient) as well as all specialist consultations outside the hospitals in Norway since 2008.[10] After each patient contact, the treating physician registers a primary code (the most important or relevant condition being treated) and several secondary codes (other conditions or comorbidities of significance). Diagnoses are coded according to the International Classification of Diseases, version 10 (ICD-10),[106] and procedures are coded according to the Nordic Medico-Statistical Committee (NOMESCO) system.[107] The NPR has been investigated for completeness and correctness, and found very suitable for clinical and healthcare studies.[108] As examples, in the NPR the validity of AF and acute myocardial infarction (AMI) diagnoses have been investigated; with positive predictive values of 89% for AF and 95.1% for AMI.[100, 109]

6.1.2 The Norwegian Prescription Database

The Norwegian Prescription Database (NorPD) contains information about all prescriptions dispensed in all Norwegian Pharmacies since 2004.[11] Data on patient, prescriber, date of dispensation, tablet strength, packet size, and commercial brand name is registered.

Medical expenses for treatment of serious and prolonged chronic illnesses are reimbursed by the Norwegian state, and the diagnosis warranting reimbursement is also recorded. This gives information on the specific condition being treated with each drug, i.e. it is possible to discern whether a patient is using an OAC for the indication venous thromboembolism or AF, or an angiotensin converting enzyme inhibitor (ACE inhibitor) to treat heart failure or hypertension. Drugs are classified according to the Anatomical Therapeutic Chemical system (ATC).[110]

6.2   Creation of study populations

The study populations in this thesis were created by linking data from NPR with data from NorPD in the following ways:

In Paper I, we identified all patients ≥18 years with an in-hospital or specialist diagnosis of AF and at least one dispensation of dabigatran, rivaroxaban or apixaban with AF as the reimbursement code in the study period from 1 January 2013 to 30 June 2015. Exclusion criteria were rheumatic valve disease, mitral stenosis or mechanical prosthetic heart valves; any dispensation of anticoagulants ≤180 days before inclusion; venous thromboembolism ≤180 days before inclusion; knee/hip surgery ≤35 days prior to inclusion; and NOAC doses not tested for the indication stroke prophylaxis in AF. In total, 21 248 patients were included: 7 925 (37.3%) starting dabigatran, 6 817 (32.1%) starting rivaroxaban, and 6 506 (30.6%) starting apixaban. Figure 4 shows a cohort creation flow-chart for paper I.
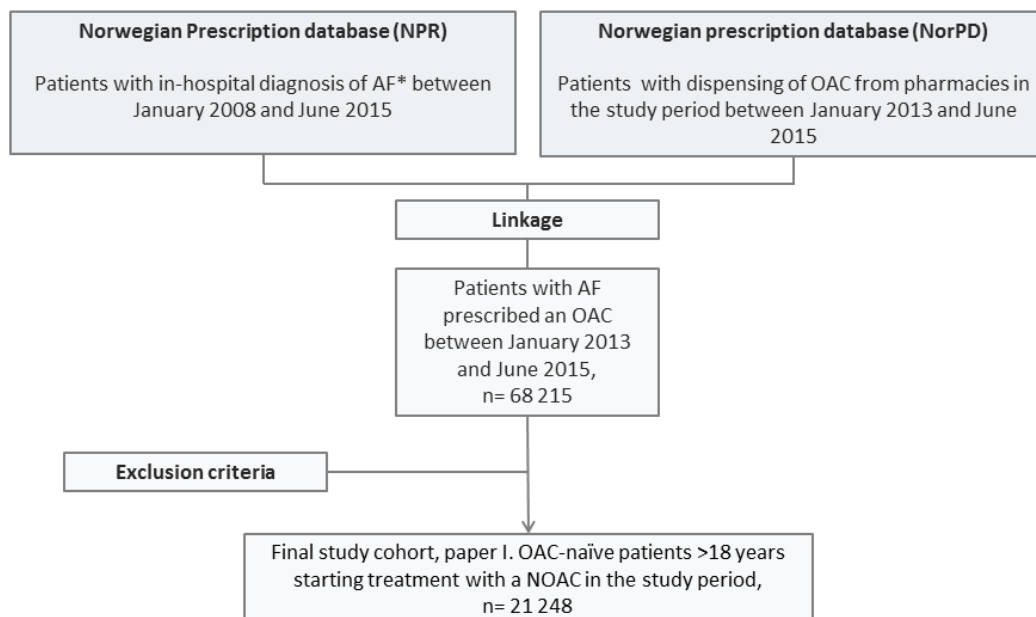
Figure 4. Cohort creation flow-chart, paper I. NPR, Norwegian Patient Registry; NorPD, Norwegian Prescription Database; AF*, atrial fibrillation in the absence of mitral stenosis or mechanical prosthetic heart valves; OAC, oral anticoagulant.

In Paper II, patients ≥18 years with an in-hospital or specialist diagnosis of AF and at least one dispensation of either warfarin, dabigatran, rivaroxaban or apixaban with AF as the re-imbursement criterion in the study period from 1 January 2013 to 31 December 2017 were included. Patients with rheumatic valve disease, mitral stenosis or mechanical prosthetic heart valves were excluded. Further exclusion criteria were any dispensation of anticoagulants during the last 12 months; a diagnosis of venous thromboembolism in the last 180 days, and knee or hip surgery in the last 35 weeks. In total, 65 563 patients were included, of which 13 087 initiated therapy with warfarin, 10 413 with dabigatran, 13 700 with rivaroxaban, and 28 363 with apixaban. Figure 5 shows a cohort creation flow-chart for paper II.
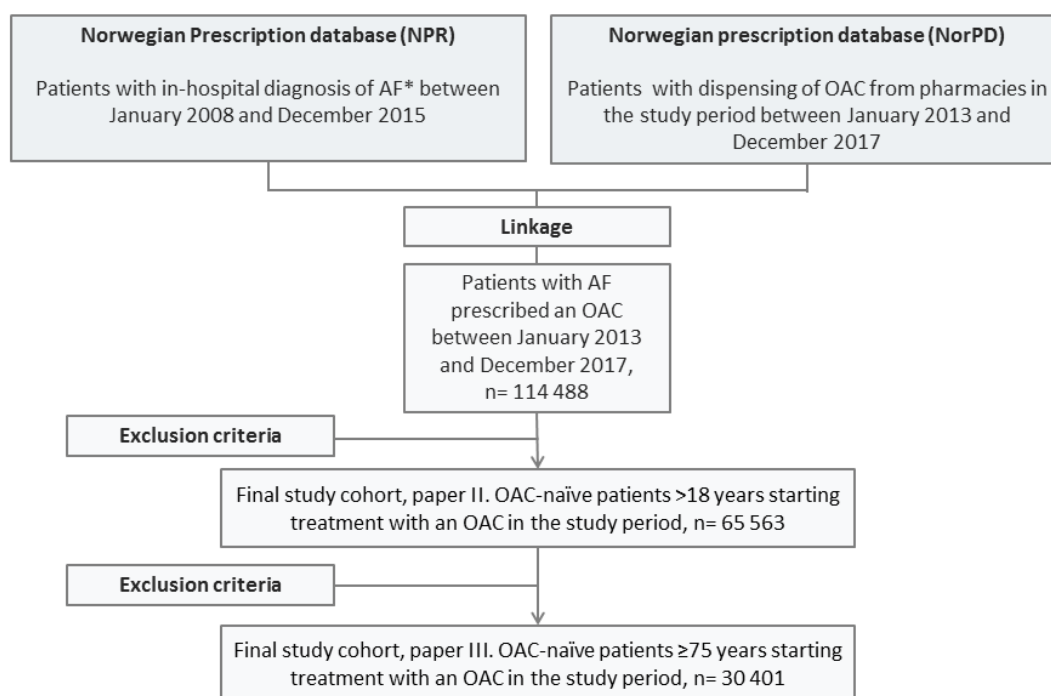
Figure 5. Cohort creation flow-chart, papers II and III. NPR, Norwegian Patient Registry; NorPD, Norwegian Prescription Database; AF*, atrial fibrillation in the absence of mitral stenosis or mechanical prosthetic heart valves; OAC, oral anticoagulant.

In paper III, patients ≥75 years with an in-hospital or specialist diagnosis of AF, and at least one dispensation of warfarin, dabigatran, rivaroxaban or apixaban for the indication AF in the study period from 1 January 2013 to 31 December 2017 were included. Exclusion criteria were the same as in study II, except that 75 years of age was the lower age limit for inclusion. A total

of 30 401 patients were included: 6 650 were users of warfarin, 3 857 were users of dabigatran, 6 108 were users of rivaroxaban and 13 786 were users of apixaban. Figure 5 shows a cohort creation flow-chart for paper III.

6.3 Study variables and definitions

From the NPR, diagnoses for all hospital admissions, consultations, and procedures in the previous 5 years before the index date (the date of the first dispensing of an OAC in the study period) were collected. This information, linked with information from the NorPD of all prescriptions dispensed (including ICD-10 diagnoses for reimbursement), was used to assemble a 5 year medical history for each included patient. After data from the NPR and NorPD was merged, follow-up periods were calculated and study outcomes identified. For all effectiveness- and safety-outcomes, only primary ICD-10 codes (the most important illnesses or conditions being treated) from the NPR were used. For comorbidities or medical history, both primary and secondary codes were identified.

All three papers in this thesis share the same definitions and codes used to compile medical history and clinical outcomes, listed in table S1 of the Supplementary material. Major bleeding was defined as any bleeding event which occurred in a critical area or organ, or any bleeding event that was accompanied by blood transfusion ≤10 days after hospital admission date. A clinically relevant non-major (CRNM) bleeding was defined in accordance with the International Society on Thrombosis and Haemostasis (ISTH) classification as any non-major bleeding necessitating intervention by a medical professional.[111]

6.4 Follow-up period and outcomes

The three papers included in this thesis are historical cohort studies. In all three papers, patients were followed from the index date (the date of the first dispensation of an OAC in the study period) until discontinuation of oral anticoagulation, switching between OACs, or end of study period. Figure 6 shows the period of data availability for papers II and III. For paper I, the only difference is that the period of data availability was shorter (from 1 January 2013 to 30 June 2015).
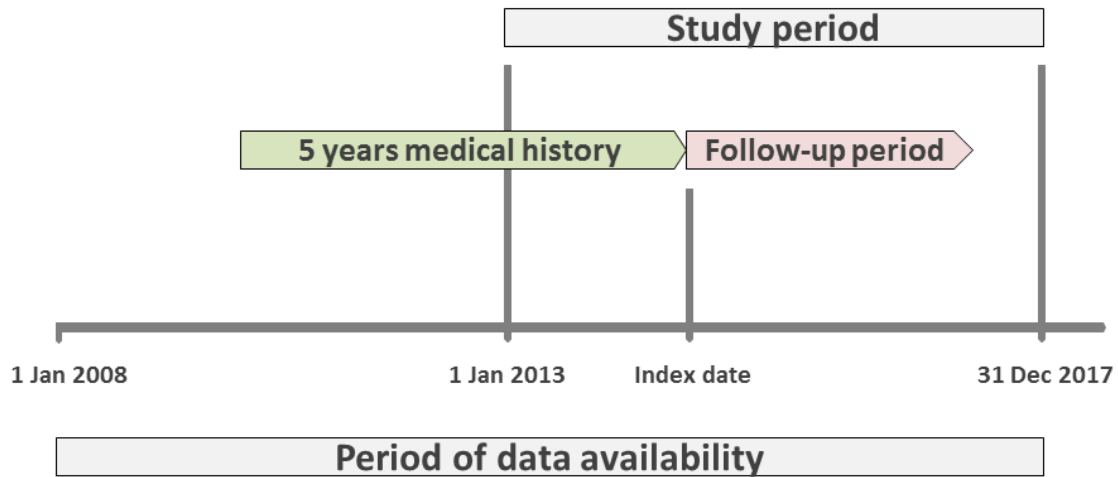
Figure 6. Period of data availability for paper II and III

In Paper I, the outcome investigated was a composite of major or CRNM bleeding.

In paper II, the effectiveness outcomes investigated were stroke (haemorrhagic or ischaemic) or systemic embolism (SE), as well as ischaemic stroke. Safety outcomes were major bleeding, CRNM bleeding, major or CRNM bleeding, intracranial bleeding, and gastrointestinal bleeding.

In paper III, effectiveness outcomes were stroke/SE, and ischaemic stroke. The main safety outcomes were major bleeding, intracranial bleeding, gastrointestinal bleeding, any (major or CRNM) bleeding, and all-cause mortality.

6.5 Ethical considerations

Registration of data into the NPR and the NorPD is mandatory in Norway and legally exempt from obtainment of patient consent. The study protocol and obtainment of registry data was approved by the Regional Ethics Committee (REC). The legal basis, under the 2018 European Union General Data Protection Regulation (GDPR),[112] was article 6, number 1e and article 9 number 2j; as well as the Norwegian health research act,[113] chapter 35. Two separate approvals were needed as the study period was extended in papers II and III to include more patients. The approval reference for paper I is 2015/162/REK Midt, and the approval reference for papers II and III is 2017/410/REK Nord. The data delivered to us were de-identified in order to ensure patient anonymity.

6.6   Statistical analysis

Categorical variables were reported as numbers and percent, continuous variables as means with standard deviations (SD), or medians with interquartile range (IQR).

In paper I, the aim was to develop a bleeding risk prediction model. We followed the general principles of the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[114] Cox proportional hazards regression was used to calculate hazards ratios specific for relevant risk factors. The proportional hazards assumption was checked using Schoenfeld residuals, and by comparing the log-log transformation of the Kaplan Meier survival curves for each variable.[115] All relevant risk factors available to us were first included in a "saturated" Cox model, before backwards elimination using an alpha level of 0.1 as threshold was done, with the 10 strongest predictors remaining. The discriminative ability of the model was assessed with Harrell's C statistic.[116] Bootstrapping using 1000 samples was performed to produce 95% confidence intervals. A risk prediction score was produced by adding rounded hazard ratios (HRs), and then annualised Kaplan-Meier event rates were calculated according to an increase in integer score. The full model including 10 covariates was reduced to a simpler three-variable model, chosen on the basis of strength of association between each variable and bleeding outcomes, the variables' reliability, and availability for the practicing physician. Level of significance was set to 5%; all confidence intervals were 95%. Statistical analyses were performed using SAS V.9.4M4 (SAS Institute) and STATA V.15 (STATA Corp LLC), and SPSS V. 25 (IBM Corp. Armonk, NY).

In paper II, we aimed to make direct comparisons between NOACs for effectiveness and safety. Cox proportional hazards regression was used to select the strongest predictor variables for stroke/SE and major bleeding, used for subsequent matching of patients. As in paper I, the proportional hazards assumption was checked using Schoenfeld residuals, and by comparing the log–log transformation of the Kaplan–Meier survival curves for each variable. Propensity score matching (PSM) was performed to account for confounding by indication of therapy. Using logistic regression, the probability of a patient being prescribed a specific NOAC was calculated on the basis of the following 16 covariates; age, gender, chronic kidney disease, hypertension, diabetes, ischaemic heart disease, peripheral artery disease, heart failure, history of stroke/SE, history of bleeding-related hospitalization, anaemia, active cancer (cancer diagnosis last 12 months), chronic lower respiratory tract disease, use of cholesterol lowering drugs, use of antiplatelet drugs, and use of non-steroidal anti-inflammatory drugs during the

last 12 months. For each patient initiating a specific NOAC, initiators of another NOAC to be compared were matched 1:1 on the logit of the propensity score using calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score.[117] Three propensity score-matched sets were constructed; dabigatran-treated patients matched with rivaroxaban-treated patients, dabigatran-treated patients matched with apixaban- treated patients, and rivaroxaban-treated patients matched with apixaban- treated patients. The balance between treatment populations was assessed by investigating absolute standardized mean differences of all baseline covariates before and after the matching, using a threshold of 0.1 to indicate imbalance. Cox regression with robust sandwich estimates was utilized for evaluating the rates of stroke and bleeding in the propensity score-matched groups.[118] As the matched sets were balanced, NOAC treatment was entered as the only independent variable.[119, 120] Subgroup analyses were performed investigating the risk of stroke and major bleeding in the following subgroups; age (<75 years vs >75 years), gender, patients with a prior stroke, and patients with a prior bleeding episode. Where standard or reduced dose NOACs were analysed separately, *de novo* PSM was performed for each dose stratum. Hazard ratios (HRs) along with P-values for interaction between treatment and the specific subgroup were calculated. Three sensitivity analyses were performed for the outcomes stroke/SE and major bleeding: (i) Restricting the follow-up time to 12months; (ii) An 'intention-to-treat'-like analysis: analyses without censoring by treatment switch or discontinuation of NOACs; (iii) Comparisons between NOACs using conventional adjustment instead of PSM to avoid exclusion of non-matched patients from the analyses. Finally, as a post hoc analysis, we performed NOAC–warfarin comparisons with conventional multivariate Cox regression. Level of significance was set to 5%. We did not adjust for multiple comparisons. All confidence intervals were 95%. Statistical analyses were performed using SAS V.9.4M6 (SAS Institute, Inc.) and STATA V.16.0 (STATACorp LLC), and SPSS V. 25 (IBM Corp. Armonk, NY).

In paper III, we assessed the comparative effectiveness and safety of OACs among elderly patients ≥75 years. In contrast to propensity score matching in paper II, we performed multivariate competing risk regression according to the method of Fine and Gray,[121] to calculate subhazard ratios (SHR) evaluating the association between exposure to different OACs and outcomes, treating death as a competing risk. Based on clinical experience and by using directed acyclic graphs (DAGs), we identified confounders relating to association between exposure to OACs on both the chosen outcomes and the competing risk of death.[122] First, NOACs were compared with warfarin, and then the NOACs were compared with each other. In both cases,

separate analyses were performed for standard and reduced doses of NOACs. Standard multivariate Cox regression was used to assess the association between OAC therapy and all-cause mortality. Robust sandwich estimates were calculated.[123] The 20 variables adjusted for were NOAC dose, gender, age, year of inclusion into the study, chronic kidney disease, hypertension, diabetes, ischaemic heart disease, peripheral artery disease (PAD), heart failure, dementia, thyroid disorders, active cancer (cancer diagnosis last 12 months), chronic lower respiratory tract disease, history of stroke/SE, history of bleeding-related hospitalisation, history of anaemia, use of cholesterol lowering drugs, use of antiplatelet drugs and use of NSAIDs during the last 12 months. Finally we performed four sensitivity analyses for the outcomes stroke/SE, major bleeding and all-cause mortality: i) Allowing a longer gap-period of 90 days between the calculated end of OAC supply and a new prescription being dispensed before censoring; ii) Analysing only truly OAC naïve patients, by excluding patients with a dispensing of any anticoagulant from pharmacies during the last 5 years (12 months was used in the main analyses); iii) standardising follow-up time for all OACs to 12 months; and iv) An "intention-to-treat"-like analysis, where patients were followed despite switching or discontinuation of NOACs. Level of significance was set to 5%. Statistical analyses were performed using SAS v.9.4M7 (SAS Institute, Inc.), STATA v.16.1 (STATACorp LLC), and SPSS V. 26 (IBM Corp. Armonk, NY).

7 Summary of results

7.1 Paper I: New score for assessing bleeding risk in patients with atrial fibrillation treated with NOACs

In this first paper, we identified risk factors for bleeding among patients with AF, being new users of NOACs between January 2013 and June 2015. Among 21 248 patients starting on a NOAC, 1 257 (5.9%) patients experienced a major or CRNM bleeding. The 10 strongest risk factors for bleeding were age, male sex, hypertension, chronic kidney disease, heart failure, prior stroke/TIA, chronic obstructive pulmonary disease, history of anaemia, prior bleeding, and hospitalisation last 12 months. Entered into a bleeding risk prediction model, these 10 variables achieved a Harrell's C-statistic of 0.68 (95% CI 0.66–0.70). We simplified the prediction model by keeping only 3 strong, very reliable and easily accessible variables; **A**ge, prior **B**leeding, and **H**ospitalisation last 12 months (the ABH score). The ABH score performed well, with a C-statistic of 0.66 (95% CI 0.65–0.68). For purposes of comparison, we used our study population to calculate C-indexes for the HAS-BLED (Hypertension, Age, Stroke, Bleeding tendency/predisposition, Labile international normalised ratios, Elderly age, Drugs or alcohol excess) score,[73] the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) score,[76] and the ORBIT (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) score.[75] The HAS-BLED, ATRIA and ORBIT scores achieved C-indexes of 0.62 (95% CI 0.60–0.63), 0.66 (95% CI 0.64–0.67) and 0.66 (95% CI 0.64–0.67), respectively. We concluded that the ABH score could be a useful clinical tool for quick and easy identification of patients with elevated bleeding risk if started on a NOAC.

7.2 Paper II: Comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in atrial fibrillation: a nationwide cohort study

In this paper, we performed direct comparisons between NOACs with respect to effectiveness and safety. We included 52 476 patients with AF starting treatment with a NOAC between January 1, 2013 and December 31, 2017. Three pairwise propensity-score matched cohorts were created: dabigatran vs rivaroxaban (20 504 patients), dabigatran vs apixaban (20 826 patients), and rivaroxaban vs apixaban (27 398 patients). The matched cohorts were very well

balanced, with standardised mean differences <0.1 for all variables. The patients starting therapy with dabigatran, were younger than new users of the other drugs, they also had less comorbidity. Investigating the risk of stroke/SE, the HRs were 0.88 (95% CI 0.76–1.02) for dabigatran vs rivaroxaban, 0.88 (95% CI 0.75–1.02) for dabigatran vs apixaban, and 1.00 (95% CI 0.89–1.14) for apixaban vs rivaroxaban. For the risk of major bleeding, the HRs were 0.75 (95% CI 0.64–0.88) for dabigatran vs rivaroxaban, 1.03 (95% CI 0.85–1.24) for dabigatran vs apixaban, and 0.79 (95% CI 0.68–0.91) for apixaban vs rivaroxaban. The reduction of bleeding risk associated with dabigatran and apixaban vs rivaroxaban was consistent for CRNM bleeding, major or CRNM bleeding, and intracranial bleeding. Dabigatran and rivaroxaban were associated with a significantly higher risk of GI bleeding compared with apixaban.

The results from the sensitivity analyses (restricting follow-up time to 12 months, an 'intention-to-treat'-like analysis, and comparisons between NOACs using conventional multivariate Cox regression instead of propensity score matching) were in line with the results from the primary analyses.

In conclusion, we found no statistically significant differences in risk of stroke/SE in propensity-score matched comparisons between users of dabigatran, rivaroxaban, and apixaban. However, dabigatran and apixaban were both associated with significantly lower risk of major bleeding compared with rivaroxaban.

7.3 Paper III: Effectiveness and safety of oral anticoagulants in elderly patients with atrial fibrillation

In the third paper, we aimed to gain insight into differences in effectiveness and safety between OACs among AF patients ≥75 years. Patients in this group have the highest risk of stroke and bleeding, as well as death. To account for this, we made comparisons performing multivariate competing risk regression, treating death as a competing risk. Among 30 401 included patients, 3 857 initiated dabigatran (standard dose 931; reduced dose 2 926); 6 108 initiated rivaroxaban (standard dose 3 630; reduced dose 2 478); 13 786 initiated apixaban (standard dose 7 631; reduced dose 6 155); and 6 650 initiated warfarin. The median age was 82 years (interquartile range 78 to 86); 53.0% of the patients were female, and the mean CHA2DS2-VASC score was 4.5 (SD 1.4). Patients starting on standard doses of NOACs were on average younger than initiators of warfarin, while initiators of reduced doses of NOACs were of similar (dabigatran)

or older age (rivaroxaban and apixaban) than initiators of warfarin. The median follow-up time was 24.4 months (standard dose) and 17.8 months (reduced dose) for dabigatran, 19.0 months (standard dose) and 16.2 months (reduced dose) for rivaroxaban, 12.7 months (standard dose) and 11.6 months (reduced dose) for apixaban, and 19.9 months for warfarin.

Comparing NOACs with warfarin, we found similar risks of stroke/SE for both standard and reduced doses of NOACs, but both doses of apixaban were associated with a lower risk of major bleeding compared with warfarin (standard dose SHR 0.74, 95% CI 0.60-0.91; reduced dose SHR 0.78, 95% CI 0.64-0.96). Investigating risk of all-cause mortality, we found no significant differences between standard dose of NOACs and warfarin, but both reduced dose rivaroxaban (HR 1.42, 95% CI 1.25-1.61) and reduced dose apixaban (HR 1.38, 95% CI 1.22-1.56) were associated with significantly higher risk.

Comparing NOACs with NOACs for risk of stroke/SE, the only significant difference was seen in the comparison between reduced dose of dabigatran and reduced dose of apixaban, favouring dabigatran (SHR 0.77, 95% CI 0.60-0.98). For risk of major bleeding, there were significant differences between standard dose of apixaban and standard dose of rivaroxaban, favouring apixaban (SHR 0.76, 95% CI 0.62-0.95); and between reduced doses of both dabigatran and apixaban compared with rivaroxaban, favouring dabigatran (SHR 0.73, 95% CI 0.60-0.98) and apixaban (SHR 0.68, 95% CI 0.55-0.85). Regarding all-cause mortality, both doses of dabigatran were associated with lower risks of death than the corresponding doses of rivaroxaban, and reduced dose dabigatran with lower risk than reduced dose apixaban.

The results of the sensitivity analyses were in line with the main analyses with respect to the main outcomes stroke/SE and major bleeding. Regarding risk of all-cause death, there was greater diversity in the results of the sensitivity analyses, and because of this we understated our findings, suspecting the results to be affected by residual confounding that could not be adjusted for.

8 Discussion

Methodological considerations in relation to the studies will be discussed first, followed by a discussion of the results.

8.1 Methodological considerations

8.1.1 Study design

The three studies presented in this thesis are historical cohort studies, which identify patients exposed to a factor of interest post hoc, and 'follow up' patients for the outcome(s) in question to occur or not. This type of observational study is inexpensive and time-efficient compared with RCTs. Often observational studies are the only way of obtaining information about an exposure it would be impractical or unethical to study in an RCT (effects of exposure to tobacco smoke or asbestos, childhood trauma).[124] Also, when RCTs could very well be done but would be very expensive or difficult to perform, observational studies may provide valuable information.[125] Furthermore, multiple comparisons can be made in observational studies, and different outcomes after exposure may be investigated. Among the most important limitations of observational studies are the lack of randomisation, the fact that the information have often been registered for different purposes than what the study aims to investigate, and that the investigator has very little control over the data collection procedure. As a result, residual confounding is bound to occur.

The target population for all three studies included in this thesis was all patients with AF and an indication for oral anticoagulation, who did not have pre-existing conditions that would preclude them from using NOACs (i.e. mitral stenosis or mechanical heart valves). The study populations in each study were derived from national registries that hold information on all patients diagnosed with AF in Norwegian hospitals, and all pharmacy dispensations of warfarin or NOACs for the indication of AF. We used the 'active comparator, new user design' in all three papers.[126] The 'new user design' involves a washout period before inclusion into the study, whereby all current users or individuals having used any anticoagulant in a time period before the index date were excluded. The included patients were then followed from the first day of therapy until an event of interest occurred. By having an active comparator, the design emulates

the intervention part of an RCT, and ensures that all patients included are in fact candidates for the treatment in question. This is meant to mitigate confounders such as confounding by indication and the healthy user bias. The 'new user design' also allows assessment of events more likely to occur early in the treatment period, such as bleeding events.

In all three papers, patients were followed up '*as-treated*'. This is the observational study equivalent to a '*per-protocol*' analysis in an RCT; which involves censoring patients upon switching between OACs or discontinuation of therapy, in addition to death or end of the study period. The aim of this approach is to record only those events occurring while the patient was using the drug of interest. The estimation of the effects or consequences of one drug compared with another is then made clearer, increasing the internal validity of the study. As a part of the sensitivity analyses, we performed 'intention-to-treat' analyses in papers II and III. The patients were followed from the index day until death or the end of the study period, regardless of whether the patient actually adhered to their assigned treatment or not. This approach is biased toward the null hypothesis with respect to effect estimates measured, but will more closely resemble the situation in the real world and has greater external validity than an as-treated approach.[127, 128]

8.1.2   Validity

The validity of a study may be described as "the degree to which the inference drawn from a study is warranted when account is taken of the study methods, the representativeness of the study sample, and the nature of the population from which it is drawn."[129] The internal validity of a study is the extent to which systematic errors are minimised, or in other words, the reliability of the results. This addresses the question of whether the findings of a study are actually true for the population investigated. The findings may of course not be true for a more general, less selected population, which is described as external validity. The external validity of a study is thus the degree to which the findings of a study can be generalised and applied on a larger, broader population.[130]

In paper I, internal validity would mean that the bleeding risk factors we identified were actually true predictors of bleeding for the study population. This requires that the medical history (risk factors) had been appropriately described for the included patients, that the bleeding episodes

recorded were true, and that the statistical analyses had been performed correctly. External validity would mean that the identified predictors of bleeding are applicable to the general population. In papers II and III, internal validity would mean that the differences in effectiveness and safety observed between OACs were true for the study populations. Similarly to paper I, this would require that medical history and outcomes were correct, that the statistical methods for adjustment of confounders were adequate, and that the statistical analyses were performed correctly. External validity of papers II and III would mean that the differences found between OAC are true, and reproducible, also in other populations.

Issues and challenges associated with internal and external validity are discussed in detail in the following chapter 8.1.3.

8.1.3 Random and systematic errors

Epidemiological studies are prone to both *random error* and *systematic error*.[131] Rothman describes *random errors* as 'that part of our experience that we cannot predict',[131] but in this setting we explain them as sampling variability. An example is people checking the wrong box accidentally in a questionnaire; or relevant to this work, a physician declaring an incorrect ICD-10 diagnosis code by accident upon discharge of an AF patient from hospital. In other words, random errors are inaccuracies in the information obtainment procedure that are randomly occurring. The important thing is the randomness of the errors. If the sample population is small, the effect of random errors will be larger; and vice versa, as sample population size increases towards infinity the effect of random error will approach zero. The studies in this thesis all include populations of such sizes that the effect of random errors are minimal. Furthermore, random errors are likely to occur equally with users of all OACs and probably be of little importance when performing OAC-OAC comparisons.

A *systematic error* on the other hand, also termed 'bias', is a difference between an observed value and a true value due to all other causes than sampling variability.[132] The inverse of bias is validity, and the presence of bias implies lack of external validity, meaning that analyses of the sample population will lead to an incorrect assumption of the association between exposure and effect in the target population. In statistics, 'bias' refers to the difference between the

average measured value of an estimator and the true value of the parameter which it seeks to estimate, which may under- or overestimate the effect of the estimator.

There are three categories of systematic errors or bias; 1) selection bias, 2) information bias, and 3) confounding.[131]

8.1.3.1 Selection bias

A selection bias occurs if sample population is not representative of the population from whence it was drawn.[131] An example could be very stringent inclusion criteria in a randomised controlled trial that ensured inclusion of the least vulnerable patients with a certain disease or condition, which in turn would give a false impression of low rates of adverse events.

Registration in the NPR and the NorPD is mandatory for all hospital/specialist visits and all pharmacy dispensations in Norway; this ensures equal inclusion of patients nationwide, regardless of age, gender, comorbidity, education, resources or socioeconomic stratum, or place of residence. There would also be virtually none *lost to follow-up*, *cases with missing or incomplete data*, and no *non-response bias*.[133] However there is one important exception. Patients admitted to an institution in Norway, be it a hospital, rehabilitation centre, or nursery home, will receive drugs from the institutions' own storage, and those drugs will not be registered in the NorPD. In 2011, 38 700 Norwegian citizens lived in an institution, accounting for 0.9% of the total population at that time, and 5.9% of patients >67 years.[134] This may have resulted in *inclusion bias*. This means that the population available to us could have been on average somewhat different from the true AF population in Norway. Furthermore, patients admitted to an institution at some point after starting oral anticoagulation, would be *selectively lost to follow-up* in our as-treated analyses if the duration of their stay in the institution was long enough for them not to renew their prescriptions. They would in any case still be included in the intention-to-treat analyses.

Another possible selection bias arises from the fact that we only included patients that were diagnosed with AF in a hospital or by a specialist at some point. If a patient was diagnosed with AF and subsequently exclusively treated by their general practitioner, they would not be visible to us. Nevertheless, the vast majority of AF will at some point be examined by echocardiography by a specialist and/or treated in a hospital, as is recommended by the guidelines.[3] Additionally, investigating patients with a hospital-confirmed AF diagnosis increases the robustness of our findings.

Matching can create a bias, either individual or frequency matching, as patients may be left out of analyses, or because statistical methods utilised to control for this may be suboptimal. Overmatching happens when non-confounder variables are matched for, which may underestimate an association.[135] *Competing risks* are a known cause of selection bias; the situation when one or more competing outcomes may affect the same patient, that are mutually exclusive. One example might be that if a patient in our studies with very high risk of stroke or bleeding dies of cancer, this would preclude them from developing a stroke or bleeding. To address these issues and also to show that our results were consistent regardless of statistical approach, we did as-treated as well as intention-to-treat analyses in papers II and III. Furthermore, we performed propensity score estimation and matching in paper II, but included sensitivity analyses applying multivariate Cox regression without matching. In paper III, we performed competing risk analyses, accounting for the competing risk of death

8.1.3.2   Information bias

Information bias occurs during data collection, and may shift the estimate both towards and away from the null hypothesis.[136]

Misclassification bias happens when the procedure by which participants are identified, labelled and included in a study has flaws. This means that there is a chance that an un-exposed individual is labelled as exposed, or that a healthy person could be labelled sick. Two types of misclassification bias are described: *differential misclassification bias* and *non-differential misclassification bias*. Differential misclassification bias arises when misclassification differs between the groups being compared. As an example, in a case-control study, patients who have developed a disease may remember exposure differently from those who have not developed the same disease. Non-differential misclassification bias arises when misclassification is similar between the groups being compared. The most common biases that lead to misclassification are *detection bias* (when sensitivity and specificity of identification of cases with a specific condition is not perfect), *recall bias* (a classic differential misclassification bias, sometimes called *exposure suspicion bias* or *participant expectation bias*), and *reporting bias* (participants reporting findings or symptoms they think the researcher is interested in; called *obsequiousness bias*).

The NPR is routinely validated for completeness, by the National Service for Validation and Completeness Analyses. Results are published in annual reports, and in general the NPR has a high level of completeness.[10] Detection bias is thus very unlikely to be present, and even less

likely to vary between OACs which could interfere with comparisons. *Recall bias* and *reporting bias* will not be found in the type of registry studies presented in this thesis.

8.1.3.3   Confounding

Confounding is a distortion of the effect of an exposure on an outcome caused by a factor not directly connected to but associated with both the exposure and the outcome.[133] *Susceptibility bias* is a synonym. A confounder must a) be a cause of the disease (or a surrogate measure of a cause), b) be correlated (positively or negatively) with exposure in the study population, and c) not be affected by the exposure.[137] Confounding will result in a measured effect of exposure that is partly explained by the exposure itself and partly by the confounder. It is of utmost importance to understand the concept of confounding and identify confounders, as confounding can be mitigated at the design stage of research (by matching, adjustment or randomisation), and causal graphs may be very helpful.[138]

Figure 7 illustrates examples of confounders that need to be adjusted for, to produce a true estimation of the association between oral anticoagulation and stroke. In paper II and III we used directed acyclic graphs (DAGs),[122] to identify confounders that should be adjusted for. In paper II, confounders for the effect of exposure to OACs on the chosen outcomes, and in paper III, confounders for the effect of exposure to OACs and all-cause mortality as well as to our chosen outcomes, were used as criteria for PSM or multivariate adjustment. [122]
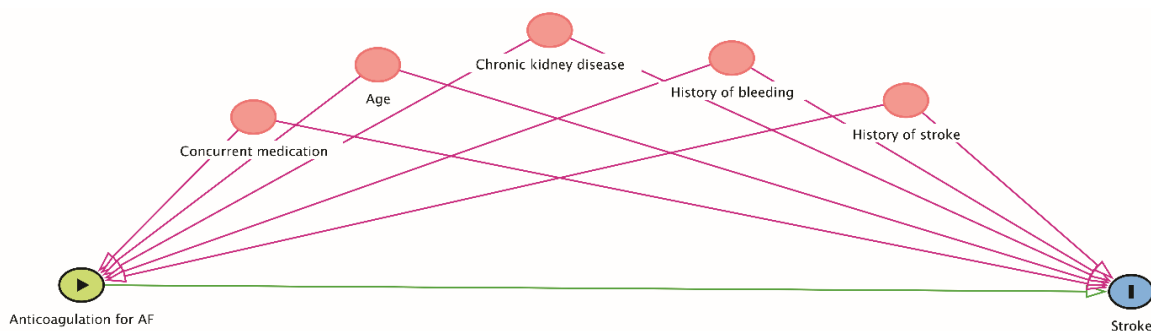
Figure 7. Directed acyclic graph (DAG) with examples of confounders modifying the association between exposure (anticoagulation for AF) and outcome (stroke). Figure produced with the R package 'dagitty'.[139]

Unfortunately, many variables of interest were not available in the Norwegian administrative health registries NPR and NorPD, such as body mass index, frailty, smoking status, socioeconomic status and more. This resulted in residual confounding. Even if we would have access to the parameters mentioned, the lack of randomisation common for all observational trials entails that some residual confounding is unavoidable.

8.2   Discussion of results

8.2.1   Derivation of a bleeding risk score

Major bleeding events are unfortunately a relatively common complication to anticoagulation, affecting between 3% and 4.5% of patients using OACs per year.[50] Identification of patients at risk of bleeding for closer monitoring and risk-factor modification could reduce the number of bleeding events per year. Unlike the case for stroke-specific risk scores, no overall benefit of withholding oral anticoagulation from patients on the basis of a high bleeding risk score has been shown. On the contrary, large observational data have shown a clear net clinical benefit from oral anticoagulation despite very high bleeding risks.[140] Also, cessation of oral anticoagulation leads to an increased risk of stroke, cardiovascular events and mortality, emphasising the importance of persistence and adherence to anticoagulation. However, looking at causes of death for patients with AF using OACs, the proportion of deaths due to bleeding events is not insignificant (around 6%).[141] This number is the same as the proportion of deaths due to ischaemic stroke. There is therefore a focus on reducing bleeding rates, and the 2020 ESC guidelines for diagnosis and management of AF recommend that clinicians use the HAS-BLED score for identification of high-risk patients in need of closer follow-up and adjustment of modifiable risk factors [3]

Despite the fact that these messages are very clearly stated in the guidelines, many AF patients with a clear indication for oral anticoagulation, do not receive such therapy. In Europe, only 72% of AF patients use OACs.[142] Reasons for abstaining may partially be explained by economic factors, but may also be influenced by fear of bleeding complications. Likewise, elevated bleeding risk often leads to discontinuation of oral anticoagulation.[143, 144]

There are currently 6 validated bleeding risk scores for use in AF patients; the HAS-BLED,[73] ATRIA,[76] ORBIT,[75] HEMORR$_2$HAGES,[74] ABC,[79] and Shireman.[78] These were derived and validated in very different patient populations, including prospective and retrospective cohorts. An example is the HAS-BLED score which was derived from the Euro Heart survey AF-population, where 64.8% of the patients were on vitamin K antagonists, and the rest received no anticoagulation,[73] and was subsequently validated in patient cohorts using NOACs.[145-147] The ATRIA bleeding risk score was derived from the ATRIA community cohort of VKA users

and later validated in the ROCKET-AF RCT population.[76] The ABC bleeding risk score was derived from the ARISTOTLE RCT population and validated in the RE-LY RCT population.[79]

To make the situation even more complex, the scores involve a multitude of variables. The only two variables they all have in common, are history of bleeding and age. Even for age, the cut-off for what is considered old enough to pose a risk varies between 50 years (ABC-score), 65 years (HAS-BLED), >70 years (Shireman), and >75 for ATRIA, ORBIT and HEMORR$_2$HAGES.

Predicting bleeding events is difficult, and all the risk scores mentioned have only moderate predictive abilities. In 2018, a registry-based study investigating the predictive abilities of the ATRIA, ORBIT and HAS-BLED scores found C-statistics for ATRIA of 0.59 (95% CI 0.57 to 0.60), HAS-BLED 0.58 (95% CI 0.57 to 0.59) and ORBIT 0.61 (95% CI 0.59 to 0.62). [82] These results are disappointing considering the fact that flipping a coin would produce a C-statistic of 0.5. The lack of precision might be one of the reasons why withholding oral anticoagulation on the basis of an elevated bleeding risk score has not been shown beneficial.

A systematic review published in 2018 of 38 studies investigating bleeding risk and compared the performance of the ATRIA, HEMORR$_2$HAGES, ABC and HAS-BLED scores, found that the HAS-BLED score had the best predictive ability for major bleeding events, but with a modest strength of evidence.[148] The recommendation in the 2020 ESC AF guidelines to utilise the HAS-BLED score is based on this assumption.

In a 2020 critical appraisal of stroke and bleeding risk stratification in AF, the authors emphasised the importance of simplicity and availability bedside for risk stratification tools, and urge to a shift toward focus on the dynamic nature of risk.[149] Repeated bleeding risk assessments and calculation of the 'delta HAS-BLED score' has been shown to increase accuracy of risk prediction compared with the baseline HAS-BLED score or identification of modifiable risk factors.[150] The ABH-score proposed in paper I is simpler than all the mentioned existing scores, and can very easily be calculated bedside, without the need for laboratory tests or imaging. Furthermore, the ABH-score contains no modifiable risk factors. It consists of unambiguous risk factors without any grading or degree of severity, leaving no room for misinterpretation. The variable "age" changes very slowly. The variables "history of bleeding" and "hospitalisaton" would raise a flag for careful review of risk factors if a bleeding or hospitalisation occurred. The hospitalisation-variable also serves as a surrogate marker for comorbidities and polypharmacy. Thus, by using the ABH score, physicians could very easily

perform repeated bleeding risk assessments, and closer investigate possibilities of risk factor modification among those at elevated risk. If validated and subsequently implemented in clinical practice, the ABH score could contribute to increased physician confidence in starting OAC and maintain persistence in their patients, as well as contribute to reduced bleeding rates.

8.2.2   Comparison of NOACs for effectiveness and safety in AF

Clinical trials and recent meta-analyses have shown that NOACs are at least as effective as warfarin in stroke prevention and are associated with a similar or reduced risk of bleeding.[6, 8, 9, 151, 152] During the last 10 years, a steadily increasing proportion of AF patients have started oral anticoagulation with a NOAC instead of warfarin,[153] and information about the differences between each of the four NOACs on the market is needed. Randomised trials comparing individual NOACs with each other are lacking. Due to the paucity of NOAC vs NOAC RCTs, the existing knowledge of the effectiveness and safety of each NOAC comes from observational trials.

When we planned the study described in paper II in the fall of 2016, very few observational studies on this topic had been published.[154-159] Of these, the majority were based on data from single hospitals or insurance databases, and only one was a nationwide study, but still included very few patients.[155]

In the following years, several observational trials making NOAC-NOAC comparisons have been published. We performed a systematic literature review by a search in Medline (access through Pubmed) and EMBase with strings combining atrial fibrillation, NOACs, and comparisons, on 1 June 2021. We narrowed the search to the time period between 2009 (after the introduction of the first NOAC on the market) and 2021, and to papers written in English (details of the search string used may be found in the Supplementary material). The search resulted in 1 925 unique articles, of which 41 articles included NOAC-NOAC comparisons for effectiveness and safety, excluding studies focusing on subgroups of AF-patients, studies making indirect comparisons, systematic reviews and meta-analyses. Table 5 lists the 41 studies by date of publication, showing author, country, study period, NOACs compared, number of patients included for each drug, and main results summarised.

Table 5. Studies comparing NOAC-NOAC comparisons for effectiveness and safety

Author, year	Country	Study design	Data Source	Study period	Comparison		N	Results
Deitelzweig et al.[156] 2016	USA	Retrospective cohort	Premier Hospital Database	2012 - 2014	R vs A D vs A	R: A: D:	37 754 4 138 32 838	Lower rates of bleeding with apixaban compared with rivaroxaban. Rates of stroke not investigated
			Cerner Health Facts Hospital Database	2012 - 2014	R vs A D vs A	R: A: D:	6 635 1 813 5 753	
Al-Khalili et al.[154] 2016	Sweden	Retrospective cohort	Stockholm Heart Center	2011 - 2015	R vs D R vs A A vs D	R: A: D:	282 251 233	Lower rates of major and minor bleeding events with dabigatran and apixaban compared with rivaroxaban. Rates of stroke not investigated
Chan et al.[155] 2016	China	Retrospective cohort	Taiwan National Health Insurance research Database	2013	R vs D	R: D:	3 916 5 921	No difference in rates of stroke. Lower rates of noncritical GI bleeding with dabigatran compared with rivaroxaban.
Noseworthy et al.[159] 2016	USA	Retrospective cohort	Optum Labs Data Warehouse	2010 - 2015	R vs D R vs A A vs D	R: D: R: A: A: D:	15 787 15 787 6 565 6 565 6 542 6 542	No differences in rates of stroke/SE. Lower rates of major bleeding with apixaban compared with dabigatran and rivaroxaban. Lower rates of ICH with dabigatran compared with rivaroxaban
Lip et al.[158] 2016	USA	Retrospective cohort	Truven MarketScan Commercial and Medicare supplemental US claims database	2013 - 2014	R vs D R vs A A vs D	R: D: R: A: A: D:	4 657 4 657 7 399 7 399 4 407 4 407	Lower rates of major bleeding with apixaban compared with rivaroxaban. Rates of stroke not investigated
Graham et al.[157] 2016	USA	Retrospective cohort	Medicare databases	2011 - 2014	R vs D	R: D:	66 651 52 240	No significant difference in rates of ischaemic stroke. Lower rates of ICH and major extracranial bleeding with dabigatran compared with rivaroxaban
Gorst-Rasmussen et al.[160] 2016	Denmark	Retrospective cohort	Danish National Prescription Registry, Danish National Patient Register, and Danish Civil Registration System	2012 - 2014	R vs D	R: D:	2 405 8 908	No significant difference in rates of stroke/SE. Lower rates of bleeding and all-cause mortality with dabigatran compared with rivaroxaban
Lamberts et al.[161] 2017	Denmark		Danish National Prescription Registry, Danish National Patient Register, and Danish Civil Registration System	2011 - 2015	R vs A D vs A	R: A: D:	6 715 7 963 15 413	Lower rates of major bleeding with apixaban compared with dabigatran and rivaroxaban. Stroke/SE not investigated
Hernandez and Zhang[162] 2017	USA	Retrospective cohort	Medicare Part D data from Centers of Medicare and Medicaid Services	2010 - 2013	R vs D	R: D:	9 303 9 138	No difference in rates of ischaemic stroke, Lower rates of thromboembolic events, bleeding events and death with dabigatran compared with rivaroxaban
Li et al.[163] 2017	China	Retrospective cohort	Hospital-based AF registry in Queen Mary Hospital, Hong Kong	2008 - 2014	R vs D	R: D:	669 467	Lower rates of ischaemic stroke with dabigatran compared with rivaroxaban. No difference

								in rates of haemorrhagic stroke
Lai et al.[164] 2017	China	Retrospective cohort	National Health Insurance claims database in Taiwan	2012 - 2014	R vs D	R: D:	4 609 10 625	No difference in risk of stroke/SE or bleeding. Lower rates of death with dabigatran compared with rivaroxaban
Dietelzweig et al.[165] 2017	USA	Retrospective cohort	Humana Research Database (Medicare coverage)	2013 - 2015	R vs A D vs A	R: A: D: A:	6 810 6 810 2 327 2 327	Lower rates of ischaemic (not haemorrhagic) stroke, and major bleeding with apixaban compared with rivaroxaban. No difference in rates of stroke or bleeding between dabigatran and apixaban
Adeboyeje et al.[166] 2017	USA	Retrospective cohort	HealthCore Integrated Research Environment (HIRE) database	2010 - 2015	R vs D R vs A A vs D	R: A: D:	8 398 3 689 8 539	Lower rates of major bleeding with apixaban compared with rivaroxaban. Lower rates of ICH with dabigatran compared with rivaroxaban and apixaban. Rates of stroke not investigated
Lin et al.[167] 2017	USA	Retrospective cohort	IMS Pharmetrics Plus database	2013 - 2015	R vs A A vs D	R: A: A: D:	4 062 4 062 2 684 2 684	Lower rates of major bleeding with apixaban compared with rivaroxaban. No difference in bleeding rate between dabigatran and apixaban. Stroke/SE not investigated
Norby et al.[168] 2017	USA	Retrospective cohort	Truven MarketScan Commercial and Medicare supplemental US claims database	2010 - 2014	R vs D	R: D:	16 957 16 957	No difference in rates of ischaemic stroke. Lower rates of GI bleeding with dabigatran compared with rivaroxaban
Hernandez et al.[169] 2017	USA	Retrospective cohort	Medicare databases	2013 - 2014	R vs D R vs A A vs D	R: A: D:	5 139 2 358 1 415	No difference in rates of stroke. Lower rates of any bleeding with dabigatran and apixaban compared with rivaroxaban
Staerk et al.[170] 2018	Denmark	Retrospective cohort	Danish National Prescription Registry, Danish National Patient Register, and Danish Civil Registration System	2012 - 2016	R vs D R vs A A vs D	R: D: A:	8 966 11 492 11 064	No differences in rates of stroke/SE. Lower rates of major bleeding with dabigatran and apixaban compared with rivaroxaban; lower rates of ICH with dabigatran compared with rivaroxaban and apixaban
Charlton et al.[171] 2018	USA	Retrospective cohort	HealthCore Integrated Research Environment (HIRE) database	2010 - 2014	R vs D	R: D:	256 442	No difference in 30- and 90-day mortality. Stroke/SE and bleeding not investigated
Brisaoulis et al.[172] 2018	USA	Retrospective cohort	Centers for Medicare & Medicaid Services	2010 - 2013	R vs D	R: D:	14 257 13 522	No difference in rates of stroke. Lower rates of any, GI-related and non-GI related bleeding with dabigatran compared with rivaroxaban
Vinogradova et al.[173] 2018	UK	Retrospective cohort	QResearch and Clinical Practice Research Datalink (CPRD) databases	2011 - 2016	D vs A R vs A	R: A: D:	37 863 18 223 7 744	No difference in rates of ischaemic stroke. Lower rates of ICH, with apixaban compared with rivaroxaban. Lower rates of major bleeding with apixaban compared with dabigatran and rivaroxaban
Mentias et al.[174] 2018	USA	Retrospective cohort	Medicare databases	2010 - 2013	R vs D	R: D:	23 177 21 979	No difference in rates of ischaemic stroke. Lower

							rates of major bleeding with dabigatran compared with rivaroxaban
Andersson et al.[175] 2018	Denmark	Retrospective cohort	Danish National Prescription Registry, Danish National Patient Register, and Danish Civil Registration System	2013 - 2016	R vs A D vs A R vs D	R: 3 676 A: 3 676 D: 3 235 A: 3 235 R: 2 720 D: 2 720	No significant differences in rates of stroke/SE or major bleeding
Tepper et al.[176] 2018	USA	Retrospective cohort	Truven MarketScan Commercial Claims and Encounter and Medicare Supplemental US claims database	2013 - 2014	D vs A R vs A	R: 30 529 A: 8 785 D: 20 963	Lower rates of bleeding with apixaban compared with rivaroxaban. Rates of stroke not investigated
Gupta et al.[177] 2018	USA	Retrospective cohort	US Department of Defence Military Health System	2012 - 2015	R vs A A vs D	R: 11 284 A: 11 284 A: 4 129 D: 4 129	Lower rates of stroke/SE and major bleeding with apixaban compared with rivaroxaban. No difference in rates of stroke/SE but lower rates of major bleeding with apixaban compared with dabigatran
Lip et al.[178] 2018	USA	Retrospective cohort	Centers for Medicare and Medicaid Services Medicare data and 4 US commercial claims databases	2013 - 2015	R vs D R vs A A vs D	R: 37 693 D: 37 693 R: 107 236 A: 107 236 A: 37 314 D: 37 314	Lower rates of stroke/SE and major bleeding with apixaban compared with dabigatran and rivaroxaban. Lower risk of major bleeding with dabigatran compared with rivaroxaban
Cerdá et al.[179] 2019	Spain	Prospective cohort	Oral Anticoagulant Treatment Unit of the Haemostasis and Thrombosis Department, Vall d'Hebron University Hospital, Spain	2015 - 2017	R vs D R vs A A vs D	R: 663 A: 352 D: 325	No difference in rates of stroke. Lower rates of major bleeding with rivaroxaban compared with dabigatran and apixaban
Meng et al.[180] 2019	China	Retrospective cohort	National Health Insurance claims database in Taiwan	2012 - 2015	R vs D	R: 6 551 D: 13 505	No difference in rates of stroke or bleeding. Lower rates of death with dabigatran compared with rivaroxaban
Mueller et al.[181] 2019	Scotland	Retrospective cohort	Scottish Prescribing Information System, Scottish Morbidity Records and National Records of Scotland	2011 - 2015	R vs D R vs A A vs D	R: 7 265 A: 6 200 D: 1 112	No difference in rates of stroke/SE. Lower rates of bleeding and death with dabigatran and apixaban compared with rivaroxaban
Villines et al.[182] 2019	USA	Retrospective cohort	US Department of Defence Military Health System	2011 - 2016	R vs D A vs D	R: 12 763 D: 12 763 A: 4 802 D: 4 802	No difference in rates of stroke/SE and major bleeding between dabigatran and apixaban. Lower rates of major bleeding with dabigatran compared with rivaroxaban
Lee et al.[183] 2019	Korea	Retrospective cohort	Korean Health Insurance Review service	2014 - 2016	R vs E	R: 12 369 E: 4 123	No significant differences in rates of stroke/SE, bleeding or death.
Graham et al.[184] 2019	USA	Retrospective cohort	Medicare databases	2010 - 2015	R vs D R vs A A vs D	R: 106 389 A: 73 039 D: 86 198	No significant difference in rates of ischaemic stroke. Lower rates of extracranial major bleeding and death for dabigatran and apixaban compared with rivaroxaban. Lower rates of ICH with dabigatran

								compared with rivaroxaban
Blin et al.[185] 2019	France	Retrospective cohort	French nationwide claims and hospitalisation database, Système National des Données de Santé	2013 - 2015	R vs D (Std.) R vs D (Red.)	R: D: R: D:	8 290 8 290 7 639 7 639	No difference in rates of stroke but lower rates of CRNM and major bleeding with standard doses of dabigatran compared with rivaroxaban. Lower rates of CRNM and major bleeding, and stroke/SE with reduced doses of dabigatran compared with rivaroxaban
Lee et al.[186] 2019	Korea	Retrospective cohort	Korean Health Insurance Review service	2015 - 2017	R vs D R vs A E vs R A vs D E vs D E vs A	R: A: D: E:	35 965 22 177 17 745 15 496	Lower rates of ischaemic stroke with apixaban and edoxaban than dabigatran and rivaroxaban. Lower rates of major bleeding with dabigatran, apixaban and edoxaban compared with rivaroxaban
Chan et al.[187] 2019	China	Retrospective cohort	Taiwan National Health Insurance research Database		R vs D R vs A E vs R A vs D E vs D E vs A	R: A: D: E:	33 022 9 952 22 371 4 577	No difference in rates of stroke. Lower rates of bleeding with apixaban compared with dabigatran and rivaroxaban. No difference in rate of bleeding with edoxaban compared with apixaban
Jansson et al.[188] 2020	Sweden	Retrospective cohort	Swedish anticoagulation quality registry Auricula	2013 - 2015	R vs D R vs A A vs D	R: A: D:	7 897 11 493 6 453	No differences in rates of stroke. Lower rates of major bleeding with standard doses of dabigatran and apixaban compared with rivaroxaban. Lower rates of major bleeding with reduced dose apixaban compared with dabigatran and rivaroxaban. Lower rates of death with dabigatran compared with apixaban and rivaroxaban
Rutherford et al.[189] 2020	Norway	Retrospective cohort	Norwegian Patient Registry and Norwegian Prescription Database	2013 - 2017	R vs D R vs A A vs D	R: D: R: A: A: D:	10 252 10 252 13 699 13 699 10 413 10 413	No differences in rates of stroke/SE. Lower risk of major bleeding with dabigatran and apixaban compared with rivaroxaban
Fralick et al.[190] 2020	USA	Retrospective cohort	Medicare databases	2012 - 2019	R vs A	R: A:	40 706 59 172	Lower rates of stroke/SE and bleeding events with apixaban compared with rivaroxaban
Bonde et al.[191] 2020	Denmark	Retrospective cohort	Danish National Prescription Registry, Danish National Patient Register, and Danish Civil Registration System	2014 - 2017	R vs A	R: A:	2 895 3 369	Lower rates of major bleeding with apixaban compared with rivaroxaban. No significant differences in associated risk of stroke or death.
Amin et al.[192] 2020	USA	Retrospective cohort	Centers for Medicare & Medicaid Services	2012 - 2014	R vs A D vs A	R: A: D: A:	38 820 38 820 20 790 20 790	Lower rates of ischaemic (not haemorrhagic) stroke and major bleeding with apixaban compared with dabigatran. Lower rates of haemorrhagic (not ischaemic) stroke and major bleeding with apixaban compared with rivaroxaban

Durand et al.[193] 2021	Canada, USA, UK	Retrospective multicentre matched cohort	7 Canadian administrative healthcare databases, the IBM MarketScan Database (USA), and the Clinical Practice Research Datalink (CPRD, UK).	2009 - 2017	R vs D R vs A A vs D	R: 92 881 A: 61 284 D: 73 414	Lower rates of stroke/SE with apixaban compared with rivaroxaban. Lower rates of major bleeding with dabigatran and apixaban compared with rivaroxaban. Lower rates of death with dabigatran compared with rivaroxaban
Perreault et al.[194] 2021	Canada	Retrospective cohort	Administrative databases of hospital discharges (Med-Echo) and drug plans from the Régie de l'Assurance Maladie du Quebec (RAMQ)	2011 - 2017	R vs A	R: 4 632 A: 6 771	Lower rates of stroke/SE, bleeding and death with apixaban compared with rivaroxaban

A, apixaban; D, dabigatran; E, edoxaban; R, rivaroxaban; ICH, intracranial haemorrhage; SE, systemic embolism

As shown in the table, not all studies included all available NOACs, or compared all of them. To summarise the findings; of the 41 studies, 33 of them investigated risk of stroke, 40 studies investigated risk of bleeding, and 9 studies investigated risk of death. Significant differences in rates of stroke were found in 10 studies; 8 of them favouring apixaban, 2 favouring dabigatran, and 1 favouring edoxaban, over rivaroxaban. Furthermore, there were 2 studies favouring apixaban over dabigatran, and one favouring edoxaban over dabigatran.

Significant differences in bleeding rates were found in 35 studies; lower rates of bleeding were found with dabigatran compared with rivaroxaban in 18 studies, for apixaban compared with rivaroxaban in 25 studies, and for edoxaban compared with rivaroxaban in 1 study. In 7 of the 9 studies investigating risk of all-cause death dabigatran was associated with lower rates than rivaroxaban. Overall, the NOACs seem to perform comparably in terms of effectiveness, but dabigatran and apixaban (and perhaps edoxaban though not as thoroughly studied) seem to perform better than rivaroxaban in terms of safety. There is so far limited information from observational trials regarding edoxaban, which will most likely be included to a much larger degree in future studies.

Two recent meta-analyses, both published in April 2021, have investigated the comparative effectiveness and safety of NOACs in AF.[195, 196] The meta-analyses included many of the studies listed in table 5, but not all, and showed no differences in risk of stroke between dabigatran, rivaroxaban and apixaban; while the risk of major bleeding was lower with dabigatran and apixaban compared with rivaroxaban; as well as with apixaban compared with dabigatran.

Despite all these observational NOAC-NOAC comparisons published during the last few years, still, at the time of its publication, paper II of this thesis was one of the first and largest studies published that involved direct comparisons of dabigatran, rivaroxaban and apixaban as the main analyses. Furthermore, our study included patients from population-based nationwide registries in contrast to most previous studies having included patients from claim databases only. Among other strengths of paper II was longer follow-up periods compared to other similar studies published at that time.[175, 178] In line with most publications, we found no significant differences in effectiveness between NOACs, but significant differences in risk of major bleeding, with dabigatran and apixaban being associated with lower risk of bleeding than rivaroxaban.

There are many weaknesses inherent in observational trials; lack of randomisation and thus inevitable residual confounding being the most important one. Another important weakness is selection bias. In the Nordic countries, Canada and in Taiwan, national administrative health registries offer the chance of studying nation-wide cohorts, resulting in very little selection bias other than differences in availability of healthcare between countries, as well as the characteristics of each country and its population. Studies using insurance claims databases on the other hand, commonly studied in the United States, require each study participant to be eligible for insurance throughout the study period, it requires the participant to actually use that insurance arrangement and not another private insurance company, and will purely be based on billing codes more relevant to insurance matters than their medical importance. Hence, studies based on insurance claims databases will systematically exclude all non-insured patients, and all patients choosing different or alternate insurance arrangements (private, work-related, government funded). Similarly, observational studies based on registries from specific hospitals will be influenced by the patient demographics characteristic of that hospital. This is important to consider when interpreting the results.

Despite the substantial amount of evidence that has been published after approval of NOACs for stroke prevention in AF, the guidelines' recommendation of choosing NOACs over warfarin is non-differentiated. The 2020 ESC guidelines for diagnosis and management of AF state that "NOAC therapy should be optimized based on the efficacy and safety profile of each NOAC in different patient subgroups".[3] It seems prudent to trust observational data at least to the degree of recommending dabigatran or apixaban over rivaroxaban for patients with elevated bleeding risk. Drug-drug interactions may play a role in the decision, as could dosing regimen. Some

patients would prefer edoxaban or rivaroxaban over dabigatran or apixaban because of the once-daily dosing.

8.2.3 Effectiveness and safety of oral anticoagulants in elderly AF patients

Oral anticoagulation in the elderly population is particularly challenging, as the risk of all complications increases with age. There is a substantially higher risk of both stroke and bleeding in elderly compared with younger patients with AF.[197] Of various reasons, oral anticoagulation is underused in elderly patients.[198] Furthermore, elderly patients who are treated with NOACs, are more likely to be underdosed.[199] Despite the elevated bleeding risk, there is clear evidence for a net clinical benefit of oral anticoagulation also in the elderly, and the ESC guidelines for diagnosis and management of AF suggest no age restrictions in the recommendations for anticoagulation.[3]

The available evidence regarding efficacy and safety of NOACs in elderly patients is limited by relatively few elderly patients being included in the pivotal RCTs comparing NOAC with warfarin.[6, 8, 9] Nevertheless, subgroup analyses of the RCTs showed that the benefits of NOACs over warfarin in the general AF-population were consistent for all age groups including elderly patients.[93, 94, 96, 200] From the RE-LY trial,[6] which included 7 258 (40%) patients ≥75 years, subgroup analyses showed that efficacy compared to warfarin was maintained in the elderly population. The findings regarding safety of dabigatran among the elderly were more mixed; the risk of extracranial major bleeding was lower among younger patients, but not among patients ≥75 years. However, the risk of intracranial bleeding was significantly lower with dabigatran compared to warfarin across all age groups and for both doses.[96] In the ROCKET-AF trial,[9] 6 229 (44%) patients ≥75 years were included. Similar to the RE-LY trial, subgroup analyses showed a consistency in the efficacy of rivaroxaban compared with warfarin, but a higher risk of major or clinically relevant non-major bleeding among the elderly.[93] In the ARISTOTLE trial,[8] subgroup analyses of the 5 678 (31%) patients ≥75 years showed that the lower risk of stroke/SE as well as major bleeding with apixaban compared to warfarin was maintained across all age groups.[94]

The elderly patients that were included in the RCTs, were quite selected and had a lower mean age and less comorbidities than elderly AF patients in clinical practice. With higher age and more comorbidities, the efficacy and safety profiles might change. In order to get more

information on the effectiveness and safety of OAC in the real-world, we performed NOAC-warfarin as well as NOAC-NOAC comparisons in patients ≥75 years, using data obtained from the nationwide registries in Norway (paper III of this thesis). In line with the RTCs, in paper III we found similar risks of stroke/SE for both standard and reduced doses of NOACs compared to warfarin, and that the risk of major bleeding was significantly lower with both doses of apixaban compared to warfarin.

Observational trials have added to the available evidence from RCTs showing similar results.[178, 201-203] Regarding NOAC-NOAC comparisons in the elderly, a recent meta-analysis including 22 studies with more than 440 000 patients ≥75 years, made indirect comparisons between NOACs according to the Bucher method and found no significant differences between NOACs regarding effectiveness, but significant differences regarding safety.[204] There were lower rates of major bleeding with apixaban and edoxaban than rivaroxaban; and also lower major bleeding rates with apixaban compared with dabigatran. Of note, when compared with vitamin K antagonists, both dabigatran and edoxaban were associated with significantly lower risks of intracranial haemorrhage (ICH); a devastating complication to anticoagulation which more than doubles in incidence in the older compared to the younger AF-population.[93, 94, 96] In line with this, in paper III of this thesis, dabigatran was the NOAC with the greatest relative reduction in rate of ICH compared with warfarin.

Finally, it should be noted that the incidence rates of major bleeding were quite high in patients ≥75 years, between 2.0% and 3.5% per year. These high rates should capture the attention of all physicians treating AF patients, urging them to apply their best judgement and utilise the evidence available to choose the safest, and at the same time most efficient therapy.

8.3   Strengths and limitations

Inclusion of data into the nationwide registries is mandatory in Norway; this reduces selection bias, participation and recall bias. The large population size increases the robustness of the findings, especially regarding complications to treatment and adverse events, but will not eliminate systematic errors. Examples of systematic errors in this thesis are the fact that we did not have access to drug use for patients admitted to an institution; we had no way of controlling patient compliance, and the outcomes were not adjudicated. In more general terms, the

advantages of nationwide registries are summarized in a recent position document from the European Heart Rhythm Association.[205]

The patients included in RCTs are usually rigorously selected, closely followed up, and outcomes are adjudicated. But often, important or relevant patient groups are systematically excluded from RCTs creating false impressions of low rates of adverse events or side effects of treatment. As a result of this, event rates reported are generally higher in observational trials than RCTs.[6, 8, 9, 105, 206] In contrast to RCTs which study treatments under ideal conditions, observational trials evaluate treatments in the real world. In our opinion, this is a strength of the studies included in this thesis.

In paper I, we investigated risk factors for bleeding and developed a bleeding risk estimation scheme. It is crucial that the risk factors evaluated, their prevalence and distribution be as close to reality as possible. In this sense a large scale observational trial is ideal, as random errors will play a much less important role.

Unfortunately, in all three papers there were relevant variables that we did not have access to, such as body weight, creatinine clearance, income and smoking status. As a result of this we might have missed important bleeding predictors (paper I), and had no way of controlling appropriateness of NOAC dosage (papers II and III).

In papers II and III we investigated the comparative effectiveness and safety of OACs compared with each other. We showed differences between OACs that could very likely be larger than what would be seen, had the patients been randomised. Although we attempted to adjust for differences in patient characteristics between therapy groups, residual confounding is bound to be present. Nonetheless the results of extensive sensitivity analyses were consistently in line with the main results, which strengthens our findings.

The studies included in this thesis did not include edoxaban, due to a limited number of users in the study periods. In a recent observational study from Germany comparing AF patients using NOACs with patients using the VKA phenprocoumon, a total of 837 430 patients were included, of whom 14 666 used edoxaban.[207] The study showed that compared with phenprocoumon, dabigatran, rivaroxaban and apixaban, but not edoxaban were associated with a higher risk of stroke. Furthermore, the risk of major bleeding was lower with dabigatran, apixaban and edoxaban, but not for rivaroxaban. Future studies will undoubtedly shed more light on the safety and effectiveness of edoxaban compared with the other NOACs.

9 Conclusions

In this study of effectiveness and safety of OACs in Norwegian patients with atrial fibrillation in the time period 2013 to 2017, we conclude that:

I. Age, male sex, hypertension, chronic kidney disease, heart failure, prior stroke/TIA, chronic obstructive pulmonary disease, history of anaemia, prior bleeding, and hospitalisation last 12 months were independent predictors of bleeding for AF patients starting treatment with a NOAC.

II. The simplified ABH-score (age, prior bleeding, and hospitalisation within the last 12 months) performed comparably to the full 10-variable score and previously published bleeding scores.

III. In a population-based nationwide cohort of OAC-treated AF patients, NOAC vs NOAC comparisons showed no statistically significant differences in the rates of stroke/SE between patients treated with dabigatran, rivaroxaban or apixaban. Dabigatran and apixaban were associated with significantly lower rates of major bleeding, each compared with rivaroxaban.

IV. In the subgroup of AF patients ≥75 years initiating OAC, the NOACs dabigatran, rivaroxaban and apixaban were associated with similar risks of stroke/SE as warfarin, and lower (apixaban) or similar (dabigatran, rivaroxaban) risks of major bleeding. The NOACs seem to be a safe option also in patients ≥75 years.

10 Clinical implications, future directions

At the time of publication of this thesis, NOACs are regarded as one homogenous group of drugs that have gained collective status as "preferred over warfarin for stroke prevention in AF". The three studies included in this thesis have added to the existing knowledge of bleeding risk factors specific for NOACs, as well as insights into possible significant differences in efficacy and safety of NOACs. The steadily growing body of evidence, mainly from observational trials, clearly pointing toward significant differences in safety of OACs will probably at some point be practice-changing. In accordance with other observational studies, we have shown that different NOACs were associated with significant differences in rates of bleeding events in a real world setting. We also showed that the NOACs seem to be a safe alternative to warfarin among the higher risk elderly AF patients, and found significant differences among individual NOACs in this group of patients. Dabigatran, apixaban and edoxaban might become the preferred drugs for stroke prevention in AF, owing to the lower risk of bleeding associated with these drugs.

To achieve the important goal of increasing the number of patients with AF treated with oral anticoagulation, a good first step would be to increase physician confidence in recommending treatment, as well as the patients' feeling of security when taking an OAC. The AHB bleeding risk score could potentially play a part in this process, if externally validated and implemented into clinical practice. By making risk stratification with respect to bleeding easy to perform and to repeat anywhere, it has the potential to be a very practical and robust tool.

 The results from observational trials are traditionally used for hypothesis generation only. A properly designed RCT comparing NOACs with NOACs is needed to assess the possible differences in efficacy and safety between NOACS in a sound way, but may very well never be done. Probably, we will have to rely on observational data for this assessment also in the future, but they could perhaps be strengthened by a more rigorous methodology. Using the framework described by sir Austin Bradford Hill in 1965,[208] the modified Hill criteria might be helpful. The criteria *strength of association*, *consistency of association*, *biological gradient, biological plausibility, and experimental evidence* were elegantly used by Leong and collaborators to judge whether the increased all-cause mortality observed among patients with atrial fibrillation was due to AF itself or was merely associated with AF, driven by comorbidity.[209]

This same approach could be used to assess the reliability of observed differences between OACs shown in this thesis, and perhaps even further strengthened by the relatively new technique of registry-based randomised controlled trials (RRCTs).[210, 211] By adding a randomisation module to existing registries, RRCTs mimic a conventional randomised controlled trial but may be done a lot faster with significantly lower cost. Good examples of RRCTs in modern cardiovascular research are the landmark studies Thrombus Aspiration during ST-Segment-Elevation Myocardial Infarction (TASTE),[212] and SAFE-PCI for Women.[213] Although there are unresolved issues or challenges with this new method that need clarification (e.g. clear definitions of what constitutes an RRCT, requirements of data quality, ethical considerations), RRCTs may represent a way to circumvent the problem of paucity in NOAC versus NOAC RCTs.

11 Synopsis in Norwegian

Den vanligste hjerterytmeforstyrrelsen, atrieflimmer (AF), medfører en gjennomsnittlig femdobling i risiko for hjerneslag. Bruk av perorale antikoagulasjonsmidler kan redusere risiko for hjerneslag med omtrent to tredjedeler og er i kraft av dette det viktigste elementet i behandlingen av AF. Samtidig medfører antikoagulasjon forhøyet risiko for blødning. Insidensen av alvorlige blødninger hos pasienter med AF som bruker antikoagulasjonsmidler, er mellom 3% og 4.5% per år. Således er det svært viktig å balansere effekt og sikkerhet ved bruk av perorale antikoagulasjonsmidler.

Siden 2009 har non-vitamin K antagonist orale antikoagulantia, forkortet 'NOAK', i stor grad erstattet konvensjonell slagforebyggende terapi med warfarin.

Selv om alle de tilgjengelige NOAK (dabigatran, rivaroksaban, apiksaban og edoksaban) er vist å være like effektive og trygge som warfarin i store randomiserte kontrollerte studier, er det mange aspekter vedrørende deres bruk som er uklare eller enda ikke undersøkt. Eksempler på disse er: hvilke er de viktigste risikofaktorene for blødning hos pasienter som bruker et NOAK? Hvilken NOAK er mest effektiv? Hvilken er tryggest å bruke? Er en NOAK bedre for én gruppe pasienter, og en annen NOAK bedre for en annen gruppe?

Denne avhandlingen er basert på tre historiske kohortstudier som alle har benyttet data fra Norsk Pasientregister og Reseptregisteret. Målet med studiene har vært å identifisere risikofaktorer for blødning blant pasienter med atrieflimmer som bruker NOAK, og å sammenlikne de ulike NOAK med henblikk på effekt og sikkerhet.

I studie I var målsetningen å finne sterke risikofaktorer for blødninger hos pasienter som bruker NOAK. Vi inkluderte 21 248 pasienter med AF som startet slagforebyggende behandling med dabigatran, rivaroksaban eller apiksaban i perioden januar 2013 til juni 2015. De ti sterkeste risikofaktorene var økende alder, mannlig kjønn, høyt blodtrykk, kronisk nyresvikt, hjertesvikt, tidligere hjerneslag eller transitorisk iskemisk anfall (TIA), kronisk obstruktiv lungesykdom, tidligere anemi, tidligere blødning, og sykehusinnleggelse i løpet av de siste 12 måneder. En risikoprediksjonsmodell med alle disse 10 variablene hadde relativt god prediksjonsevne sammenliknet med andre eksisterende skåringsverktøy, med en Harrell's C-verdi på 0.68 (95% konfidensintervall (KI) 0.66–0.70). Vi forenklet modellen ved kun å beholde tre meget sikre, utvetydige variable: alder, tidligere blødning, og sykehusinnleggelse siste 12 måneder. Denne

forenklede skåren (age, bleeding, hospitalisation; forkortet 'ABH'), hadde også relativt god prediksjonsevne med en Harrell's C-verdi på 0.66 (95% KI 0.65–0.68).

I studie II gjorde vi direkte sammenlikninger og estimerte risiko for hjerneslag/systemisk embolisme (SE) eller alvorlige blødninger hos pasienter med AF som brukte NOAK. Vi inkluderte 52 476 pasienter som startet behandling i perioden 2013 til 2017, og gjorde 'propensity score matching' slik at brukere av forskjellige NOACs ble matchet på en rekke variabler, og da kunne sammenliknes direkte. I denne studien fant vi ingen signifikante forskjeller mellom de 3 NOAK i risiko for hjerneslag/SE, men at det derimot var signifikante forskjeller i blødningsrisiko mellom de forskjellige medikamentene. Dabigatran (hasardratio (HR) 0.75, 95% KI 0.64-0.88) og apiksaban (HR 0.79, 95% KI 0.68-0.91) var begge assosiert med lavere risiko for alvorlige blødninger enn rivaroksaban.

I studie III undersøkte vi undergruppen eldre pasienter ≥75 år fra studiepopulasjonen i studie II. Vi gjorde sammenlikninger ved å gjøre 'competing risk regression', hvor vi tok høyde for konkurrerende risiko for død, og undersøkte forskjeller i risiko for slag/SE og alvorlige blødninger blant pasienter som brukte warfarin, dabigatran, rivaroksaban og apiksaban. Vi inkluderte 30 401 pasienter som startet behandling mellom 2013 og 2017. Da vi sammenliknet NOAK med warfarin, fant vi ingen signifikante forskjeller i risiko for hjerneslag/SE, men både standard og redusert dose apiksaban var forbundet med lavere risiko for alvorlige blødninger. Ved direkte NOAK-NOAK sammenlikninger fant vi at standard dose apiksaban var forbundet med lavere risiko for alvorlige blødninger enn standard dose rivaroksaban.

Dersom validert og implementert i klinisk praksis kan 'ABH-skåren' potensielt bidra til sikrere bruk av antikoagulasjonsmidler ved AF, ved å gi klinikere en svært enkel måte å identifisere pasienter med forhøyet blødningsrisiko, og da vurdere om det er mulig å modifisere risikofaktorer hos disse. Funnene i studie II og III understøtter funn fra tilsvarende kohortstudier, med den konklusjon at det sannsynligvis er signifikant forskjell i blødningsrisiko mellom de perorale antikoagulasjonsmidlene som brukes ved AF. En endring i retningslinjene, slik at dabigatran og apiksaban anbefales fremfor rivaroksaban, særlig hos pasienter med forhøyet blødningsrisiko, kunne også bidra til sikrere bruk av NOAK blant pasienter med AF.

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Supplementary material for

Dissertation

Supplementary table S1

ICD-10 (International Classification of Diseases, 10th revision) and NOMESCO (Nordic Medico-Statistical Committee) codes used in definitions of co-morbidities and outcomes. Comorbidities were recognized either by ICD-10 diagnoses from hospital stays, or by a combination of hospital diagnoses and drugs dispensed. ATC (Anatomical Therapeutic Chemical system) codes from NorPD identified disease-specific drugs (e.g. anti-diabetics) and ICD-10 or International Classification for Primary Care 2 (ICPC-2) codes used as reasons for reimbursement of drugs for chronic illnesses for less specific drugs (e.g. beta blockers).

Conditions	ICD-10 code or procedure codes (NOMESCO) from NPR	ATC code or reimbursement code in NorPD
Atrial fibrillation	I48	Reimbursement code: I48 , K78 (ICPC)
Additional diagnoses to identify "valvular atrial fibrillation"	ICD10: I050, I052, I342, Z952 NOMESCO codes: FKD00, FKA, FMD00,	
Hypertension	I10, I11, I12, I13, I15	Reimbursement codes: I10-I13, I15 (ICD10) or K86, K87 (ICPC)
Chronic kidney disease	N00, N01, N02, N03, N04, N05, N06, N07, N08, N14, N15, N16, N181, N182, N183, N184, N185, N189, N19	
Ischemic heart disease	I20, I21, I22, I23, I24, I25	
Heart failure	I500, I501, I509	Reimbursement codes: I50 (ICD10) or K77 (ICPC)
Diabetes	E10, E11, E12, E13	ATC code A10A or A10B
Chronic lower respiratory tract disorders	J40 – J47	Reimbursement codes: J44 , J45 (ICD10) or R95 (ICPC
Active cancer	C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C44, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C77, C78, C79, C80, C81, C82, C83, C84, C85, C86, C88, C90, C91, C92, C93, C94, C95, C96, C97	
Thyroid disorders	Hypothyroidism: E010, E011, E012, E018, E030, E031, E032, E033, E034, E035, E038, E039 Hyperthyroidism: E050, E051, E052, E053, E054, E055, E058, E059	
Peripheral artery disease	I70, I71, I72, I73, I74, I77, I78, I79	
Inflammatory polyarthropathies	M05 – M14	
Ischaemic stroke	I630, I631, I632, I633, I634, I635, I636, I638, I639, I64	
Transient ischaemic attack (TIA)	G450, G451, G452, G453, G454, G458, G459, G46	

Conditions	ICD-10 code or procedure codes (NOMESCO) from NPR	ATC code or reimbursement code in NorPD
Ischaemic or haemorrhagic stroke	I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I612, I613, I614, I615, I616, I618, I619, I620, I621, I629, I630, I631, I632, I633, I634, I635, I636, I638, I639, I64,	
Major bleeding	K920, K921, I600-I609, I610-I619, I620-I629, I230, I312, M250, H431, H356, H313, H450, J942, K661 *Addition: A CRNM-bleeding diagnosis will be converted to a major bleeding diagnose if blood transfusion (NCMP REGG00, RXGG02) is coded within 10 days.*	
Systemic embolism	I74	
Intracranial bleeding	I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I612, I613, I614, I615, I616, I618, I619, I620, I621, I629	
Gastrointestinal bleeding	K920, K921, K922, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K228, K221, K290, K528, K625, I850	
CRNM bleeding	K922, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K228, K221, K290, K528, K625, I850, H113, R040, R041, R042, R048, R049, N836, N837, N920, N921, N922, N923, N924, N925, N926, N930, N938, N939, A985, N421, N857, N921, O721, S064, S065, S066, S068, T140, T141, T142, T143, T144, T145, T146, T147, T148, T149, D683, D698, D699, N02, R31, R58, D62	
Anaemia	D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D61, D62, D63,D64	
Alcoholism	E244, E52, G312, G621, G721, I426, K70, K860, O354, T51, Z714, Z721	
Use of NSAID		M01A
Use of antiplatelet drugs		B01A C
Use of cholesterol lowering drugs		C10A, C10B

NPR, Norwegian Patient Registry; NorPD,Norwegian Prescription Database; NCMP, Norwegian Classification of Medical Procedures; CRNM bleeding, clinically relevant non-major bleeding; NSAID, non-steroidal anti-inflammatory drug;

Supplementary table S2; ICD-codes used to calculate risk scores

CHADS2-VASC

Point	Condition	Definition
1	Heart Failure	use definition from baseline covariates (Table 1)
1	Hypertension	use definition from baseline covariates (Table 1)
1	Diabetes mellitus	use definition from baseline covariates (Table 1)
2	Stroke, TIA or systemic embolism	use definition from baseline covariates (Table 1)
1	Vascular Disease (myocardial infarction or peripheral arterial disease)	Combined definitions from baseline covariates "Ischaemic Heart Disease" , and "Vascular disease" in table 1.
1	Female gender	
1	Age 65-<75 years	
2	Age≥ 75 years	

HAS-BLED

Point	Condition	Definition
1	Hypertension	Use definition for "Hypertension" from baseline comorbidities
1	Abnormal kidney function	Use definition for "Chronic kidney disease" from baseline comorbidities
1	Abnormal liver function:	Use definition for "Liver disease" from baseline comorbidities
1	Stroke, TIA	use definition "History of stroke" from baseline comorbidities
1	Any bleeding other than haemorrhagic stroke	Use definition of Major and CRNM bleeding from baseline comorbidities, excluding codes for haemorrhagic stroke I60, I61, I690-I692
N/A	Labile INR	Not available
1	Age≥ 65 years	1 point for age 65 years or older
1	Alcohol/ Drug Therapy	Use definition of "Alcoholism" , "Use of NSAIDs last 12 months" and "Use of antiplatelet drugs last 12 months, from baseline comorbidities.

Values are numbers (percent) unless otherwise specified. TIA, transient ischaemic attack; NSAIDs, non-steroidal inti-inflammatory drugs; INR, International Normalised Ratio; CHA2DS2-VaSc, congestive heart failure (or left ventricular systolic dysfunction), hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack or systemic embolism, vascular disease, age ≥ 65 years, sex category; HAS-BLED, hypertension, abnormal renal function/ abnormal liver function, prior stroke, prior major bleeding, labile international normalised ratio (INR), elderly age ≥ 65 years, prior alcohol or drug abuse / use of medications that predispose to bleeding (antiplatelet agents, NSAIDs).

Supplementary table S2

Search strings for systematic review on 1 June 2021, for Pubmed, adapted for EMBase

	Search strings
1. NOACs	direct oral anticoagulant*[tiab] OR direct oral anti-coagulant*[tiab] OR direct oral anticoagulation[tiab] OR direct oral anti-coagulation[tiab] OR direct-acting oral anticoagulant*[tiab] OR direct-acting oral anti-coagulant*[tiab] OR direct-acting oral anticoagulation[tiab] OR direct-acting oral anti-coagulation[tiab] OR DOAC[tiab] OR novel oral anticoagulant*[tiab] OR novel oral anti-coagulant*[tiab] OR Novel oral anticoagulation[tiab] OR Novel oral anti-coagulation[tiab] OR NOAC[tiab] OR Rivaroxaban[tiab] OR Apixaban[tiab] OR Edoxaban[tiab] OR Dabigatran[tiab] OR "Non VKA Oral Anticoagulant"[tiab] OR "Non Vitamin K Antagonist Oral Anticoagulant"[tiab]
2. Comparison	comparative effectiveness research[mesh] OR comparative effectiveness[tiab] OR real-world[tiab] OR reallife[tiab] OR cohort studies[mesh] OR cohort[tiab]
3. AF	atrial fibrillation[tiab]
4. Limits	Time period 2009 - 2021, Language: English

Paper I

openheart

New score for assessing bleeding risk in patients with atrial fibrillation treated with NOACs

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ABSTRACT

Background Information is needed on bleeding risk factors specific for patients with atrial fibrillation (AF) treated with non-vitamin K oral anticoagulants (NOACs). We aimed to identify risk factors in a large real-world cohort and to derive a bleeding risk score for patients with AF treated with NOACs.

Methods From nationwide registries (the Norwegian Patient Registry and the Norwegian Prescription Database), we identified patients with AF with a first prescription of a NOAC between January 2013 and June 2015. Cox proportional-hazards analysis was used to identify the strongest risk factors for major or clinically relevant non-major (CRNM) bleeding. Based on these, a risk prediction score was derived. Discrimination was assessed with Harrel's C-index. C-indexes for the modified Hypertension, Age, Stroke, Bleeding tendency/predisposition, Labile international normalised ratios, Elderly age, Drugs or alcohol excess (HAS-BLED), the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) and the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT) scores were also calculated from the same cohort.

Results Among 21 248 NOAC-treated patients with a median follow-up time of 183 days, 1257 (5.9%) patients experienced a major or CRNM bleeding. Ten independent risk factors for bleeding were identified, which when included in a risk prediction model achieved a C-index of 0.68 (95% CI 0.66 to 0.70). A simplified score comprising three variables; age, history of bleeding and non-bleeding related hospitalisation within the last 12 months, yielded a c-index of 0.66 (95% CI 0.65 to 0.68). In the same cohort, the modified HAS-BLED, ATRIA and ORBIT scores achieved c-indexes of 0.62 (95% CI 0.60 to 0.63), 0.66 (95% CI 0.64 to 0.67) and 0.66 (95% CI 0.64 to 0.67), respectively.

Conclusions Our proposed simplified bleeding score could be a useful clinical tool for quick estimation of risk of bleeding in patients with AF treated with NOACs.

INTRODUCTION

Atrial fibrillation (AF) is associated with an overall fivefold increase in the risk of embolic stroke and a twofold increase in the risk of death.[1 2] Numerous trials and meta-analyses have concluded that oral anticoagulation (OAC) is highly effective in preventing stroke and reducing mortality in patients with AF.[3]

Key messages

What is already known about this subject?
► Oral anticoagulation (OAC) is highly effective in preventing stroke and reducing mortality in patients with atrial fibrillation.
► Non-vitamin K oral anticoagulants (NOACs) have gradually replaced vitamin K antagonists as drugs of choice. Before prescribing OAC, the doctors should determine the patients' risk of bleeding.

What does this study add?
► Several risk scores for bleeding have previously been published, but none have been derived from real-world cohorts consisting solely of patients using NOACs.
► In a large real-world cohort of patients using NOACs, we have identified strong predictors of bleeding and subsequently derived a simple risk score for bleeding, requiring no laboratory or radiological tests, and therefore being available for use by physicians anywhere.

How might this impact on clinical practice?
► This study sheds light on predictors of bleeding specific for patients using NOACs and offers the physician a tool for rapidly identifying individuals at increased risk for bleeding, being in need of closer follow-up.

Historically, dose-adjusted vitamin K antagonism (warfarin) has been the only available option, but in recent years, four non-vitamin K oral anticoagulants (NOACs) have been approved for stroke prevention in non-valvular AF (dabigatran, rivaroxaban, apixaban and edoxaban). NOACs are gradually replacing warfarin as the drugs of choice for anticoagulation in patients with AF.[4 5]

A major concern with the use of anticoagulants is the associated bleeding risk. According to a recent registry-based study of 54 321 patients with AF on OAC, 4.5% experienced a major bleeding event during an average follow-up period of 403 days.[6] In the Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In

Myocardial Infarction (ENGAGE AF–TIMI 48) trial, 579 (1.22%) of 21 105 patients developed major gastrointestinal bleedings per year.[7] It is likely that a substantial number of these bleeding events could be prevented, if patients at high risk of bleeding were identified, and preventive measures were taken prior to initiation of, or during treatment with OAC. The tools available to estimate the risk of bleeding associated with use of NOACs are limited, as most of the existing bleeding risk scores were developed in the pre-NOAC era.[8–10] Furthermore, most risk scores were developed using data from randomised trials and/or selected registries rather than from real-life cohorts. The aim of this cohort study was to identify risk factors for bleeding in a nationwide cohort of patients with AF being treated with NOACs and to derive a bleeding risk-score for patients with AF treated with NOACs.

METHODS

Data sources

The nationwide cohort used in this study has already been investigated in a previous study.[11] The cohort is based on data from two nationwide registries: the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD). The NPR was established in 2008 and holds information on all patient visits from all hospitals in Norway (emergency, inpatient and outpatient consultations), including relevant diagnoses, procedures performed and duration of stay.[12] Diagnoses are coded according to the International Classification of Diseases, 10th revision (ICD10). Medical and surgical procedures are coded according to the Nordic Medico-Statistical Committee (NOMESCO) coding system. Both primary and secondary codes related to each admission were taken into account in the analyses.

The NorPD is a registry containing information on all prescriptions dispensed at pharmacies nationwide (drugs are coded according to the Anatomical Therapeutic Chemical system, ATC).[13] The Norwegian system of general reimbursement of medicine expenses for treatment of serious and prolonged chronic illnesses requires the prescribing physician to state the relevant underlying disease for each drug. The NorPD also contains information about date of dispensation, quantity and strength of drugs dispensed and time of all-cause death.

Cohort creation and study design

All patients≥18 years diagnosed with non-valvular AF in the study period were identified from the NPR, and this dataset was then linked to the NorPD to identify all patients with AF with at least one NOAC dispensation in the study period (1 January 2013 to 30 June 2015). Non-valvular AF was defined in accordance with the 2016 European Society of Cardiology guidelines as AF in the absence of rheumatic valvular disease or mechanical heart valves.[14] Only doses recommended for stroke prevention in AF were included: apixaban 2.5 mg or 5 mg;

rivaroxaban 15 mg or 20 mg or dabigatran 110 mg or 150 mg. Edoxaban was still not approved for stroke prevention in AF in the study period and thus not included in this study. Index date was defined as the first dispensation of a NOAC in the study period. To establish an OAC naïve cohort, patients were excluded if they had been exposed to OACs in the 180 days before index date, diagnosed with deep venous thrombosis during the last 180 days before index date or having had knee-replacement or hip-replacement surgery performed within the last 35 days before the index date. For this specific study, we selected all patients from this cohort being treated with a NOAC.[11] A cohort creation chart is presented in figure 1, and the study design is presented in figure 2.

Comorbidity and medication history

The diagnoses for all hospital consultations including procedures performed were extracted from the NPR. From a prespecified list, a medication history during the preindex period, including the relevant diagnosis-specific reimbursement codes, was completed from the NorPD (see online supplementary table S1).

Oral anticoagulant supply

For each dispensation, length of OAC supply was computed using information on date of dispensation, the number of packages and the pack-size dispensed. As NOACs are prescribed in fixed doses, the number of days of supply strictly corresponds to amount dispensed. The NorPD contains information on tablet strength, pack-size and number of packages dispensed, and we assumed, according to the labelling, two times per day dosing for apixaban and dabigatran and once daily dosing for rivaroxaban. To estimate the end of OAC supply date, we accounted for incomplete adherence by allowing a gap period of 30 days after the calculated end of OAC supply. Patients were censored on discontinuation or switching of OAC, death or end of follow-up, whichever occurred first.

Bleeding complications

Bleeding episodes were identified through search for prespecified ICD10-codes in the NPR between index date and 30 days after the calculated end of OAC supply. Bleeding events were categorised as major or clinically relevant non-major (CRNM) bleeding. Major bleeding was defined as any bleeding event which occurred in a critical area or organ or any bleeding event that was accompanied by blood transfusion ≤10 days after hospital admission date (see online supplementary table S2). This is a slight modification of the classification according to the International Society on Thrombosis and Haemostasis (ISTH) because no information was available in our data set on haemoglobin levels.[15] A CRNM bleeding was defined in accordance with the ISTH classification as any bleeding requiring medical intervention by a healthcare professional or leading to hospitalisation or increased level of care or prompting a face-to-face evaluation, which
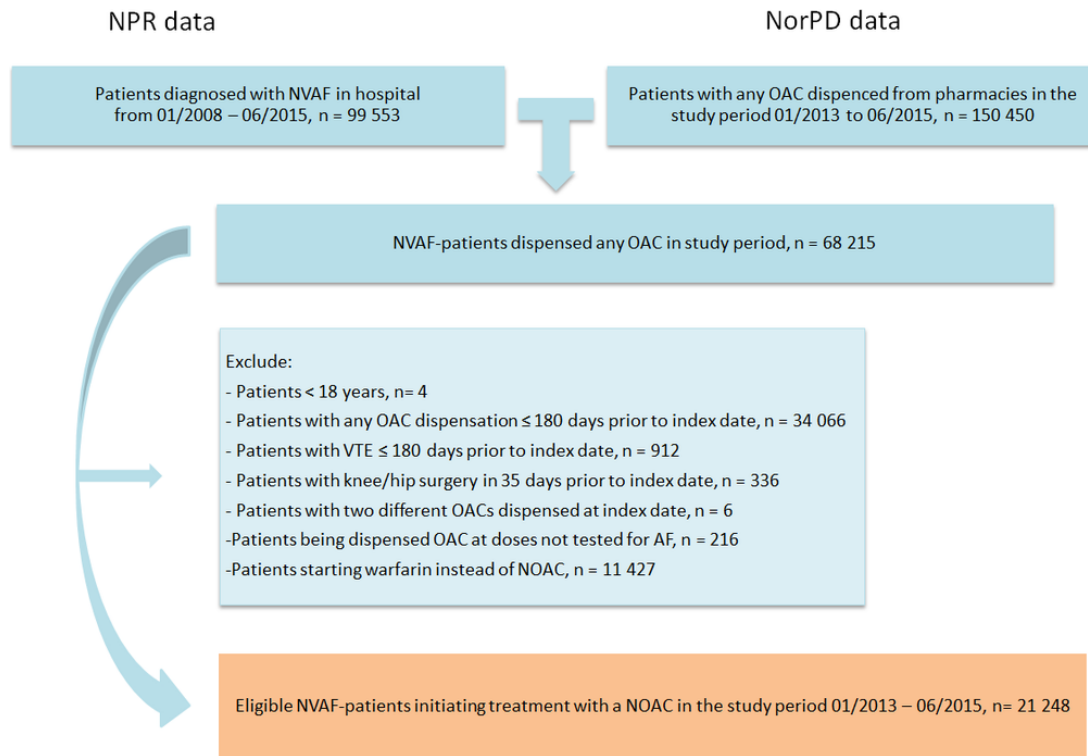
Figure 1 Cohort creation flowchart. NorPD, Norwegian Prescription Database; NPR, Norwegian Patient Registry; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant; VTE, venous thromboembolism.

did not fit the criteria for major bleeding.[16] In this study, major and CRNM bleeding were analysed together.

Ethics

Registration of information in NPR and NorPD is mandatory in Norway and legally exempt from obtainment of patient consent. All people resident in Norway are given a Norwegian national identification number, which allows for linkage of the two databases on an individual level.

Statistical analysis

Categorical variables are reported by numbers and percent, continuous variables by mean±SD or median (25th–75th percentiles). To develop the risk prediction
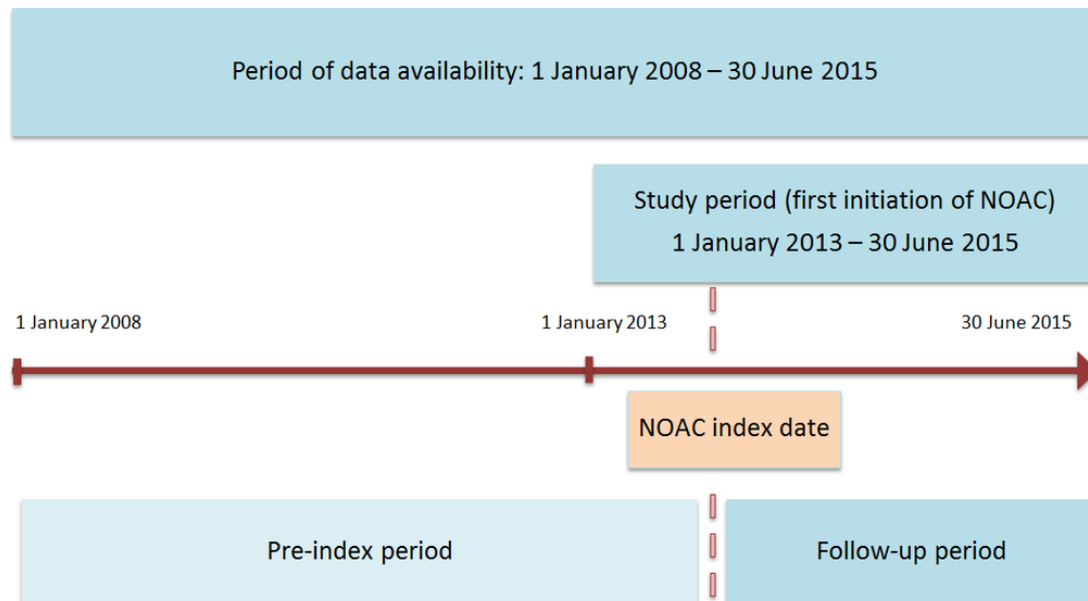
Figure 2 Study design. NOAC index date was the date of the first OAC dispensation (warfarin, apixaban, rivaroxaban, dabigatran) in the study period (January 2013–June 2015). Each patient was followed from the index date to the date of discontinuation orswitching of OAC therapy, date of death, or end of the study period. OAC, oralanticoagulant.

model, general principles from the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement were followed.[17] Cox proportional-hazards regression was used to analyse the time to the first bleeding episode taking censoring into account. Cases with missing data were handled by listwise deletion. After resolving issues of multicollinearity by excluding affected variables, the proportional hazard assumption was checked using Schoenfeld residuals and by comparing the log-log transformation of the Kaplan Meier survival curves for each variable.[18] A gender-stratified saturated Cox proportional-hazards model was fitted. Age was included as the only continuous variable. From the saturated model, an alpha level of 0.1 was used as a threshold to enter a variable predictor into a backwards elimination model.

Discrimination was assessed by Harrell's C-statistic and by comparing Kaplan-Meier curves and HRs.[19] Each model was internally validated by bootstrapping using 300 samples. A risk prediction score was derived from the Cox model by adding rounded HRs.

Annualised Kaplan-Meier event rates using person-time of follow-up were calculated according to an increase in integer score and then categorised into four categories: low risk (0–2 points), low intermediate risk (3–4 points), high intermediate risk (5–6 points) and high risk (7–12 points).

The full model was reduced to a three-variable model, based on the variables' predictive abilities, reliability and simplicity. The performance of the simplified model was assessed by Harrell's C-statistic. In a manner similar to that described for the full model, an integer risk score was created, annualised Kaplan-Meier event-rates calculated according to an incremental increase in integer score and then categorised into three categories: low risk (0–1 points), intermediate risk (2–3 points) and high risk (4–5 points). The simple model was internally validated by bootstrapping using 300 samples.

For comparison, the C-indexes for three previously published scores were calculated on the same cohort: the Hypertension, Age, Stroke, Bleeding tendency/predisposition, Labile international normalised ratios, Elderly age, Drugs or alcohol excess (HAS-BLED) score,[8] the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score[10] and the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT) score.[9]

As some of the variables in these three scores were unavailable to us (elevated liver enzymes, drug abuse and labile INR in the HAS-BLED score; renal failure with eGFR <30 mL/min in the ATRIA score), they were modified to include the variables available. For the modified ATRIA score, patients with chronic kidney disease (CKD) stages 3 and 4 (ICD10 code N183 and N184) were included, and the definitions used for the construction of the modified HAS-BLED score are listed in online supplementary table S7.

Statistical analyses were performed using SAS V.9.4 (SAS Institute) and STATA V.15 (STATA). Level of significance was set to 5%; all CIs are 95%.

RESULTS

The cohort included 21 248 patients, of whom 12 205 (57%) were men and the mean age was 73 years. Due to missing data, 186 (0.9%) patients were removed by listwise deletion. Table 1 shows the baseline characteristics. A total of 7925 (37.3%) patients were treated with dabigatran, 6817 (32.1%) with rivaroxaban and 6506 (30.6%) with apixaban. Hypertension was the most common comorbidity, affecting 13 431 (63.2%) of the patients and one quarter had ischaemic heart disease. The mean CHA_2DS_2-VASc score was 2.76. During a median follow-up time of 183 days (91-358), and 14 155 person-years, 1257 (5.9%) patients experienced a major or CRNM bleeding, corresponding to 8.9 bleeding events/100 person years.

The strongest predictors of bleeding were: age, history of bleeding (major or CRNM), CKD, chronic obstructive pulmonary disease (COPD), previous stroke/transient ischaemic attack (TIA), male sex, anaemia diagnosed during the last 12 months, heart failure, hypertension and non-bleeding related hospital admission during the last 12 months (table 2). We constructed an integer risk score based on these 10 variables. For the purpose of clarification of the cumulative hazards-illustration (figure 3), the age variable was divided into three groups;<65 years, 65–75 years and >75 years. The model showed a Harrel's C-index of 0.68 (95% CI 0.66 to 0.70). Table 3 shows distribution of patients within the risk score and the 1 year cumulative bleeding risks.

A simplified version of the score was subsequently derived using the following three variables: Age (<65 years, 65–75 years and >75 years), history of Bleeding (major or CRNM) and non-bleeding related Hospitalisation within the last 12 months. The three variables were chosen for their unambiguity and accessibility bedside. This simplified 'ABH-score' showed a C-index of 0.66 (95% CI 0.65 to 0.67). Table 4 shows the specific statistics for the simplified score and figure 4 shows the cumulative hazard of bleeding in the different risk groups. The results of internal validation by bootstrapping for the two models are shown in online supplementary tables S4 and S5. Receiver operating characteristic curves comparing the full 10-variable score with the ABH-score are shown in the online supplementary file 1.

Applied on the same cohort, the modified HAS-BLED score showed a C-index of 0.62 (95% CI 0.60 to 0.63), the modified ATRIA score a C-index of 0.66 (95% CI 0.64 to 0.67) and the ORBIT score a C-index of 0.66 (95% CI 0.64 to 0.67).

DISCUSSION

This study aimed to identify predictors of bleeding in a large real-world population of patients with AF treated with NOACs. We identified 10 independent predictors of

Table 1 Baseline characteristics of the study population (n=21 248)

Male sex	**12 205 (57.4)**
Age, years	
Mean (SE)	73 (11.2)
Median (25th–75th percentile)	73 (66–82)
≥75 years	9786 (46.1)
Type NOAC used	
Dabigatran	7925 (37.3)
Rivaroxaban	6817 (32.1)
Apixaban	6506 (30.6)
Medical history	
Hypertension	13 431 (63.2)
Chronic kidney disease	1046 (4.9)
Chronic heart failure	3979 (18.7)
Ischaemic heart disease	5230 (24.6)
History of stroke/TIA	2746 (12.9)
COPD	1665 (7.8)
Diabetes	2413 (11.4)
Dementia	369 (1.7)
Anaemia (last year)	559 (2.6)
Active cancer (last year)	1776 (8.4)
Previous bleeding hospitalisation	2881 (13.6)
Non-bleeding related hospitalisation (last year)	13 294 (62.6)
Medication before index date	
Previous use of OAC (>180 days prior to index)	2175 (10.2)
Antiplatelet therapy	11 217 (52.8)
Low-dose aspirin (last year)	10 612 (49.9)
Non-aspirin platelet inhibitor	605 (2.8)
NSAIDs (last year)	5018 (23.6)
Risk scores	
Modified HAS-BLED score ≥3	9169 (43.2)
CHA$_2$DS$_2$-VASc score	
Mean	2.76
≥2	16 905 (79.6)
Comorbidity score ≥1	11 891 (56.0)
Reduced NOAC dose at index date	6303 (29.7)

Values are numbers (percentages) unless otherwise stated.
COPD, chronic obstructive pulmonary disease; NOAC, non-vitamin K oral anticoagulant; NSAIDs, non-steroidal anti-inflammatory drugs; OAC, oral anticoagulant; TIA, transient ischaemic attack.

Table 2 Individual predictors of bleeding in full model

Risk factor	HR (95% CI)	P value	Score
Male sex	1.242 (1.106 to 1.394)	<0.001	1
Age (continuous)	1.036 (1.029 to 1.043)	<0.001	
Age (categorical)			
<65 years	1.00 (reference)		1 for age 65–75
65–75 years	1.637 (1.291 to 1.043)		
>75 years	2.544 (2.047 to 3.147)		2 for age >75
Hypertension	1.197 (1.061 to 1.351)	0.003	1
Chronic kidney disease	1.257 (1.028 to 1.584)	0.041	1
Chronic heart failure	1.260 (1.114 to 1.426)	<0.001	1
Stroke/TIA in history	1.250 (1.100 to 1.421)	0.001	1
COPD	1.276 (1.0579 to 1.538)	0.011	1
Anaemia diagnosed last 12 months	1.400 (1.052 to 1.865)	0.021	1
Bleeding in history	1.996 (1.743 to 2.284)	<0.001	2
Hospitalisation (non-bleeding related), last 12 months	1.165 (1.013 to 1.339)	0.032	1
SUM	**12**		

COPD, chronic obstructive pulmonary disease; TIA, transient ischaemic attack.

clinician with a tool that is easily remembered and can be used bedside, we derived a three-variable simplified version of the score that was given the acronym 'ABH-score'. This simplified score showed comparable predictive ability to previously published scores (C-statistic 0.66 (0.65 to 0.67)).

A recently published Danish study investigated the predictive abilities of the ATRIA, ORBIT and HAS-BLED scores in a very similar cohort of Danish patients with AF treated with NOACs.[20] They found C-statistics for ATRIA of 0.59 (95% CI 0.57 to 0.60), HAS-BLED 0.58 (95% CI 0.57 to 0.59) and ORBIT 0.61 (95% CI 0.59 to 0.62). Although they investigated major bleeding only, the
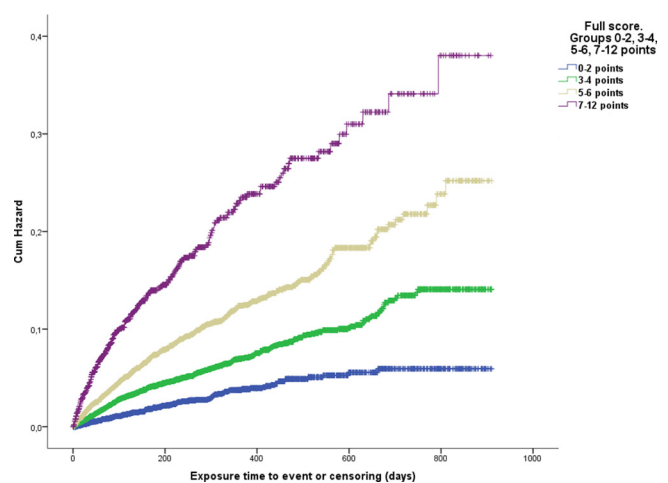

Figure 3 Cumulative hazard of bleeding in relation to score level (full score). Blue line, 0–2 points; green line, 3–4 points; brown line, 5–6 points; purple line 7–12 points.

bleeding and derived a bleeding risk score which showed a good discriminative ability (C-statistic 0.68 (95% CI 0.66 to 0.70)). Risk prediction scores that involve many predictor variables are often difficult to remember and require detailed knowledge of the patient's medical history and laboratory parameters. To provide the

Table 3 Distribution of patients within model and cumulative bleeding risk

Score	Total N	No. of events	1 year cumulative risk (%)
0	206	3	1.96
1	1734	31	3.24
2	3139	85	4.10
3	4625	206	6.37
4	4601	268	7.61
5	3330	253	11.35
6	1820	180	14.63
7	979	130	22.23
8	445	64	24.52
9	149	29	28.10
10	31	7	24.45
11	3	1	N/A
12	0	0	N/A

C-statistics were modest and in line with our estimates for the three scores based on our cohort.

The HAS-BLED score was derived from the EuroHeart survey AF population on vitamin K antagonist (VKA)[8] and has subsequently been validated in patient cohorts taking OAC (VKA and Idraparinux).[21] The ATRIA bleeding score was derived from the ATRIA community cohort of VKA users and later validated in the ROCKET-AF trial population.[10] The ORBIT score was derived from the ORBIT registry composed mostly of VKA users.[9] Despite being validated in patients using NOACs, and also in real-world populations, none of the existing risk scores were initially derived from real-world population cohorts.

Table 4 ABH-Score

Risk factor	HR (95% CI)	P value	Score
Age groups			
<65 years	1.00 (reference)		
65–75 years	1.666 (1.398 to 1.998)	<0.001	1 for age 65–75
75 years	2.681 (2.109 to 3.287)	<0.001	2 for age >75
History of bleeding	2.208 (1.914 to 2.447)	<0.001	2
Hospitalisation (non-bleeding related) last 12 months	1.365 (1.215 to 1.486)	<0.001	1

Distribution with in score	Total N	No. of events	1-year cumulative risk (%)
0	1948 (9.2)	28	2.34
1	4704 (22.1)	139	4.48
2	6 352 (29.9)	341	7.13
3	5 864 (27.6)	450	11.46
4	946 (4.5)	116	19.35
5	1 434 (6.7)	183	20.29
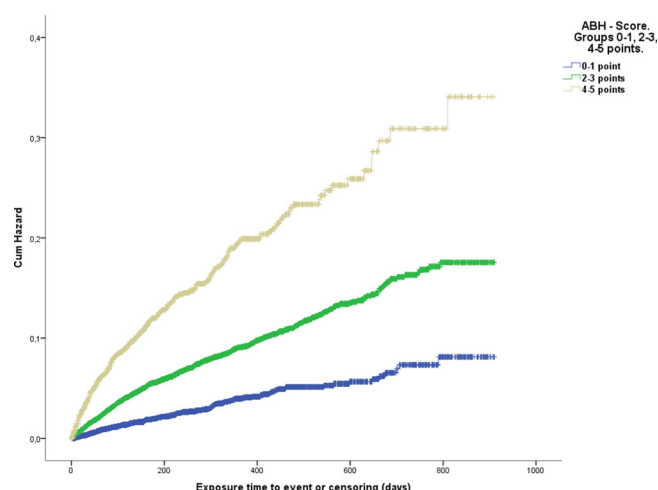
Figure 4

Unlike stroke-specific risk scores, there have been no randomised trials that have proven an overall benefit of withholding OAC from patients on the basis of a high bleeding risk score. Although the risk of bleeding is dynamic and repeated bleeding risk assessments have been shown to increase accuracy of risk prediction, there is no bleeding risk threshold above which the beneficial effect of anticoagulation is offset by the risk of serious bleeding.[22] Large observational data have shown a clear net clinical benefit from OAC despite very high bleeding risks.[23] Also, cessation of OAC leads to increased risk of stroke, cardiovascular events and mortality. Simultaneously, studies have shown that 30%–60% of American patients with AF do not receive anticoagulation when indicated, probably mainly due to fear of bleeding, and that elevated bleeding risk often leads to discontinuation of OAC.[24 25] To increase the likelihood of physicians prescribing anticoagulants for patients of AF, it is of utmost importance that they are familiar with the properties of NOACs and that their judgement of risks and benefits are based on solid evidence.

The two risk scores we present in this study seem to perform comparably. The importance of our full score lies in the presentation of distinct risk factors for patients with AF on NOACs. Several of the risk factors are potentially modifiable, such as hypertension, heart failure, CKD and COPD. It is logical to assume that modification of these may reduce the risk of bleeding. Physician awareness of these treatable chronic illnesses is thus especially important. The simplified version of the score has no modifiable risk factors; instead it consists of unambiguous risk factors without any grading or degree of severity, thereby leaving no room for misinterpretation. Also, it can be assessed without need for blood tests or imaging and still has a comparable discriminative ability to the alternative scores. In the simplified ABH-score, the variable 'non-bleeding related hospitalisation' serves as a surrogate marker of disease burden, emphasising the importance of considering the patient's comorbidities as a whole. In general, a high bleeding risk score should

not deter the clinician from prescribing OAC, but rather prompt a careful evaluation of each patient's individual set of risk factors, with subsequent modification whenever possible.[26]

Concomitant use of antiplatelet drugs, but not non-steroidal anti-inflammatory drugs (NSAIDs), was associated with increased risk of bleeding in the univariate analysis. However, use of antiplatelet drugs was not included in our scores (online supplementary table S3), since it did not achieve statistical significance in the multivariate analysis. Nonetheless, other studies have shown that such a combination of drugs increases the risk of bleeding. Discontinuation of antiplatelet and avoidance of concomitant use of NSAIDs are recommended in all patients treated with NOACs, if these drugs are not strictly indicated. In general, use of risk scores does not imply that well known risk factors not being included in the risk score should be disregarded. The simple risk score could be used as a practical and quick tool for risk estimation, but other risk factors should also be taken into consideration.

Strengths and limitations

The strength of our study is that it retrieved data from mandatory and nationwide registries in a public healthcare system that covers all residents. As a result, the dataset gave us a complete list of all hospital contacts and prescriptions dispensed nationwide for the entire study period. This complete coverage of data eliminates selection bias and recall bias that is an apparent problem using other databases based on selected hospitals, health insurance schemes, self-reported questionnaires or clinical trials where the patients are highly selected and subjected to thorough follow-up which may reduce the risk of bleeding. Our score may be more suitable to assess the risk of bleeding in patients in the routine practice. With the exception of apixaban being granted general reimbursement 6 months after rivaroxaban and dabigatran, the same conditions for OAC prescribing were valid nationwide and throughout the study period.

One limitation of the study was that we did not have access to information on laboratory tests such as thrombocyte and erythrocyte count, estimated glomerular filtration rate, liver enzymes or cardiac markers as well as other important characteristics such as smoking and body weight. One other caveat that influences the external validity of the results is that the AF diagnosis was retrieved from hospital level only, meaning that patients with AF who were solely managed in primary care were not included in the study. However, most of the patients with AF in Norway are referred to the hospital for evaluation and initiation of therapy.

Due to the registry-based nature of this study, bleeding endpoints were not adjudicated. Therefore, some bleeding episodes may have been overlooked. Likewise, bleeding tendencies may be identified earlier in patients enrolled in clinical trials, due do closer follow-up,

accordingly, major or fatal bleedings that would have occurred in real life may not be seen in trial cohorts.

The study participants were largely white Europeans. This may limit the generalisability of the results. Due to the relatively small number of patients on each separate NOAC, we did not consider possible differences in bleeding risk factors between the different NOACs. Although all prescribed drugs were included in our data set, use of non-prescription drugs (eg, NSAIDs) would go undetected. Bleeding episodes or other significant comorbidities only revealed in the primary care setting would not be visible in our data set and may thus be under-represented. There is also a risk of misclassification related to coding errors of hospital admissions; however, for serious conditions like bleeding, this is unlikely. No formal validation studies of the AF diagnosis in NPR against health records have been conducted. We studied drug exposure at the level of pharmacy dispensation and have no information on patient's actual NOAC intake. The full-scale and the simplified scores have so far only been internally validated. The scores' discriminative abilities were assessed with Harrel's C-statistic, a measure chosen on account of its widespread use and assumed physician familiarity, but will naturally be restricted by any and all inherent weaknesses of the C-statistic.

CONCLUSION

In this nationwide cohort study on patients with AF being prescribed NOACs, we have identified strong predictors of bleeding, several of which are potentially modifiable. A simplified, easy to remember bleeding risk score was derived that could allow the clinician to rapidly identify high-risk patients in need of closer attention and follow-up, without the need for laboratory or radiological tests.

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Correction notice This paper has been updated since first published. In Table 4, row 4, column 'Score', data has been revised from 'for age > 75' to '2 for age>75'.

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Correction: *New score for assessing bleeding risk in patients with atrial fibrillation treated with NOACs*

Rutherford OW, Jonasson C, Ghanima W, *et al*. New score for assessing bleeding risk in patients with atrial fibrillation treated with NOACs. *Open Heart* 2018;5: e000931.doi:10.1136/openhrt-2018-000931.

In Table 4, row 4, column 'Score', data should read '2 for age>75' and not 'for age > 75'.

Check for updates

Supplementary material for

Paper I

Supplementary table S1

Definition of co-morbidities (according to International Classification of Diseases, 10th revision (ICD10)) and co-medications (Anatomical Therapeutic Chemical (ATC) system). For typical primary care co-morbidities (heart failure, hypertension, diabetes and COPD) a dispensation (using ATC code or reimbursement codes) of drug dispensation was used as a proxy for an underlying condition.

Conditions	Period prior to index*	ICD-10 code from NPR	ATC code or reimbursement code in NorPD
Alcoholism	2008	E244, G312, G621, G721, I426, K860, O354, Z714, Z721, E52, K70, T51	
Chronic kidney disease	2008	N183, N184	
Congestive Heart Failure	2008		Reimbursement codes: I50 (ICD10) or K77 (ICPC)
Dementia	2008	F00-F04, G30	
Diabetes	2008		ATC code A10A or A10B
History of stroke, TIA or thromboembolism	2008	I64, I630, I631, I632, I633, I634, I635, I636, I638, G450, G451, G452, G453, G454, G458, G459, I690, I691, I692, I60, I61, I62	
Hypertension	2008		Reimbursement codes: I10-I13, I15 (ICD10) or K86, K87 (ICPC)
Peripheral Artery Disease	2008	I739	
Ischemic heart disease	2008	I20, I23, I24, I25	
Previous bleeding hospitalisation	2008	See supplementary table I for bleeding definitions	
Prior OAC use	2008		B01AA03, B01AE, B01AF
Viral hepatitis	2008	B15 toB19	
COPD	Last year		Reimbursement codes: J44 (ICD10) or R95 (ICPC
Active cancer	Last year	C00-C97	
Thrombocytopenia	Last year	D692, D693, D694, D695, D696, D698, D699	
Anaemia	Last year	D65-D67, D680, D681, D682, D683, D684, D685, D686, D688, D689, D50-D53, D55-D59, D60-D64	
NSAID	Last year		M01A
Low-dose aspirin as anti-thrombotic	Last year		B01A C06
Non-aspirin anti-platelet inhibitors	Last year		B01AC (not B01A C06)

Supplementary table S2

ICD10 and procedure codes applied to define first bleeding event. Here presented according to severity of bleeding.

All bleeds
Major bleeding:

Major bleeding:
- I60 subarachnoid haemorrhage
- I61 intracerebral haemorrhage
- I62 other non-traumatic intracranial haemorrhage
- K920 hematemesis
- K921 melena
- I690 sequelae of subarachnoid haemorrhage
- I691 sequelae of intracerebral haemorrhage
- I692 sequelae of other non-traumatic intracranial haemorrhage
- I230 haemopericardium as complication of MI
- I312 haemopericardium, not elsewhere classified
- M250 haemathrosis
- H431 vitreous haemorrhage
- H356 retinal haemorrhage
- H313 choroidal haemorrhage and rupture
- H450 vitreous haemorrhage in diseases classified elsewhere
- H448 other disorders of the globe, haemophtlamos
- J942 haemothorax
- K661 haemoperitoneum
- A CRNM bleeding was re-classified to major bleeding if blood transfusion (procedure codes; REGG00 (transfusion of allogeneic erythrocytes) or RXGG02 (transfusion with full blood, allogeneic)) occurred ≤ 10 days after admission date for CRNM bleeding.

Clinically relevant non-major bleeding (CRNM):
- R04 haemorrhage from respiratory passages
- N02 recurrent and persistent haematuria
- R31 unspecified haematuria
- N92 excessive, frequent and irregular menstruation
- N93 other abnormal uterine and vaginal bleeding
- R58 bleeding, not elsewhere classified
- T14 superficial injury of unspecified region, hematoma
- D62 acute posthaemorrhagic anemia
- K922 unspecified GI bleeding
- K250 gastric ulcer with bleeding
- K252 gastric ulcer with both perforation and bleeding
- K254 chronic or unspecified gastric ulcer with bleeding
- K256 chronic or unspecified gastric ulcer with both perforation and bleeding
- K260 duodenal ulcer with bleeding
- K262 duodenal ulcer with both perforation and bleeding
- K264 chronic or unspecified duodenal ulcer with bleeding
- K266 chronic or unspecified gastric ulcer with both perforation and bleeding
- K270 unspecified peptic ulcer with bleeding
- K272 unspecified peptic ulcer with both perforation and bleeding
- K274 chronic or unspecified peptic ulcer with bleeding
- K276 chronic or unspecified peptic ulcer with both perforation and bleeding
- K280 gastrojejunal ulcer with bleeding
- K282 gastrojejunal ulcer with both perforation and bleeding
- K284 chronic or unspecified gastrojejunal ulcer with bleeding
- K286 chronic or unspecified gastric ulcer with both perforation and bleeding
- K625 haemorrhage from anus and rectum
- K228 haemorrhage of the oesophagus

- K221 ulcer of esophagus with bleeding
- K290 acute gastritis with bleeding
- I850 esophageal varices with bleeding
- H113 conjunctival haemorrhage
- N836 haematosalpinx)
- N837 hematoma of the broad ligament
- A985 haemorrhagic fever with renal symptoms
- N421 congestion and haemorrhage of prostate
- N857 hematometra
- O721 other immediate postpartum haemorrhage
- S064 epidural haemorrhage
- S065 traumatic subdural haemorrhage
- S066 traumatic subarachnoid haemorrhage
- S068 other intracranial injuries, traumatic haemorrhage
- D683 haemorrhagic disorder due to circulating anticoagulants
- D698 other specified haemorrhagic conditions
- D699 haemorrhagic condition, unspecified

Time to first bleeding was calculated for the combined endpoint major or CRNM bleeding.

All registered bleeding events were taken into consideration; analyses were not restricted to admissions with bleeding as the primary (first) code.

Supplementary table S3

Univariate Cox proportional hazards regression results

Univariate Cox proportional hazards

Variable	HR (95% CI)	p-value
Gender (male gender)	1.019 (0.911 – 1.139)	0.744
Age	1.043 (1.038 – 1.049)	0.000
Myocardial Infarction	1.386 (1.154 – 1.665)	0.000
Ischaemic Heart Disease	1.478 (1.312 – 1.665)	0.000
Heart failure	1.780 (1.572 – 2.015)	0.000
Vascular disease	1.491 (1.290 – 1.723)	0.000
Peripheral Arterial Disease	1.703 (1.040 – 2.789)	0.034
Cerebrovascular disease (Stroke/TIA)	1.557 (1.355 – 1.790)	0.000
History of Stroke	1.630 (1.380 – 1.925)	0.000
History of Stroke or TIA	1.581 (1.375 – 1.818)	0.000
Diabetes	1.225 (1.041 – 1.442)	0.014
Hypertension	1.447 (1.280 – 1.637)	0.000
CHADSVASc score	1.296 (1.247 – 1.348)	0.000
Chronic Kidney Disease (ICD-10 N18.3&4)	2.316 (1.696 – 3.161)	0.000
Chronic Renal Failure (ICD N18+19)	2.072 (1.701 – 2.524)	0.000
Viral Hepatitis (Liver Failure)	1.107 (0.277 – 4.432)	0.886
NSAID use last 12 mos.	1.002 (0.880 – 1.141)	0.974
Alcoholism	1.856 (0.832 – 4.139)	0.131
Major Bleeding last 12 mos.	4.528 (3.456 – 5.933)	0.000
History of Bleeding	2.591 (2.288 – 2.935)	0.000
Modified HAS-BLED score	1.457 (1.370 – 1.550)	0.000
Dementia	1.700 (1.197 – 2.414)	0.003
COPD	1.421 (1.209 – 1.669)	0.000
Ulcer disease (Bleeding)	2.049 (1.657 – 2.533)	0.000
Cancer, including "cured" patients	1.410 (1.231 – 1.615)	0.000
Comorbidity score	1.267 (1.224 – 1312)	0.000
OAC use last 12 Mo	1.089 (0.913 – 1.298)	0.343
NSAID use last 12 Mo	1.002 (0.880 – 1.141)	0.974
All antiplatelet use last 12 Mo	1.309 (1.169 – 1.465)	0.000
Low-dose aspirin as antiplatelet therapy	1.238 (1.107 – 1.383)	0.000
Thrombocytopaenia	0.965 (0.311 – 2.997)	0.965
Anaemia	2.556 (2.011 – 3.247)	0.000
Hospitalisation last 12 Mo	1.645 (1.452 – 1.864)	0.000
COPD prescription last 12 Mo	1.491 (1.244 – 1.787)	0.000
Active cancer (C-diagnosis last 12 Mo)	1.450 (1.216 – 1.728)	0.000

Supplementary table S4

Bootstrapping results, full model

Individual predictors of bleeding in full model

Risk factor	HR (95% CI)	SE	P-value	Bootstrapping, 300 samples HR (95% CI)	SE	P-value
Male sex	1.242 (1.106 – 1.395)	0.059	<0.001	1.242 (1.106 – 1.394)	0.073	<0.001
Age (continuous)	1.036 (1.030 – 1.043)	0.003	<0.001	1.036 (1.029 – 1.043)	0.0035	<0.001
Hypertension	1.197 (1.056 – 1.358)	0.064	0.005	1.197 (1.061 – 1.351)	0.073	0.003
Chronic Kidney Disease	1.257 (1.024 – 1.542)	0.104	0.029	1.257 (1.028 – 1.584)	0.148	0.041
Chronic Heart Failure	1.260 (1.106 – 1.436)	0.067	0.001	1.260 (1.114 – 1.426)	0.079	<0.001
Stroke/TIA in history	1.250 (1.082 – 1.444)	0.074	0.002	1.250 (1.100 – 1.421)	0.081	0.001
COPD	1.276 (1.061 – 1.533)	0.094	0.010	1.276 (1.0579 – 1.538)	0.121	0.011
Anaemia diagnosed last 12 months.	1.400 (1.092 – 1.796)	0.127	0.008	1.400 (1.052 – 1.865)	0.204	0.021
Bleeding in history	1.996 (1.752 – 2.273)	0.067	<0.001	1.996 (1.743 – 2.284)	0.137	<0.001
Hospitalisation (non-bleeding related), last 12 months	1.165 (1.019 – 1.331)	0.068	0.025	1.165 (1.013 – 1.339)	0.082	0.032

HR, hazard ratio; CI, confidence interval.

Supplementary table S5

Bootstrapping results, ABH - score

Individual predictors of bleeding in ABH - score

Risk factor	HR adjusted	SE	P-value	Bootstrapping, 300 samples HR (95% CI)	SE	P-value
Age groups < 65 yrs.	1.00 (reference)			1.00 (reference)		
65 – 75 yrs.	1.666 (1.337 – 2.077)	0.112	<0.001	1.666 (1.398 – 1.998)	0.114	<0.001
>75 yrs.	2.681 (2.178 – 3.300)	0.106	<0.001	2.681 (2.109 – 3.287)	0.100	<0.001
History of bleeding	2.208 (1.945 – 2.507)	0.065	<0.001	2.208 (1.914 – 2.447)	0.068	<0.001
Hospitalisation (non-bleeding related) last 12 months.	1.365 (1.202 – 1.549)	0.065	<0.001	1.365 (1.215 – 1.486)	0.063	<0.001

Supplementary table S6

Receiver operating characteristic (ROC) – curves with coordinate tables

Area Under the Curve
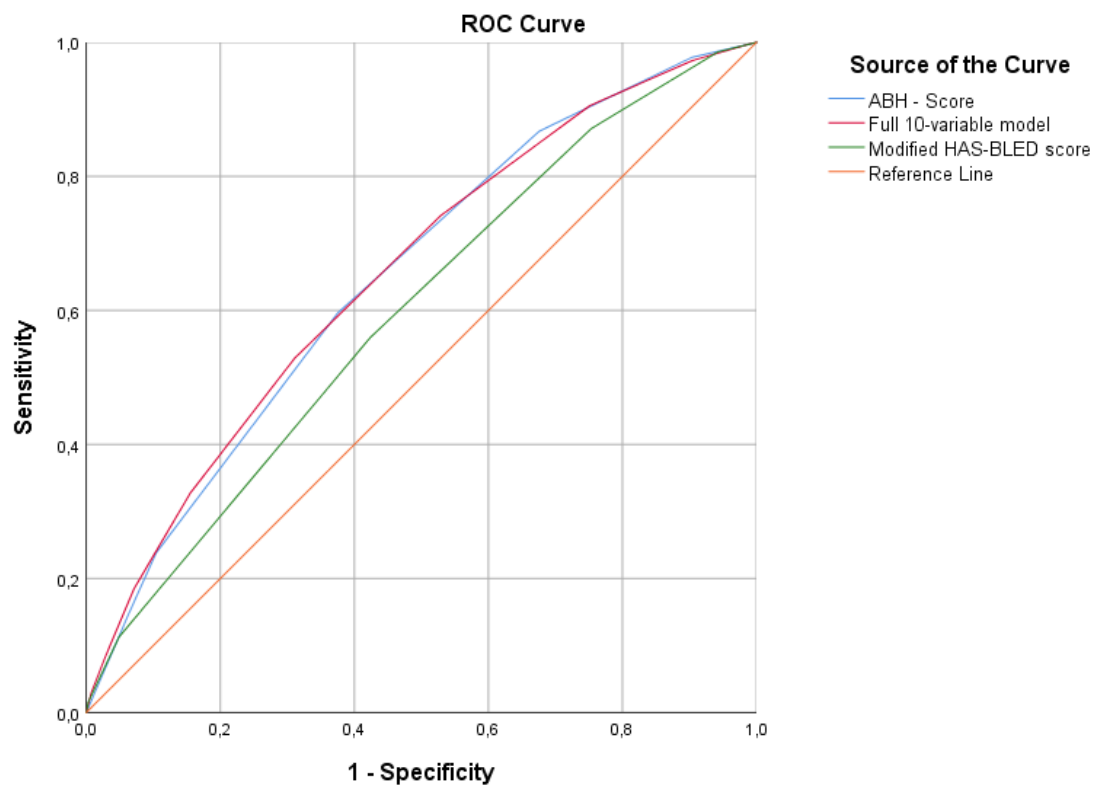
Test Result Variable(s)	Area	Std. Error	Sig.	95% Confidence Interval Lower Bound	Upper Bound
ABH - Score	0,651	0,008	0,000	0,636	0,666
Full 10-variable model	0,655	0,008	0,000	0,640	0,670
Modified HAS-BLED score	0,597	0,008	0,000	0,582	0,613

Supplementary table S7

Definition used for the construction of the modified HAS-BLED risk score. Diagnose codes was according to the International Classification of Disease, 10th edition (ICD10) and medication codes was according to the Anatomical Therapeutic Chemical system (ATC). For hypertension definition a dispensation of a drug for the treatment of hypertension was used as a proxy for the underlying diagnosis.

Factor	Definition in study	Score at index (baseline) Total score 0-8
Hypertension	NorPD reimbursement codes for hypertension: I10-13, I15 (ICD10) or K86, K87 (ICPC)	1 point
Renal impairment	CKD stage 3 and 4 (ICD10 code N183 and N184)	1 point
Liver impairment	ICD10 B15-B19	1 point
Stroke	Stroke ICD10 I60-I64	1 point
Prior major bleeding during last year before index	K920, K921, I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I612, I613, I614, I615, I616, I618, I619, I620, I621, I629, I230, I312, M250, H431, H356, H313, H450, H448, J942, K661	1 point
Age ≥ 65 years	Age ≥ 65 years at index	1 point
Therapy with either Nonsteroidal Anti-inflammatory Drugs (NSAID) or anti-platelets in the previous year before index date	ATC code M01A or B01AC	1 point
Alcoholism	ICD10: E52, K70, T51, E244, G312, G621, G721, I426, K860, O354, Z714, Z721	1 point

Paper II

II

Comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in atrial fibrillation: a nationwide cohort study

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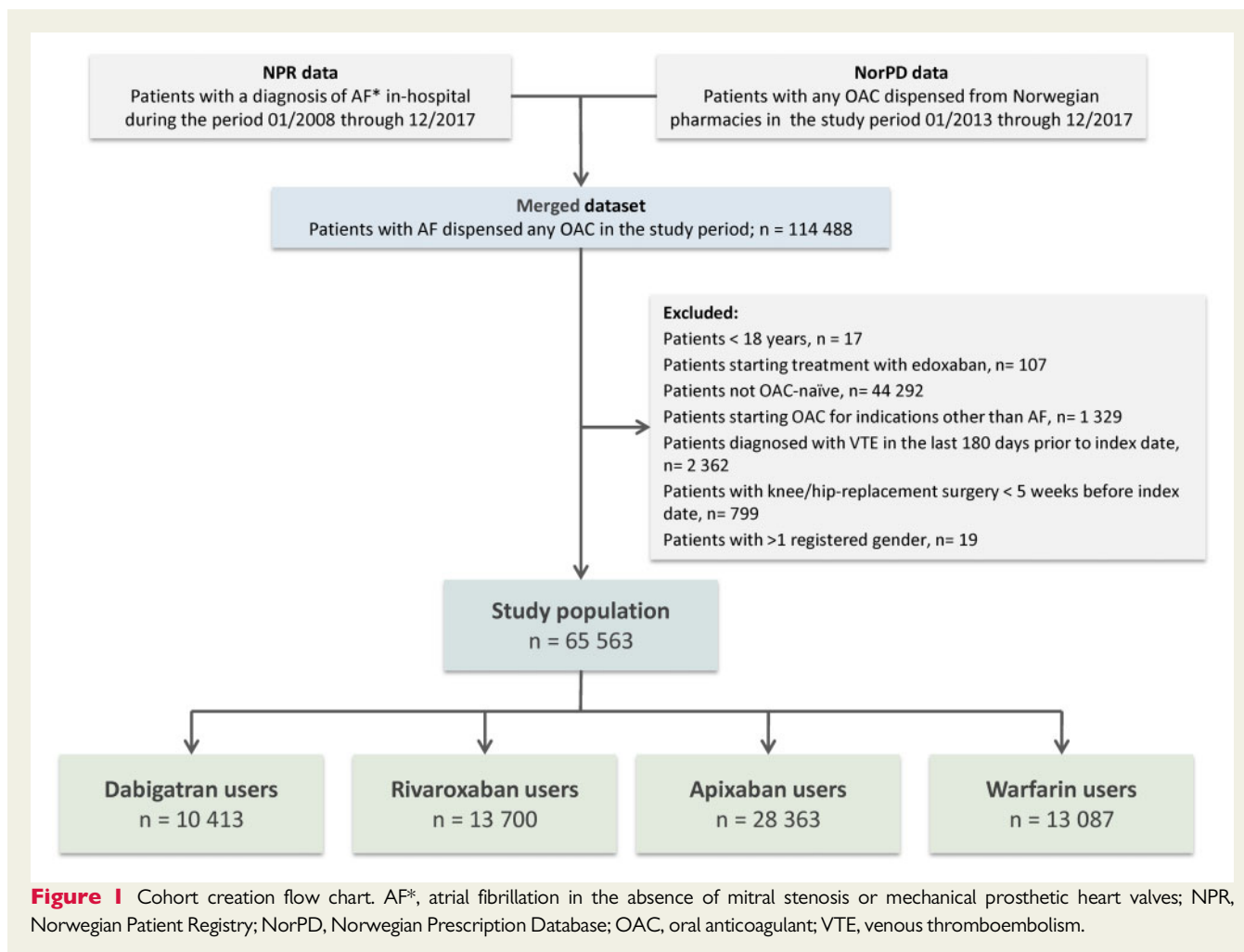|	
Aims	The aim of this study was to compare the risk of stroke or systemic embolism (SE) and major bleeding in patients with atrial fibrillation (AF) using dabigatran, rivaroxaban, and apixaban in routine clinical practice.
Methods and results	Using nationwide registries in Norway from January 2013 to December 2017, we established a cohort of 52 476 new users of non-vitamin K antagonist oral anticoagulants (NOACs) with AF. Users of individual NOACs were matched 1:1 on the propensity score to create three pairwise-matched cohorts: dabigatran vs. rivaroxaban (20 504 patients), dabigatran vs. apixaban (20 826 patients), and rivaroxaban vs. apixaban (27 398 patients). Hazard ratios (HRs) for the risk of stroke or SE and major bleeding were estimated. In the propensity-matched comparisons of the risk of stroke or SE, the HRs were 0.88 [95% confidence interval (CI) 0.76–1.02] for dabigatran vs. rivaroxaban, 0.88 (95% CI 0.75–1.02) for dabigatran vs. apixaban, and 1.00 (95% CI 0.89–1.14) for apixaban vs. rivaroxaban. For the risk of major bleeding, the HRs were 0.75 (95% CI 0.64–0.88) for dabigatran vs. rivaroxaban, 1.03 (95% CI 0.85–1.24) for dabigatran vs. apixaban, and 0.79 (95% CI 0.68–0.91) for apixaban vs. rivaroxaban.
Conclusion	In this nationwide study of patients with AF in Norway, we found no statistically significant differences in risk of stroke or SE in propensity-matched comparisons between dabigatran, rivaroxaban, and apixaban. However, dabigatran and apixaban were both associated with significantly lower risk of major bleeding compared with rivaroxaban.
Keywords	Atrial fibrillation • Non-vitamin K antagonist anticoagulants • Stroke • Bleeding

Introduction

Oral anticoagulants (OACs) are effective in preventing stroke and systemic embolism (SE) in patients with atrial fibrillation (AF) but are associated with an increased risk of bleeding.[1] Guidelines recommend use of non-vitamin K antagonist oral anticoagulants (NOACs) over traditional therapy with vitamin K antagonists in most patients,[2] and the number of patients being treated with NOACs has increased

rapidly during the last few years.[3] In the pivotal randomized controlled trials (RCTs) leading to their approval, each NOAC was compared with warfarin,[4–6] however, no head-to-head comparison between the individual NOACs has been performed. In the absence of RCTs, observational studies utilizing data from clinical practice may add useful information regarding comparative effectiveness and safety of the individual NOACs. The aim of this study was to assess the association between the use of dabigatran, rivaroxaban, and

Figure 1 Cohort creation flow chart. AF*, atrial fibrillation in the absence of mitral stenosis or mechanical prosthetic heart valves; NPR, Norwegian Patient Registry; NorPD, Norwegian Prescription Database; OAC, oral anticoagulant; VTE, venous thromboembolism.

apixaban and the risk of stroke or SE and bleeding in a nationwide cohort of patients with AF.

Methods

Data sources

The Norwegian Patient Registry (NPR) is a nationwide registry that covers all hospital admissions and outpatient consultations as well as all specialist consultations in Norway. Each admission or consultation is assigned a primary (the disease or condition being treated) and secondary cause (relevant comorbidities). Diagnoses are coded according to the International Classification of Diseases, 10th revision (ICD-10)[7] system and surgical procedures are coded according to the Nordic Medico-Statistical Committee (NOMESCO) coding system.[8,9]

The Norwegian Prescription Database (NorPD) holds information on all drug prescriptions dispensed from pharmacies nationwide. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) system.[10] The Norwegian system of general reimbursement of medicine expenses requires the prescribing physician to state the relevant underlying disease warranting each drug's reimbursement. The NorPD also contains information about date of dispensation, quantity, and strength of drugs dispensed.

Cohort creation and study design

The study cohort was generated by linkage of data from the NPR and the NorPD (*Figure 1*). The study population included all patients ≥18 years diagnosed with AF with at least one OAC dispensation (dabigatran 110 mg or 150 mg, rivaroxaban 15 mg or 20 mg, apixaban 2.5 mg or 5 mg, or warfarin 2.5 mg) in the study period (January 2013 to December 2017) but being anticoagulant naïve before start of the study. Patients initiating warfarin were included to enable comparisons between our findings and previous studies including patients treated with warfarin. Patients were excluded if they had mitral stenosis or mechanical prosthetic heart valves. Anticoagulant-naïve was defined as no dispensing of anticoagulants from pharmacies in the preceding 12 months before the index date. The index date was defined as the date of the first dispensation of an OAC in the study period. Due to limited usage in the study period, patients initiating edoxaban were excluded (*n* = 107). Patients with a history of venous thromboembolism during the last 180 days, or knee- or hip replacement surgery during the last 35 days before the index date were excluded. Details of the cohort creation procedure are shown in *Figure 1*, and ICD-10 codes used for inclusion- and exclusion criteria are listed in the Supplementary material online, *Table S1*.

Patients treated with a NOAC were matched with respect to propensity score, and three pairwise-matched cohorts were created: dabigatran

vs. rivaroxaban; dabigatran vs. apixaban; and apixaban vs. rivaroxaban. Details of the propensity score matching (PSM) are found in the section on statistical analysis.

Comorbidities

Diagnoses for all hospital admissions, consultations, and procedures in the previous 5 years before the index date were retrieved from the NPR. A medication history of 5 years, including all relevant diagnosis-specific reimbursement codes, was completed from the NorPD. This information was used to compile a set of comorbidities and medication history for each patient, using primary as well as secondary codes related to each admission. The ICD-10 codes included for each diagnosis are shown in Supplementary material online, Table S1, and Supplementary material online, Table S2 shows in detail how CHA_2DS_2-VASc- and HAS-BLED scores were calculated.

Oral anticoagulant supply

For each OAC, the days of supply were computed using information on dates of dispensing, the pack-size dispensed, and the number of packages. As the NOACs are prescribed in fixed doses, to be taken once daily (rivaroxaban) or twice daily (dabigatran and apixaban), the number of days of supply strictly corresponds to the amount dispensed. The days of warfarin supply were estimated as previously described.[11] To account for incomplete adherence, a 30-day gap period between the calculated end of OAC supply and the date of a new prescription was allowed, before patients were censored.

Outcomes and follow-up

Outcome measures of effectiveness were time to first stroke (haemorrhagic or ischaemic) or SE, and time to first ischaemic stroke. Outcome measures of safety were time to first major bleeding, clinically relevant non-major bleeding (CRNM bleeding), major or CRNM bleeding, gastrointestinal bleeding (GI bleeding), and intracranial haemorrhage. Major bleeding was defined as previously described as any bleeding into a critical area or organ, or any bleeding accompanied by blood transfusion ≤10 days after hospital admission date.[11] CRNM bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) classification,[12] as any bleeding necessitating intervention by a medical professional. ICD-10 and NOMESCO codes used for identification of outcomes are listed in Supplementary material online, Table S1. Patients were followed from the index date until discontinuation or switching of OACs, death, or end of study period (31 December 2017), whichever occurred first. For the identification of effectiveness- and safety outcomes, only primary (first listed) ICD-10 codes for each hospital stay were used.

Ethics

Registration of data into the NPR and the NorPD is mandatory in Norway and legally exempt from obtainment of patient consent. This study was approved by the Regional Ethical Committee (Ref. No. 2017/410/REK North).

Statistical analysis

Categorical variables are reported by numbers and percent, continuous variables by means with standard deviations. Cox proportional hazards regression was used to select the strongest predictor variables for stroke/SE and major bleeding. The proportional hazards assumption was checked using Schoenfeld residuals, and by comparing the log–log transformation of the Kaplan–Meier survival curves for each variable.[13]

To account for confounding by indication of therapy, PSM was performed. Using logistic regression, the probability of a patient being

prescribed a specific NOAC was calculated on the basis of the following 16 covariates; age, gender, chronic kidney disease, hypertension, diabetes, ischaemic heart disease, peripheral artery disease, heart failure, history of stroke/SE, history of bleeding-related hospitalization, anaemia, active cancer (cancer diagnosis last 12 months), chronic lower respiratory tract disease, use of cholesterol lowering drugs, use of antiplatelet drugs, and use of non-steroidal anti-inflammatory drugs during the last 12 months. For each patient initiating a specific NOAC, initiators of another NOAC to be compared were matched 1:1 on the logit of the propensity score using calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score.[14] Three propensity score-matched sets were constructed; dabigatran matched with rivaroxaban, dabigatran matched with apixaban, and rivaroxaban matched with apixaban. The balance between treatment populations was assessed by investigating absolute standardized mean differences of all baseline covariates before and after the matching, using a threshold of 0.1 to indicate imbalance. Cox regression with robust sandwich estimates was utilized for evaluating the rates of stroke and bleeding in the propensity score-matched groups.[15] As the matched sets were balanced, NOAC treatment was entered as the only independent variable.[16,17] Subgroup analyses were performed investigating the risk of stroke and major bleeding in specific subgroups; age (<75 years vs. >75 years), gender, history of stroke, and history of bleeding. For the analyses stratified on the initial dose, de novo PSM within the initial dose defined subgroups were performed. Adjusted hazard ratios (HRs) along with P-values for interaction between treatment and the specific subgroup were calculated.

Three sensitivity analyses were performed: (i) the analyses of the outcomes stroke/SE and major bleeding in the PSM cohorts were repeated restricting the follow-up time for all NOACs to 12 months; (ii) an 'intention-to-treat'-like analysis: the analyses of the outcomes stroke/SE and major bleeding in the PSM cohorts were performed without censoring by treatment switch or discontinuation of NOACs. (iii) The comparative analyses of the outcomes stroke/SE and major bleeding were repeated in the full dataset using conventional adjustment instead of PSM to avoid exclusion of non-matched patients from the analyses.

Finally, as a post hoc analysis, we performed NOAC–warfarin comparisons. The risk of stroke/SE and major bleeding were compared between users of dabigatran, rivaroxaban, apixaban, and users of warfarin, using a Cox proportional hazards model with conventional adjustment.

Level of significance was set to 5%. We did not adjust for multiple comparisons. Statistical analyses were performed using SAS v.9.4 (SAS Institute, Inc.) and STATA v.15 (STATACorp LLC).

Results

A total of 65 563 new users of OACs were identified and included in the study population; 10 413 initiated dabigatran, 13 700 rivaroxaban, 28 363 apixaban, and 13 087 initiated warfarin (Figure 1). Baseline characteristics for the unmatched groups are shown in Supplementary material online, Table S3. New users of dabigatran were more likely to be younger than new users of the other drugs, and they also had less comorbidity. The mean CHA_2DS_2-VASc- and HAS-BLED scores were lowest in users of dabigatran. The standard dose for stroke prevention was used in 63.9% of dabigatran patients, 75.6% of rivaroxaban patients, and 74.6% of apixaban patients.

Table I Baseline characteristics, propensity-matched groups

	Dabigatran–rivaroxaban-matched cohort (n = 20 504)			Dabigatran–apixaban-matched cohort (n = 20 826)			Apixaban–rivaroxaban-matched cohort (n = 27 398)		
	Dabigatran (n = 10 252)	Rivaroxaban (n = 10 252)	SMD	Dabigatran (n = 10 413)	Apixaban (n = 10 413)	SMD	Apixaban (n = 13 699)	Rivaroxaban (n = 13 699)	SMD
Age									
Mean (SD)	70.9 (10.95)	70.9 (11.21)	0.004	70.6 (11.18)	70.6 (11.67)	<0.001	72.7 (11.66)	72.7 (11.08)	<0.001
Median	71	71		71	71		73	73	
<65 years	2526 (24.6)	2614 (25.5)	0.005	2687 (25.8)	2794 (26.8)	0.003	2934 (21.4)	2786 (20.3)	0.000
65–74 years	3869 (37.7)	3748 (36.6)	0.006	3869 (37.2)	3759 (36.1)	0.010	4596 (33.5)	4805 (35.1)	0.014
≥75 years	3857 (37.6)	3890 (37.9)	0.004	3857 (37.0)	3860 (37.1)	0.004	6169 (45.0)	6108 (44.6)	0.002
OAC dose									
Standard dose	6498 (63.4)	8115 (79.2)		6652 (63.9)	8514 (81.8)		10 508 (76.7)	10 362 (75.6)	
Reduced dose	3754 (36.6)	2137 (20.8)		3761 (36.1)	1899 (18.2)		3191 (23.3)	3337 (24.4)	
Male gender	6286 (61.3)	6313 (61.6)	0.005	6433 (61.8)	6447 (61.9)	0.003	7946 (58.0)	7943 (58.0)	0.000
Hypertension	6656 (64.9)	6628 (64.7)	0.006	6693 (64.3)	6641 (63.8)	0.010	9376 (68.4)	9288 (67.8)	0.014
Ischaemic heart disease	2107 (20.6)	2089 (20.4)	0.004	2119 (20.3)	2101 (20.2)	0.004	3050 (22.3)	3061 (22.3)	0.002
Vascular disease	743 (7.2)	757 (7.4)	0.005	743 (7.1)	720 (6.9)	0.009	1265 (9.2)	1262 (9.2)	0.001
Heart failure	2103 (20.5)	2100 (20.5)	0.001	2140 (20.6)	2079 (20.0)	0.015	3029 (22.1)	3043 (22.2)	0.002
Chronic kidney disease	245 (2.4)	258 (2.5)	0.008	245 (2.4)	255 (2.4)	0.006	657 (4.8)	627 (4.6)	0.010
Diabetes mellitus	1318 (13.2)	1352 (13.2)	0.010	1324 (12.7)	1294 (12.4)	0.009	1923 (14.0)	1887 (13.8)	0.008
Chronic lower respiratory tract diseases	1137 (11.1)	1122 (10.9)	0.005	1141 (11.0)	1128 (10.8)	0.004	1654 (12.1)	1632 (11.9)	0.005
Active cancer (diagnosis last 12 months)	769 (7.5)	770 (7.5)	0.000	770 (7.4)	773 (7.4)	0.001	1276 (9.3)	1263 (9.2)	0.003
History of stroke/SE	1341 (13.1)	1330 (13.0)	0.003	1356 (13.0)	1322 (12.7)	0.010	1860 (13.6)	1792 (13.1)	0.015
History of anaemia	456 (4.4)	447 (4.4)	0.004	458 (4.4)	432 (4.1)	0.012	801 (5.8)	757 (5.5)	0.014
History of bleeding	1142 (11.1)	1142 (11.1)	0.000	1144 (11.0)	1097 (10.5)	0.015	1723 (12.6)	1715 (12.5)	0.002
Use of antiplatelet drugs last 12 months	5109 (49.8)	5079 (49.5)	0.006	5125 (49.2)	5016 (48.2)	0.021	7312 (53.4)	7207 (52.6)	0.015
Use of NSAIDs last 12 months	2485 (24.2)	2467 (24.1)	0.004	2512 (24.1)	2492 (23.9)	0.004	3047 (22.2)	3148 (23.0)	0.018
Use of cholesterol lowering drugs	4603 (44.9)	4598 (44.8)	0.001	4629 (44.5)	4516 (43.4)	0.022	6356 (46.4)	6315 (46.1)	0.006
Mean CHA_2DS_2-VASc score (SD)	2.99 (1.73)	2.98 (1.71)	0.006	2.96 (1.74)	2.93 (1.72)	0.017	3.23 (1.74)	3.22 (1.71)	0.006
Mean HAS-BLED score (SD)	2.30 (1.14)	2.29 (1.12)	0.009	2.25 (1.15)	2.25 (1.16)	0.000	2.43 (1.15)	2.43 (1.12)	0.000

Values are expressed as numbers (percent), unless otherwise stated.
NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; SE, systemic embolism; SMD, absolute standardized mean difference.
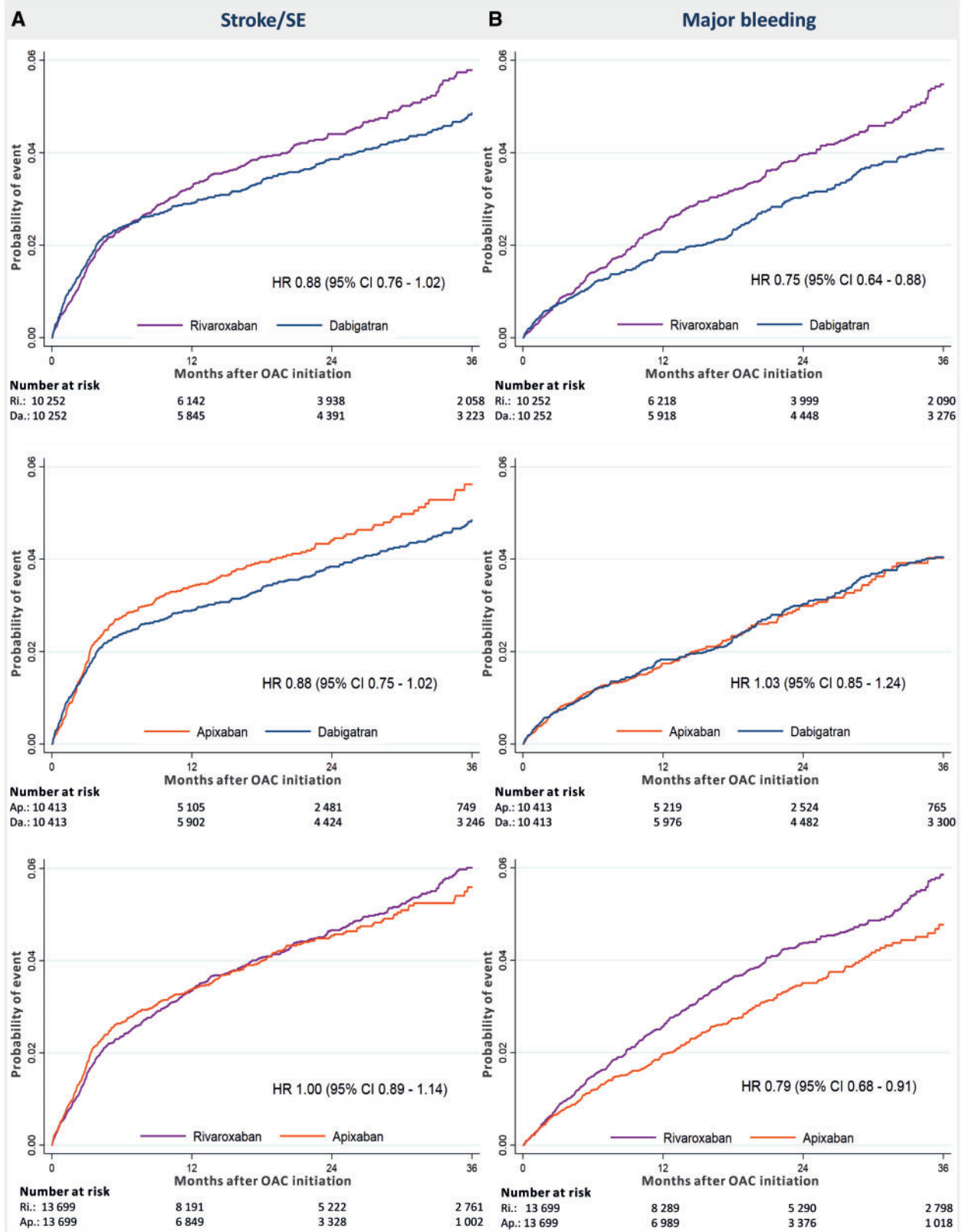
Figure 2 Cumulative incidence of stroke or systemic embolism (*A*) and major bleeding (*B*) in the propensity score-matched groups. CI, confidence interval; HR, hazard ratio; OAC, oral anticoagulant; SE, systemic embolism.
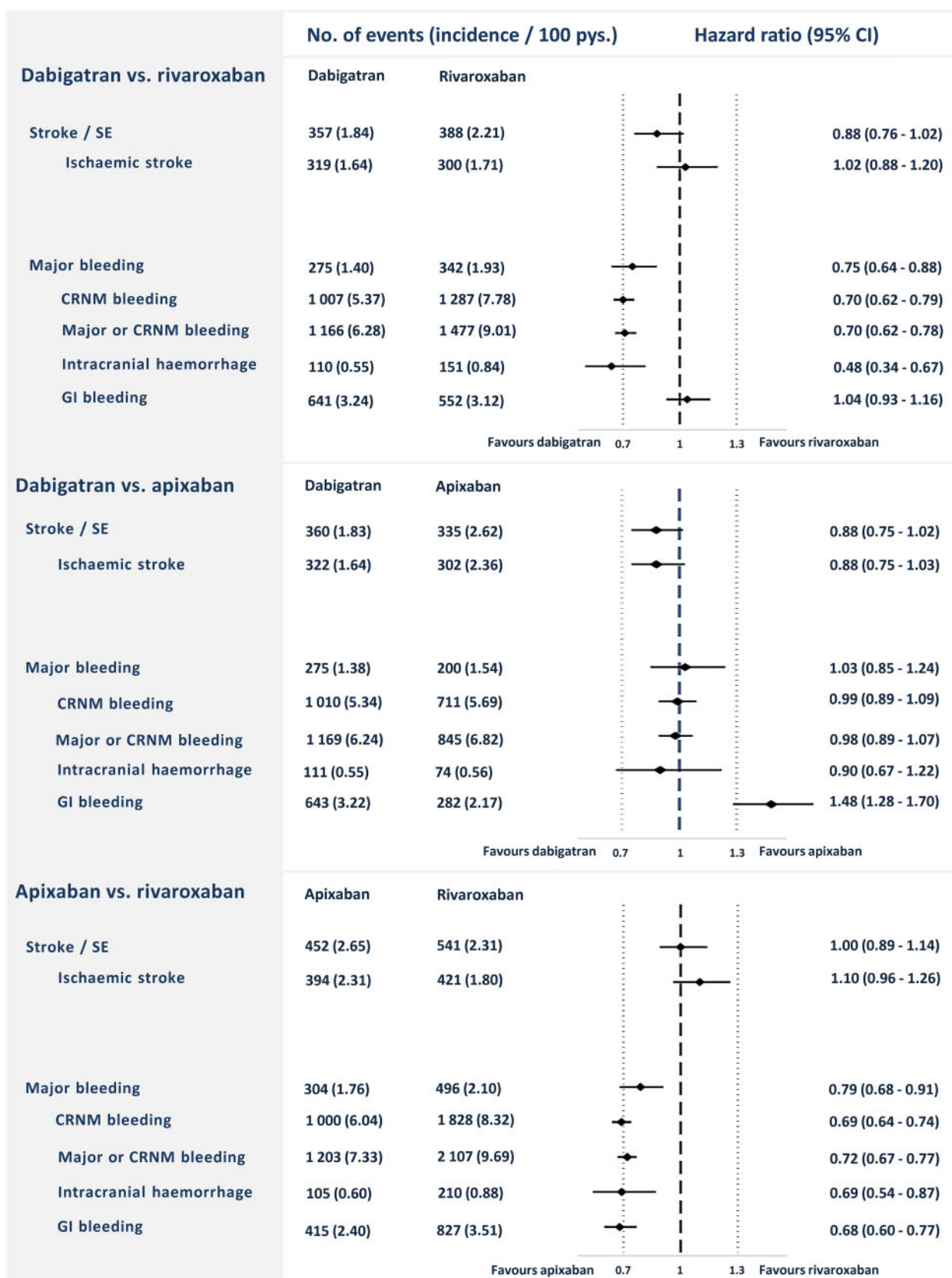
Figure 3 Number of events, incidence rates, and hazard ratios for primary and secondary outcomes in the three propensity score-matched cohorts. CI, confidence interval; CRNM, clinically relevant non-major; GI, gastrointestinal; Pys., person-years; SE, systemic embolism.
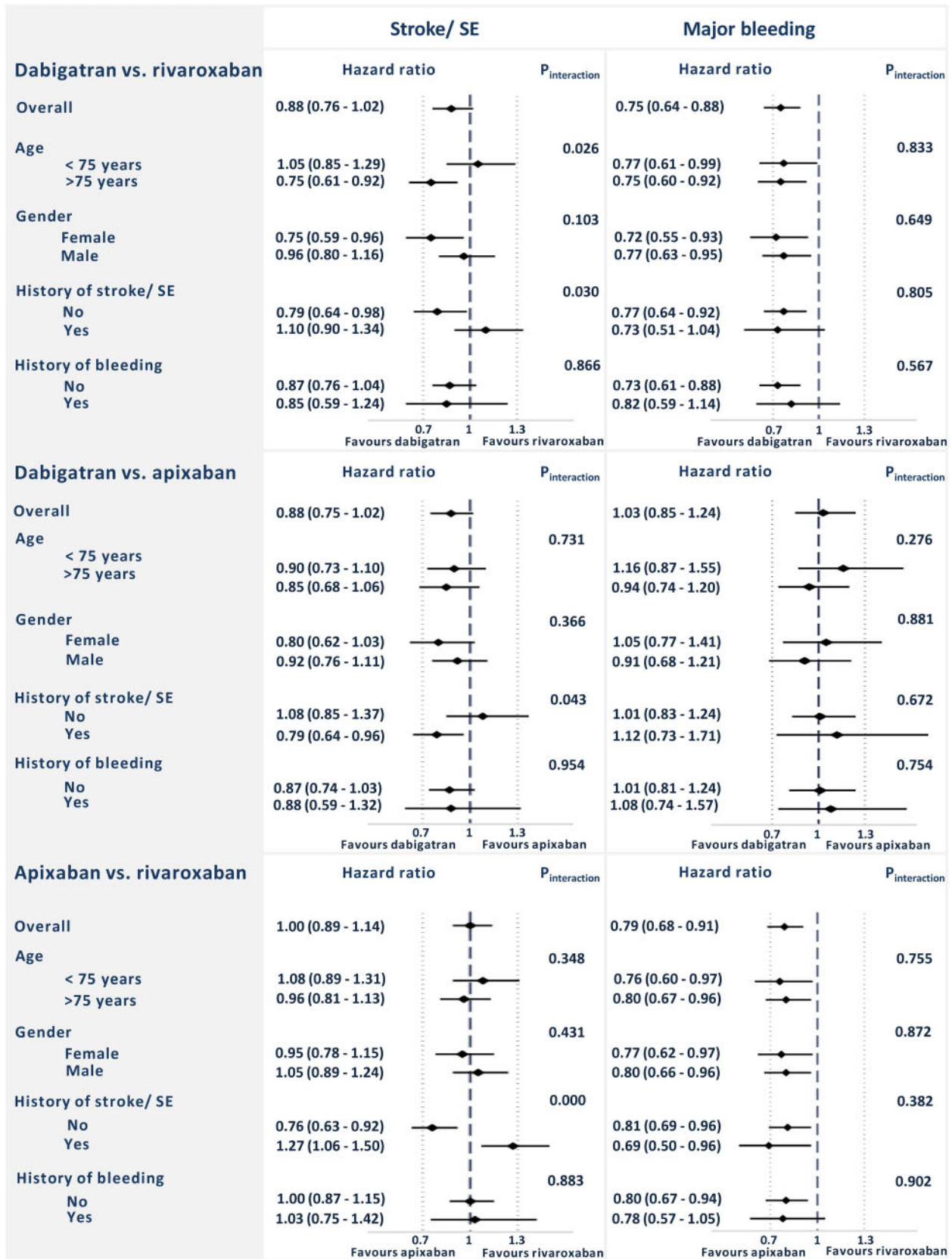
Figure 4 The risk of stroke or systemic embolism and major bleeding in selected subgroups. SE, systemic embolism.
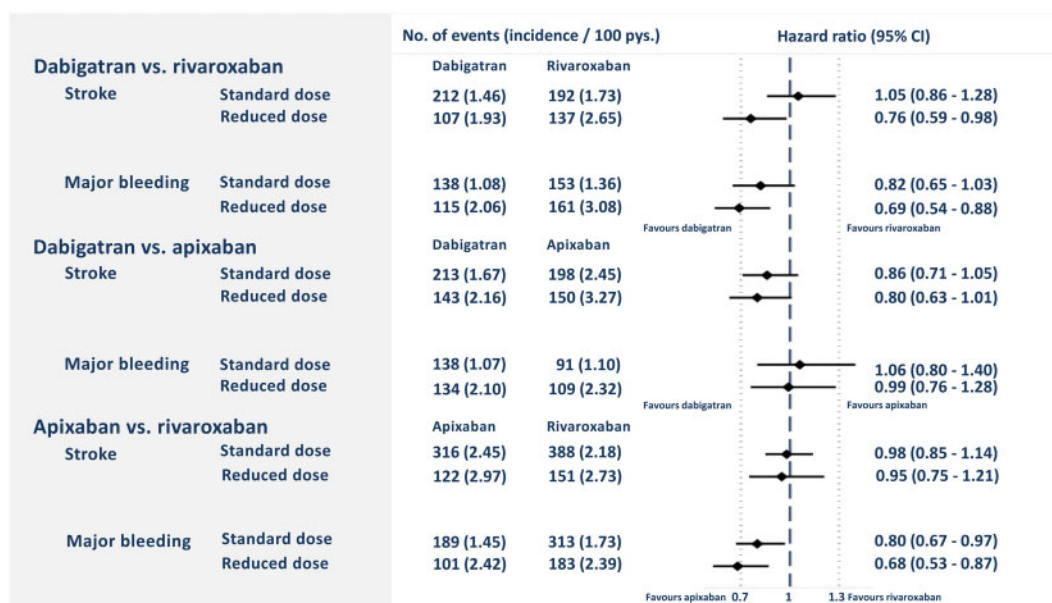
Figure 5 The risk of stroke or systemic embolism and major bleeding for patients using standard or reduced dose non-vitamin K antagonist oral anticoagulants. CI, confidence interval; Pys., person-years.

Non-vitamin K antagonist oral anticoagulant–non-vitamin K antagonist oral anticoagulant comparisons

After PSM in a 1:1 ratio, the cohorts used in the analyses of dabigatran vs. rivaroxaban included a total of 20 504 patients, dabigatran vs. apixaban included a total of 20 826 patients, and rivaroxaban vs. apixaban included a total of 27 398 patients. In each of the matched cohorts, baseline characteristics were well-balanced between the groups (*Table 1*). Plots of propensity scores before and after matching are shown in the Supplementary material, *Figure S1*. *Figure 2* shows Kaplan–Meier curves for the risk of stroke/SE and major bleeding, whereas *Figure 3* shows the incidence rates and HRs of the outcomes stroke/SE and major bleeding for the three PSM cohorts. The proportional hazard assumption was fulfilled for all primary analyses.

Dabigatran–rivaroxaban-matched cohort

The median follow-up time was 18.6 months for dabigatran and 18.2 months for rivaroxaban. In the dabigatran group, stroke/SE occurred with an event rate of 1.84/100 person-years compared with 2.21/100 person-years in the rivaroxaban group [HR 0.88; 95% confidence interval (CI) 0.76–1.02]. A major bleeding event occurred at a rate of 1.40/100 person-years in the dabigatran group, and 1.93 in the rivaroxaban group (HR 0.75; 95% CI 0.64–0.88).

Dabigatran–apixaban-matched cohort

The median follow-up time was 18.2 months for dabigatran users and 12.2 months for apixaban users. Among dabigatran users, stroke/SE occurred at a rate of 1.83/100 person-years, while the event rate was 2.62/100 person-years for apixaban users (HR 0.88; 95% CI 0.75–1.02). Major bleeding occurred at an event rate of 1.38/100 person-

years in the dabigatran group vs. 1.54/100 person-years in the apixaban group (HR 1.03 95% CI 0.85–1.24). The risk of GI bleeding was significantly higher for dabigatran with event rates of 3.22/100 person-years vs. 2.17/100 person-years in the apixaban group (HR 1.48; 95% CI 1.28–1.70).

Apixaban–rivaroxaban-matched cohort

The median follow-up time was 18.1 months in the rivaroxaban group, and 12.5 months in the apixaban group. The event rate of stroke/SE was 2.65/100 person-years for the apixaban group vs. 2.31/100 person-years for the rivaroxaban group (HR 1.00; 95% CI 0.89–1.14). The event rates of major bleeding were 1.76/100 person-years vs. 2.10/100 person-years in the apixaban- and rivaroxaban groups, respectively (HR 0.79; 95% CI 0.68–0.91).

Subgroup analyses

The risks of stroke or SE and major bleeding in selected subgroups are shown in *Figure 4*. No significant heterogeneity between subgroups was found with respect to risk of major bleeding. In the dabigatran–rivaroxaban-matched cohort, significant heterogeneity regarding risk of stroke/SE was seen in two subgroups; namely age <75 vs. >75 years, and patients with or without prior stroke/SE. Also, in the two other cohorts, heterogeneity was seen with respect to risk of stroke/SE in the subgroup of patients with or without prior stroke/SE.

Patients initiating standard or reduced dose NOACs differed in baseline characteristics; the patients receiving reduced doses were more likely to be older and having more comorbidities than patients starting standard doses (Supplementary material online, *Table S5*). After propensity score re-matching on initial doses, both reduced-

and standard-dose patients showed broadly consistent results to the main analysis (*Figure 5*).

Sensitivity analyses

The results of the sensitivity analyses are shown in Supplementary material online, *Table S6* and were in line with the primary analyses.

Non-vitamin K antagonist oral anticoagulant–warfarin comparisons

Comparing each NOAC with warfarin, we found no significant differences in the adjusted HRs of stroke/SE for any NOAC compared with warfarin, while dabigatran and apixaban were both associated with lower risk of major bleeding (Supplementary material online, *Table S4*).

Discussion

In this study, we compared the risks of stroke or SE and major bleeding associated with use of dabigatran, rivaroxaban, and apixaban in a large nationwide cohort of anticoagulant-naïve patients with AF. In propensity score-matched analyses, we found no statistically significant differences in the risk of stroke or SE between NOACs, but dabigatran and apixaban were associated with significantly lower risk of major bleeding compared with rivaroxaban. The reduction of bleeding risk associated with dabigatran and apixaban was consistent for CRNM bleeding, major or CRNM bleeding, and intracranial bleeding. Dabigatran and rivaroxaban were associated with a significantly higher risk of GI bleeding compared with apixaban.

Clinical trials and recent meta-analyses have shown that the NOACs are at least as effective as warfarin in stroke prevention and are associated with a similar or reduced risk of bleeding.[4–6,18,19] In registry-based observational studies comparing the NOACs with warfarin, very similar results have been found.[20–23] As the proportion of patients with AF being started on a NOAC instead of warfarin is increasing,[24] knowledge of the comparative effectiveness and safety profiles of the different NOACs in clinical practice is needed.

Our study is one of very few studies designed to directly compare the effectiveness and safety of three individual NOACs in clinical practice. As treatment with NOACs is the standard of care in AF today,[2] such a comparison seems more relevant for the practicing clinician.

The NOACs were examined pairwise in PSM analyses. A strength of our study is the inclusion of all anticoagulant-naïve new users of a NOAC from a nationwide cohort; this should eliminate selection and participation bias often present in observational cohort studies. Furthermore, the follow-up times were longer and the number of patients included in the matched cohorts larger in our study compared with most previous studies.[23,25]

Our current findings are in line with similar studies.[23,25–27] In a recent Danish study by Staerk et al.,[27] including 31 522 patients with AF, multivariate Cox regression was chosen over PSM. In line with our findings, dabigatran and apixaban were associated with lower bleeding risk compared with rivaroxaban, but no significant differences were seen between the NOACs in terms of effectiveness. In another Danish study by Andersson et al.,[25] including 12 638 new users of NOACs, PSM was performed, and no significant differences in

associated risk of stroke/SE or major bleeding were found between NOACs. However, due to the low number of patients in each matched cohort, this study might have been underpowered. Similarly, Noseworthy et al.[26] found no significant differences in effectiveness between the NOACs in their PSM cohorts, and both dabigatran and apixaban were associated with significantly lower bleeding risk compared with rivaroxaban. In the largest observational study to date, Lip et al.[23] studied 285 292 patients pooled from the US Centers for Medicare and Medicaid Services Medicare data and four commercial claims databases in the USA (the ARISTOPHANES study). After PSM of patients with AF treated with a NOAC, apixaban was associated with significantly lower risk of both stroke or SE and major bleeding compared with dabigatran and rivaroxaban. Dabigatran compared with rivaroxaban was associated with a similar risk of stroke/SE but significantly lower risk of bleeding. A major limitation of the ARISTOPHANES study was the very short median follow-up time in all cohorts of just over 4 months. Another limitation involves the use of healthcare claims databases, necessitating Medicare or Medicaid eligibility for patient inclusion and relying on billing codes to define all baseline characteristics and outcomes. This increases risk of selection bias and loss to follow-up bias.

Our *post hoc* analysis comparing NOACs with warfarin were also generally in line with the results from similar real-world studies,[20–23] showing non-significant differences in the risk of stroke/SE associated with NOACs, and significantly lower risks of major bleeding for both dabigatran and apixaban. Comparing our results with the RCTs,[4–6] we did not find the reductions in stroke risk with dabigatran 150 mg and apixaban compared with warfarin that was shown in the RE-LY and ARISTOTLE trials.[5,6] This has, however, been the case in several previous real-world studies.[21–23] Minor discrepancies from the RCTs are to be expected, since these are not randomized comparisons. Despite adjustments, remaining unmeasured confounders will always exist.

In the subgroup analyses performed in our study, significant interactions were seen between groups using NOACs as primary or secondary stroke prophylaxis. These findings are difficult to explain. Since they represent interactions based on subgroup analyses of non-randomized comparisons, they are most likely due to chance. The risks of stroke/SE and major bleeding in the cohorts rematched on standard and reduced doses were broadly consistent with the main findings.

Strengths and limitations

There are fundamental differences between observational studies and RCTs, where the higher event rates often seen in registry studies reflect some of these differences.[4–6,28,29] Inclusion of data into the nationwide registries is mandatory in Norway; this eliminates selection, participation, and recall bias. It also ensures a study population large enough for robust calculations. These advantages of nationwide registries are summarized in a recent position document from the European Heart Rhythm Association.[30]

The Norwegian system of general reimbursement of medical expenses for the treatment of serious and prolonged chronic illnesses ensures that all patients included in the study are in fact using OACs for AF, and not venous thromboembolism or any other

condition; a challenge for similar studies based on registries where information on indication for treatment is unavailable.[31,32]

A well-known limitation is that conventional multivariate regression, as well as PSM cannot control for unknown or unmeasurable confounders.[33] In the total study population, before PSM was performed, patients starting rivaroxaban and apixaban were generally older and sicker than patients starting dabigatran (Supplementary material online, Table S3). It seems likely that the patients starting rivaroxaban and apixaban could also have other comorbidities or underlying factors that we have not taken into account, as well as a higher degree of frailty; an element which is difficult to measure in this type of study based on nationwide administrative registries, but which in this case likely is driving the estimates in favour of dabigatran.

The events recorded were not adjudicated. There was also very likely a certain degree of miscoding and under-reporting of comorbidities and events. Despite nationwide inclusion of patients, because of demographics the study participants were still largely White northern Europeans. This may limit the generalizability of the results. Another limitation is that the registries do not supply information on relevant laboratory analyses such as estimated glomerular filtration rate, cardiac troponins, erythrocyte count, thrombocyte count, or liver enzymes; or other important patient characteristics such as body weight, lifestyle, or smoking habits.

Dabigatran was the first, rivaroxaban the second, and apixaban the third NOAC available in Norway, and all drugs were available in the whole study period. The proportion of patients starting on apixaban increased steadily throughout the study period (Supplementary material online, Table S3). Temporal changes in prescription patterns for NOACs might influence the number of events in each group. However, we found no significant differences between the NOACs regarding associated risk of stroke/SE; and dabigatran (the first NOACs on the market) and apixaban (the last NOAC on the market) were both associated with significantly lower risks of major bleeding compared with rivaroxaban (the second NOAC on the market). In addition, we created well-balanced cohorts in terms of risk factors; thus, it seems unlikely that temporal changes have played any important role for our results. To account for the approximately 6 months average shorter follow-up time for apixaban compared with dabigatran and rivaroxaban we performed a separate sensitivity analysis restricting the follow-up time to 12 months with results in line with the main analyses.

Evaluation of the appropriateness of the dose prescribed (standard or reduced dose of NOAC) requires knowledge not only of patient age but also of serum creatinine and body weight. The variables serum creatinine and body weight are unfortunately not available from the nationwide registries in Norway, like in many other registries.[23,25–27] Although we were unable to identify users of NOACs per label regarding dose, we have attempted to compensate for this by performing *de novo* propensity score estimation and matching within dosage groups. Furthermore, based on a recent study from UK, there are reasons to believe that the majority of AF patients are prescribed appropriate doses of NOACs; the UK study found between 75% and 85% of patients to be appropriately dosed.[34]

We studied drug exposure at the level of pharmacy dispensation and have no information on patient's real intake of OAC. However, it is unlikely to expect any differences between groups in this respect.

Due to the limitations of our study, the results should be interpreted with caution and need to be confirmed by findings from NOAC vs. NOAC RCTs. This is especially the case for the subgroup analyses, where we after careful consideration did not adjust for multiple comparisons (e.g. Bonferroni correction).

Conclusion

In this large registry-based study including 65 563 anticoagulant-naïve patients with AF initiating OAC therapy, we found no statistically significant differences in risk of stroke or SE between dabigatran, rivaroxaban, and apixaban, while both dabigatran and apixaban were associated with significantly lower risks of major bleeding compared with rivaroxaban.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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Supplementary material for

Paper II

Supplementary table S1

ICD-10 (International Classification of Diseases, 10th revision) and NOMESCO (Nordic Medico-Statistical Committee) codes used in definitions of co-morbidities and outcomes. Comorbidities were recognized either by ICD-10 diagnoses from hospital stays, or by a combination of hospital diagnoses and drugs dispensed. ATC (Anatomical Therapeutic Chemical system) codes from NorPD identified disease-specific drugs (e.g. anti-diabetics) and ICD-10 or International Classification for Primary Care 2 (ICPC-2) codes used as reasons for reimbursement of drugs for chronic illnesses for less specific drugs (e.g. beta blockers).

Conditions	ICD-10 code or procedure codes (NOMESCO) from NPR	ATC code or reimbursement code in NorPD
Atrial fibrillation	I48	Reimbursement code: I48 , K78 (ICPC)
Additional diagnoses to identify "valvular atrial fibrillation"	ICD10: I050, I052, I342, Z952 NOMESCO codes: FKD00, FKA, FMD00,	
Hypertension	I10, I11, I12, I13, I15	Reimbursement codes: I10-I13, I15 (ICD10) or K86, K87 (ICPC)
Chronic kidney disease	N181, N182, N183, N184, N185, N189, N19	
Ischemic heart disease	I20, I21, I22, I23, I24, I25	
Heart failure	I500, I501, I509	Reimbursement codes: I50 (ICD10) or K77 (ICPC)
Diabetes	E10, E11, E12, E13	ATC code A10A or A10B
Chronic lower respiratory tract disorders	J40 – J47	Reimbursement codes: J44 , J45 (ICD10) or R95 (ICPC
Active cancer	C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C44, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C77, C78, C79, C80, C81, C82, C83, C84, C85, C86, C88, C90, C91, C92, C93, C94, C95, C96, C97	
Peripheral artery disease	I70, I71, I72, I73, I74, I77, I78, I79	
Inflammatory polyarthropathies	M05 – M14	
Ischaemic stroke	I630, I631, I632, I633, I634, I635, I636, I638, I639, I64	
Transient ischaemic attack (TIA)	G450, G451, G452, G453, G454, G458, G459, G46	
Ischaemic or haemorrhagic stroke	I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I612, I613, I614, I615, I616, I618, I619, I620, I621, I629, I630, I631, I632, I633, I634, I635, I636, I638, I639, I64,	
Major bleeding	K920, K921, I600-I609, I610-I619, I620-I629, I230, I312, M250, H431, H356, H313, H450, J942, K661 *Addition: A CRNM-bleeding diagnosis will be converted to a major bleeding diagnose if blood transfusion (NCMP REGG00, RXGG02) is coded within 10 days.*	

Conditions	ICD-10 code or procedure codes (NOMESCO) from NPR	ATC code or reimbursement code in NorPD
Systemic embolism	I74	
Intracranial bleeding	I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I612, I613, I614, I615, I616, I618, I619, I620, I621, I629	
Gastrointestinal bleeding	K920, K921, K922, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K228, K221, K290, K528, K625, I850	
CRNM bleeding	K922, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K228, K221, K290, K528, K625, I850, H113, R040, R041, R042, R048, R049, N836, N837, N920, N921, N922, N923, N924, N925, N926, N930, N938, N939, A985, N421, N857, N921, O721, S064, S065, S066, S068, T140, T141, T142, T143, T144, T145, T146, T147, T148, T149, D683, D698, D699, N02, R31, R58, D62	
Anaemia	D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D61, D62, D63,D64	
Alcoholism	E244, E52, G312, G621, G721, I426, K70, K860, O354, T51, Z714, Z721	
Use of NSAID		M01A
Use of antiplatelet drugs		B01A C
Use of cholesterol lowering drugs		C10A, C10B

NPR, Norwegian Patient Registry; NorPD,Norwegian Prescription Database; NCMP, Norwegian Classification of Medical Procedures

Supplementary table S2; ICD-codes used to calculate risk scores

CHADS2-VASC		
Point	**Condition**	**Definition**
1	Heart Failure	use definition from baseline covariates (Table 1)
1	Hypertension	use definition from baseline covariates (Table 1)
1	Diabetes mellitus	use definition from baseline covariates (Table 1)
2	Stroke, TIA or systemic embolism	use definition from baseline covariates (Table 1)
1	Vascular Disease (myocardial infarction or peripheral arterial disease)	Combined definitions from baseline covariates "Ischaemic Heart Disease" , and "Vascular disease" in table 1.
1	Female	
1	Age 65-<75 years	
2	Age≥ 75 years	
HAS-BLED		
Point	Condition	**Definition**
1	Hypertension	Use definition for "Hypertension" from baseline comorbidities
1	Abnormal kidney function	Use definition for "Chronic kidney disease" from baseline comorbidities
1	Abnormal liver function:	Use definition for "Liver disease" from baseline comorbidities
1	Stroke, TIAor TIA	use definition "History of stroke" from baseline comorbidities
1	Any bleeding other than haemorrhagic stroke	Use definition of Major and CRNM bleeding from baseline comorbidities, excluding codes for haemorrhagic stroke I60, I61, I690-I692
N/A	Labile INR	Not available
1	Age≥ 65 years	1 point for age 65 years or older
1	Alcohol/ Drug Therapy	Use definition of "Alcoholism" , "Use of NSAIDs last 12 months" and "Use of antiplatelet drugs last 12 months, from baseline comorbidities.

Values are numbers (percent) unless otherwise specified. TIA, transient ischaemic attack; NSAIDs, non-steroidal inti-inflammatory drugs; INR, International Normalised Ratio

Supplementary table S3. Baseline characteristics of total study population

	Dabigatran n= 10 413	Apixaban n= 28 363	Rivaroxaban n= 13 700	Warfarin n=13 087	Total n= 65 563
Year of entry into study					
2013	4 476 (43.0)	371 (1.3)	2 995 (21.9)	6 078 (46.4)	13 920 (21.2)
2014	3 219 (30.9)	3 438 (12.1)	2 980 (21.8)	3 648 (27.9)	13 285 (20.3)
2015	1 106 (10.6)	6 751 (23.8)	3 230 (23.6)	1 898 (14.5)	12 985 (19.8)
2016	837 (8.0)	8 562 (30.2)	2 736 (20.0)	966 (7.4)	13 101 (20.0)
2017	775 (7.4)	9 241 (32.6)	1 759 (12.8)	497 (3.8)	12 272 (18.7)
OAC dose					
Standard	6 652 (63.9)	21 149 (74.6)	10 363 (75.6)	13 087 (100)	51 251 (78.2)
Reduced	3 761 (36.1)	7 214 (25.4)	3 337 (24.4)		14 312 (21.8)
Age					
Mean (SD)	70.6 (11.2)	73.76 (11.3)	72.7 (11.1)	73.4 (12.1)	73.0 (11.4)
Median (25th – 75th percentile)	71 (64 – 79)	74 (67 – 82)	73 (66 – 81)	75 (66 – 83)	73 (66 – 81)
<65 yrs.	2 687 (25.8)	5 267 (18.6)	2 787 (20.3)	2 744 (21.0)	13 508 (20.6)
65 to 74 yrs.	3 869 (37.2)	9 310 (32.8)	4 805 (35.1)	3 693 (28.2)	21 723 (33.1)
≥ 75 yrs.	3 857 (37.0)	13 786 (48.6)	6 108 (44.6)	6 650 (50.8)	30 439 (46.4)
Male sex	6 433 (61.8)	15 890 (56.0)	7 944 (58.0)	7 923 (60.5)	38 258 (58.3)
Hypertension	6 693 (64.3)	19 234 (67.8)	9 289 (67.8)	9 222 (70.5)	44 506 (67.8)
Ischaemic heart disease	2 119 (20.3)	6 979 (24.6)	3 061 (22.3)	4 557 (34.8)	16 733 (25.5)
Vascular disease	1 308 (12.6)	4 884 (17.2)	2 065 (15.1)	3 207 (24.5)	11 487 (17.5)
Heart failure	2 140 (20.6)	7 147 (25.2)	3 043 (22.2)	4 593 (35.1)	16 940 (25.8)
History of stroke	1 356 (13.0)	3 822 (13.5)	1 792 (13.1)	1 720 (13.1)	8 696 (13.2)
Chronic Kidney Disease	245 (2.4)	1 991 (7.0)	627 (4.6)	1 634 (12.5)	4 502 (6.9)
Diabetes Mellitus	1 324 (12.7)	4 189 (14.8)	1 887 (13.8)	2 282 (17.4)	9 692 (14.8)
Inflammatory polyarthropathies	474 (4.6)	1 532 (5.4)	678 (4.9)	897 (6.9)	3 584 (5.5)
COPD	2 500 (24.0)	7 660 (27.0)	3 529 (25.8)	3 383 (25.9)	17 102 (26.0)
Active cancer (diagnosis last 12 months)	770 (7.4)	2 774 (9.8)	1 263 (9.2)	1 307 (10.0)	6 119 (9.3)
History of anaemia	458 (4.4)	2 126 (7.5)	757 (5.5)	1 143 (8.7)	4 489 (6.8)
History of bleeding	1 144 (11.0)	3 915 (13.8)	1 715 (12.5)	2 022 (15.5)	8 804 (13.4)
Use of antiplatelet drugs last 12 months	5 125 (49.2)	14 380 (50.7)	7 208 (52.6)	6 930 (53.0)	33 700 (51.3)
Use of NSAIDS last 12 months	2 512 (24.1)	6 198 (21.9)	3 148 (23.0)	2 657 (20.3)	14 538 (22.1)
Use of cholesterol lowering drugs	4 629 (44.5)	13 863 (48.9)	6 315 (46.1)	6 834 (52.2)	31 702 (48.3)
Mean CHA2DS2 VaSc – score (SD)	2.9 (1.7)	3.3 (1.7)	3.1 (1.7)	3.4 (1.8)	3.2 (1.7)
Men HAS-BLED – score (SD)	2.2 (1.1)	2.3 (1.1)	2.4 (1.1)	2.5 (1.1)	2.3 (1.1)

Values are numbers (percent) unless otherwise specified. SD, standard deviation; TIA, transient ischaemic attack; NSAIDs, non-steroidal inti-inflammatory drugs.

Supplementary table S4. NOACs compared with warfarin. Number of events, crude incidence rates and hazard ratios of stroke/SE and major bleeding.

		No of events (incidence / 100 person years)	Hazard ratio (95% CI)*
Stroke/SE			
Warfarin		519 (2.20)	Ref.
Dabigatran	Standard and reduced dose	360 (1.83)	0.94 (0.82 - 1.08)
	150 mg bid.	213 (1.67)	0.97 (0.82 – 1.15)
	110 mg bid.	147 (2.13)	0.89 (0.73 – 1.07)
Rivaroxaban	Standard and reduced dose	541 (2.31)	1.03 (0.91 - 1.16)
	20 mg od.	388 (2.18)	1.05 (0.91 – 1.20)
	15 mg od.	153 (2.75)	1.08 (0.90 - 1.30)
Apixaban	Standard and reduced dose	941 (2.70)	1.04 (0.94 - 1.17)
	5 mg bid.	641 (2.44)	1.02 (0.90 – 1.15)
	2.5 mg bid.	300 (3.50)	1.10 (0.95 - 1.28)
Major bleeding			
Warfarin		607 (2.51)	Ref.
Dabigatran	Standard and reduced dose	275 (1.38)	0.74 (0.64 - 0.86)
	150 mg bid.	138 (1.07)	0.69 (0.56 – 0.84)
	110 mg bid.	137 (1.97)	0.82 (0.68 – 0.99)
Rivaroxaban	Standard and reduced dose	496 (2.10)	0.97 (0.86 - 1.10)
	20 mg od.	313 (1.73)	0.89 (0.77 – 1.03)
	15 mg od.	183 (3.27)	1.17 (0.99 - 1.39)
Apixaban	Standard and reduced dose	673 (1.90)	0.76 (0.68 - 0.85)
	5 mg bid.	418 (1.57)	0.73 (0.64 – 0.83)
	2.5 mg bid.	255 (2.92)	0.85 (0.73 - 0.99)

Abbreviations: NOAC, non-vitamin K antagonist oral anticoagulant; SE, systemic embolism; CI, confidence interval; od, omne die (once daily); bid, bis in die (twice daily).

*Multivariate Cox proportional hazards regression using the same 16 covariates as in the propensity score matched main analyses: age, gender, chronic kidney disease, hypertension, diabetes, ischaemic heart disease, peripheral artery disease (PAD), heart failure, history of stroke/SE, history of bleeding-related hospitalisation, anaemia, active cancer (cancer diagnosis last 12 months), chronic lower respiratory tract disease, use of cholesterol lowering drugs, use of antiplatelet drugs and use of NSAIDs during the last 12 months.
Standard and reduced doses of NOACs are analysed together.

Supplementary tables S5. Baseline characteristics after propensity score matching of patients using standard and reduced dose NOACs separately

A. Baseline characteristics, propensity matched groups, standard dose NOACs

	Dabigatran – rivaroxaban matched cohort n= 13 076			Dabigatran – apixaban matched cohort n= 13 304			Apixaban - rivaroxaban matched cohort n= 20 726		
	Dabigatran, n= 6 538	Rivaroxaban n= 6 538	SMD	Dabigatran n= 6 652	Apixaban n= 6 652	SMD	Apixaban n=10 363	Rivaroxaban n=10 363	SMD
Age			0.004			0.013			0.006
Mean (SD)	65.9 (9.0)	65.9 (9.5)		65.6 (9.3)	65.7 (10.0)		70.4 (10.4)	70.4 (10.5)	
Median	67	67		67	67		71	71	
< 65 yrs.	2 375 (36.3)	2 466 (37.7)		2 489 (37.4)	2 624 (39.4)		2 527 (24.4)	2 574 (24.8)	
65-74 yrs.	3 232 (49.4)	3 020 (46.2)		3 232 (48.6)	2 899 (43.6)		4 190 (40.4)	4 159 (40.1)	
≥ 75 yrs.	931 (14.2)	1 052 (16.1)		931 (14.0)	1 129 (17.0)		3 646 (35.2)	3 630 (35.0)	
Male gender	4 533 (69.3)	4 537 (69.4)	0.001	4 644 (69.8)	4 664 (70.1)	0.007	6 266 (60.5)	6 304 (60.8)	0.008
Hypertension	3 844 (58.8)	3 910 (59.8)	0.022	3 869 (58.2)	3 805 (57.2)	0.020	6 663 (64.3)	6 669 (64.4)	0.003
Ischaemic heart disease	1 045 (16.0)	1 024 (15.7)	0.002	1 058 (15.9)	1 051 (15.8)	0.002	1 968 (19.0)	1 937 (18.7)	0.003
Vascular disease	366 (5.6)	324 (5.0)	0.015	368 (5.5)	359 (5.4)	<0.001	852 (8.2)	805 (7.8)	0.009
Heart failure	982 (15.0)	961 (14.7)	0.011	1 002 (15.1)	949 (14.3)	0.023	1 830 (17.7)	1 819 (17.6)	0.005
Chronic kidney disease	60 (0.9)	46 (0.7)	0.022	60 (0.9)	50 (0.8)	0.015	225 (2.2)	207 (2.0)	0.011
Diabetes mellitus	784 (12.0)	804 (12.3)	0.009	789 (11.9)	797 (12.0)	0.003	1 418 (13.7)	1 369 (13.2)	0.012
Chronic lower respiratory tract diseases	1 538 (23.5)	1 634 (25.0)	0.001	1 549 (23.3)	1 624 (24.4)	0.006	2 696 (26.0)	2 689 (25.9)	0.002
Active cancer (diagnosis last 12 months)	382 (5.8)	377 (5.8)	0.001	383 (5.8)	398 (6.0)	0.009	853 (8.2)	866 (8.4)	0.007
History of stroke /TIA	691 (10.6)	672 (10.3)	0.011	698 (10.5)	726 (10.9)	0.012	1 296 (12.5)	1 272 (12.3)	0.006
History of anaemia	173 (2.6)	157 (2.4)	0.016	174 (2.6)	128 (1.9)	0.046	443 (4.3)	423 (4.1)	0.009
History of bleeding	579 (8.9)	583 (8.9)	0.003	580 (8.7)	540 (8.1)	0.022	1 222 (11.8)	1 151 (11.1)	0.021
Use of antiplatelet drugs last 12 months	2 863 (43.8)	2 884 (44.1)	0.006	2 875 (43.2)	2 855 (42.9)	0.006	5 182 (50.0)	5 145 (49.6)	0.007
Use of NSAIDS last 12 months	1 697 (26.0)	1 703 (26.0)	0.002	1 714 (25.8)	1 772 (26.6)	0.020	2 538 (24.5)	2 470 (23.8)	0.015
Use of cholesterol lowering drugs	2 721 (41.6)	2 747 (42.0)	0.008	2 740 (41.2)	2 761 (41.5)	0.006	4 562 (44.0)	4 587 (44.3)	0.005
Mean CHA2DS2 VaSc – score (SD)	2.3 (1.5)	2.3 (1.4)	0.004	2.3 (1.5)	2.3 (1.5)	0.001	3.0 (1.7)	2.9 (1.6)	0.015
Mean HAS-BLED – score (SD)	2.0 (1.1)	2.0 (1.1)	0.005	2.0 (1.1)	2.0 (1.1)	0.023	2.3 (1.2)	2.3 (1.2)	0.011

Values are numbers (percent) unless otherwise specified. SD, standard deviation; SMD, absolute standardised mean difference; TIA, transient ischaemic attack; NSAIDs, non-steroidal inti-inflammatory drugs.

B. Baseline characteristics, propensity matched groups, reduced dose NOACs

	Dabigatran – rivaroxaban matched cohort n= 6 148			Dabigatran – apixaban matched cohort n= 7 276			Apixaban - rivaroxaban matched cohort n= 6 640		
	Dabigatran, n= 3 074	Rivaroxaban n= 3 074	SMD	Dabigatran n= 3 638	Apixaban n= 3 638	SMD	Apixaban n=3 320	Rivaroxaban n= 3 320	SMD
Age			0.003			0.023			0.002
Mean (SD)	79.8 (8.3)	79.8 (9.6)		80.0 (8.3)	80.0 (9.2)		80.0 (9.8)	80.0 (9.5)	
Median	81	81		81	82		82	82	
< 65 yrs.	150 (4.9)	204 (6.6)		180 (4.9)	233 (6.4)		248 (7.5)	203 (6.1)	
65-74 yrs.	510 (16.6)	594 (19.3)		566 (15.6)	638 (17.5)		591 (17.8)	640 (19.3)	
≥ 75 yrs.	2 414 (78.5)	2 276 (74.0)		2 892 (79.5)	2 767 (76.1)		2 481 (74.7)	2 477 (74.6)	
Male gender	1 466 (47.7)	1 469 (47.8)	0.002	1 700 (46.7)	1 730 (47.6)	0.017	1 656 (49.9)	1 624 (48.9)	0.019
Hypertension	2 329 (75.8)	2 350 (76.4)	0.017	2 733 (75.1)	2 738 (75.3)	0.001	2 563 (77.2)	2 576 (77.6)	0.012
Ischaemic heart disease	868 (28.2)	862 (28.0)	0.001	974 (26.8)	967 (26.6)	0.001	1 020 (30.7)	992 (29.9)	0.019
Vascular disease	334 (10.9)	324 (10.5)	0.001	352 (9.7)	356 (9.8)	0.011	385 (11.6)	376 (11.3)	0.006
Heart failure	1 034 (33.6)	1 032 (33.6)	0.003	1 088 (29.9)	1 044 (28.7)	0.027	1 228 (37.0)	1 198 (36.1)	0.021
Chronic kidney disease	185 (6.0)	182 (5.9)	0.003	185 (5.1)	182 (5.0)	0.003	413 (12.5)	414 (12.5)	<0.001
Diabetes mellitus	427 (13.9)	442 (14.4)	0.012	511 (14.0)	501 (13.8)	0.010	519 (15.6)	507 (15.3)	0.009
Chronic lower respiratory tract diseases	785 (25.5)	761 (24.8)	0.005	926 (25.5)	953 (26.2)	0.006	883 (26.6)	831 (25.0)	0.002
Active cancer (diagnosis last 12 months)	300 (9.8)	325 (10.6)	0.020	359 (9.9)	371 (10.2)	0.005	343 (10.3)	363 (10.9)	0.016
History of stroke /TIA	465 (15.1)	447 (14.5)	0.014	622 (17.1)	642 (17.6)	0.016	487 (14.7)	491 (14.8)	0.004
History of anaemia	269 (8.8)	256 (8.3)	0.015	284 (7.8)	249 (6.8)	0.034	339 (10.2)	332 (10.0)	0.009
History of bleeding	484 (15.7)	490 (15.9)	0.005	551 (15.1)	539 (14.8)	0.008	573 (17.3)	559 (16.8)	0.010
Use of antiplatelet drugs last 12 months	1 865 (60.7)	1 871 (60.9)	0.004	2 188 (60.1)	2 209 (60.7)	0.012	2 053 (61.8)	2 055 (61.9)	0.001
Use of NSAIDS last 12 months	636 (20.7)	634 (20.6)	0.002	776 (21.3)	756 (20.8)	0.013	681 (20.5)	672 (20.2)	0.007
Use of cholesterol lowering drugs	1 563 (50.8)	1 559 (50.7)	0.003	1 843 (50.7)	1 866 (51.3)	0.013	1 726 (52.0)	1 721 (51.8)	0.003
Mean CHA2DS2 VaSc – score (SD)	4.1 (1.5)	4.1 (1.6)	0.046	4.1 (1.5)	4.1 (1.5)	0.036	4.0 (1.4)	4.0 (1.4)	0.001
Mean HAS-BLED – score (SD)	2.8 (1.0)	2.8 (1.0)	0.022	2.8 (1.0)	2.7 (1.0)	0.004	2.9 (1.1)	2.9 (1.0)	0.006

Values are numbers (percent) unless otherwise specified. SD, standard deviation; SMD, absolute standardised mean difference; TIA, transient ischaemic attack; NSAIDs, non-steroidal inti-inflammatory drugs.

Supplementary table S6. Results from sensitivity analyses. Hazard ratios of stroke/SE and major bleeding

	Main analysis[a]	Sensitivity analyses		
		Follow-up restricted to 12 months[b]	Intention-to-treat analysis[c]	Multivariate Cox regression[d]
Dabigatran vs rivaroxaban				
Stroke/SE	0.88 (0.76 - 1.02)	0.93 (0.78 - 1.10)	0.88 (0.78 - 0.99)	0.92 (0.80 - 1.05)
Major bleeding	0.75 (0.64 - 0.88)	0.79 (0.64 - 0.98)	0.84 (0.74 - 0.96)	0.77 (0.67 - 0.90)
Dabigatran vs apixaban				
Stroke/SE	0.88 (0.75 - 1.02)	0.87 (0.73 - 1.03)	0.87 (0.78 - 1.01)	0.91 (0.80 - 1.03)
Major bleeding	1.03 (0.85 - 1.24)	1.04 (0.82 - 1.31)	1.06 (0.91 - 1.24)	1.00 (0.87 - 1.16)
Apixaban vs rivaroxaban				
Stroke	1.00 (0.89 - 1.14)	1.04 (0.90 - 1.20)	0.98 (0.87 - 1.10)	1.01 (0.90 - 1.13)
Major bleeding	0.79 (0.68 - 0.91)	0.77 (0.64 - 0.93)	0.81 (0.71 - 0.92)	0.77 (0.68 - 0.86)

a. Main analysis (propensity score matching (PSM) on the basis of 16 covariates: age, gender, chronic kidney disease, hypertension, diabetes, ischaemic heart disease, peripheral artery disease (PAD), heart failure, history of stroke/SE, history of bleeding-related hospitalisation, anaemia, active cancer (cancer diagnosis last 12 months), chronic lower respiratory tract disease, use of cholesterol lowering drugs, use of antiplatelet drugs and use of NSAIDs during the last 12 months, and subsequent univariate Cox regression

b. Analysis of PSM cohorts, with follow-up time restricted to 12 months

c. Analysis of PSM cohorts, "Intention-to-treat"-like analysis where patients were not censored upon switching or discontinuation of NOACs, and were followed from index date until death or end of study period.

d. Analysis of total study population, multivariate Cox proportional hazards regression as alternative to propensity score matching (all 16 variables used in PSM).

Supplementary figure S1. Propensity scores before and after matching

Paper III

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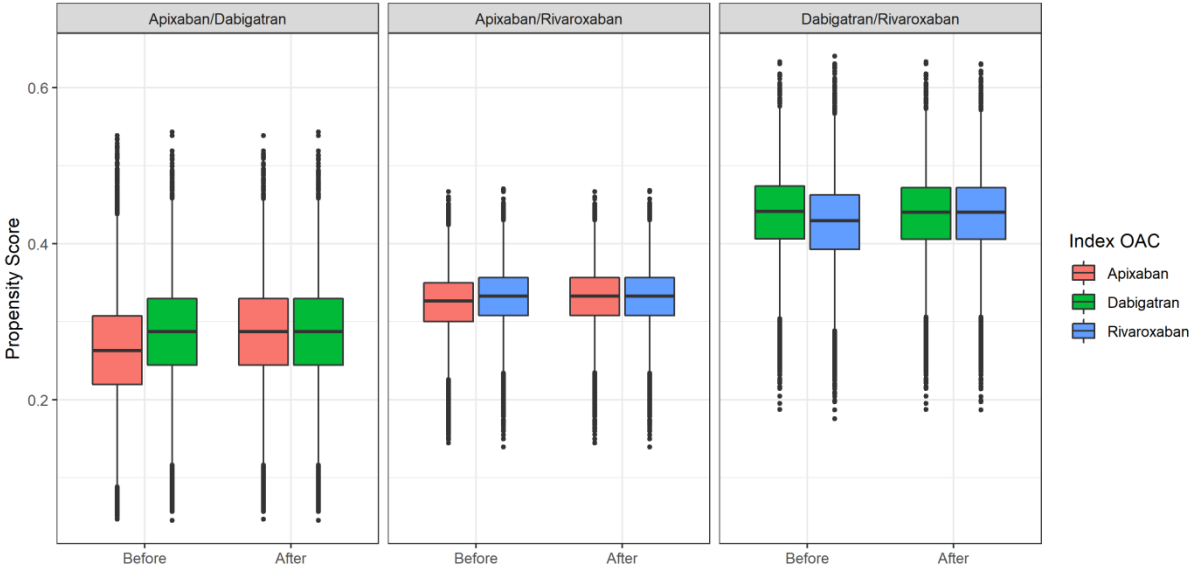
Original research

Effectiveness and safety of oral anticoagulants in elderly patients with atrial fibrillation

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ABSTRACT

Objectives To assess the risk of stroke/systemic embolism (SE) and major bleeding associated with the use of oral anticoagulants in elderly patients with atrial fibrillation (AF) in a real-world population.

Methods We identified all anticoagulant-naive initiators of warfarin, dabigatran, rivaroxaban and apixaban for the indication AF in Norway between January 2013 and December 2017. Multivariate competing risk regression was used to calculate subhazard ratios (SHRs) describing associations between non-vitamin K antagonist oral anticoagulants (NOACs) compared with warfarin for risk of stroke/SE and major bleeding.

Results Among 30 401 patients ≥75 years identified (median age 82 years, 53% women, mean CHA_2DS_2-VaSc score 4.5), 3857 initiated dabigatran, 6108 rivaroxaban, 13 786 apixaban and 6650 warfarin. Reduced dose was initiated in 11 559 (49%) of the NOAC-treated patients. For stroke, the SHRs for standard dose NOAC against warfarin were 0.80 (95% CI 0.57 to 1.13) for dabigatran; 1.07 (95% CI 0.89 to 1.30) for rivaroxaban and 0.95 (95% CI 0.78 to 1.15) for apixaban. For major bleeding, the SHRs against warfarin were 0.75 (95% CI 0.52 to 1.08) for dabigatran; 0.96 (95% CI 0.78 to 1.16) for rivaroxaban and 0.74 (95% CI 0.60 to 0.91) for apixaban. Comparing reduced doses of NOACs with warfarin yielded similar results. Sensitivity analyses were in accordance with the main results.

Conclusion In this nationwide cohort study of patients ≥75 years initiating oral anticoagulation for AF, standard and reduced dose NOACs were associated with similar risks of stroke/SE as warfarin and lower or similar risks of bleeding. The NOACs seem to be a safe option also in elderly patients.

INTRODUCTION

Age is a strong and independent risk factor for both stroke and bleeding in patients with atrial fibrillation (AF).[1] Oral anticoagulation is associated with a net clinical benefit in elderly patients despite their elevated bleeding risk,[2] and the 2020 European Society of Cardiology (ESC) guidelines for the management of AF recommend non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention over vitamin K antagonists (VKAs), without age restrictions.[3]

In the pivotal randomised controlled trials (RCTs) leading to the approval of the NOACs, the median age was just over 70 years and approximately 65% of the patients included were men.[4–6]

In the real world, approximately half of patients with AF starting on oral anticoagulants (OACs) are 75 years or older, and approximately half of these are women.[7] No RCT has investigated the efficacy and safety of NOACs specifically in elderly patients, but subgroup analyses of the RCTs,[8–11] and observational studies,[12 13] indicate that the benefits of NOACs over VKAs are maintained in the elderly population. More insight into the comparative abilities of anticoagulants to reduce the risk of stroke while keeping bleeding risk low in elderly patients is needed.

In this study, we aimed to compare the risks of stroke or systemic embolism (SE), and major bleeding, between standard and reduced doses of dabigatran, rivaroxaban, apixaban and warfarin, in a Norwegian nationwide cohort of patients ≥75 years with AF. In Norway, data from all hospital contacts and prescription dispensations are routinely collected through national registries,[14] making it possible to follow individuals over time with virtually no selection bias.

METHODS

Data sources

Data were collected from the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD). The NPR contains diagnoses from all hospital admissions, outpatient consultations and specialist consultations in Norway.[14] For each contact, the primary (the primary disease/condition treated) and secondary codes (relevant comorbidities) are recorded. Diagnoses are coded according to the International Classification of Diseases (10th revision, ICD-10) system, and surgical procedures according to the Nordic Medico-Statistical Committee (NOMESCO) coding system.[15]

The NorPD contains information from all pharmacies in Norway on dispensations including drug codes (Anatomical Therapeutic Chemical system (ATC)), drug strength, pack-size and vital status of patients.[16] Drug expenses for treatment of serious chronic illnesses are reimbursed in Norway, and the NorPD contains the relevant ICD-10/International Classification of Primary Care (ICPC-2) codes warranting reimbursement. Linkage of individual-level data across NPR and NorPD was enabled via unique personal identification numbers.

Cohort creation and study design

All patients diagnosed with AF, but without mitral stenosis or mechanical heart valves, between January
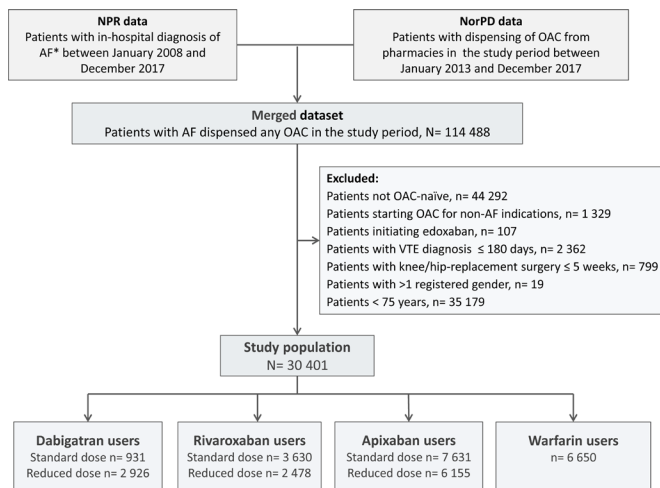
Figure 1 Cohort creation flow-chart. AF*, atrial fibrillation in the absence of mitral stenosis or mechanical prosthetic heart valves; NPR, Norwegian Patient Registry; NorPD, Norwegian Prescription Database; OAC, oral anticoagulant; VTE, venous thromboembolism.

2008 and December 2017 were identified from the NPR. From the NorPD, we identified all patients with at least one dispensation of an OAC between January 2013 and December 2017. These data were linked to create a cohort of patients diagnosed with AF, initiating treatment with an OAC (figure 1). The index date was set to the day of the first dispensing of an OAC (dabigatran 110 mg/150 mg, rivaroxaban 15 mg/20 mg, apixaban 2.5 mg/5 mg or warfarin 2.5 mg) for the indication AF in the study period. We chose an 'active-comparator, new-user' design: the drug of interest was compared with another agent used for the same indication rather than with no treatment. This ensures that treatment groups have similar treatment indications, minimising differences in patient characteristics. With the new-user design, patients were included from the time of treatment initiation, enabling capture of all events occurring during follow-up.[17] The design involves a washout period before inclusion; patients with a dispensing of any anticoagulant in the preceding 12 months before the index date; a history of venous thromboembolism during the last 180 days; or knee or hip replacement surgery during the last 35 days before the index date were excluded. Due to limited usage in the study period, patients initiating edoxaban were excluded (n=107). Finally, all patients <75 years were excluded, creating a cohort of anticoagulant-naive AF patients ≥75 years starting treatment with warfarin, dabigatran, rivaroxaban or apixaban (figure 1). ICD-10 codes used for inclusion/exclusion criteria, comorbidities and outcomes are listed in online supplemental table 1.

OAC supply
The days of warfarin supply were estimated as previously described.[18] The period of supply of NOACs was estimated by the pack-size/number of packs prescribed, given a fixed dosing of NOACs. To account for incomplete adherence, a 30-day grace period between the calculated end of NOAC supply and the date of a new prescription was allowed.

Comorbidities
Using ICD-10-diagnoses from NPR, and ICD/ICPC-2-diagnoses from NorPD, a set of comorbidities was compiled for the last 5 years before the index date for each patient. Online supplemental table S2 shows in detail how CHA_2DS_2-VASc and HAS-BLED

scores were calculated. For identification of comorbidities, both primary and secondary ICD-10 and NOMESCO codes from the NPR were used.

Outcomes and follow-up period
The main outcomes investigated were stroke or SE (effectiveness outcome) and major bleeding (safety outcome). Other outcomes included ischaemic stroke, intracranial haemorrhage, gastrointestinal haemorrhage, any haemorrhage and all-cause mortality. Major bleeding was defined as any bleeding into a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, intramuscular with compartment syndrome, major gastrointestinal and/or any bleeding accompanied by blood transfusion ≤10 days after hospital admission. For identification of outcomes, only primary (first listed) ICD-10 and NOMESCO codes for each hospital stay were used (online supplemental table S1). Patients were followed until discontinuation or switching of OAC, death or end of study period (31 December 2017), whichever occurred first.

Statistical analysis
Categorical variables are reported as numbers and per cent, continuous variables as means with SD or medians with 25th–75th percentiles. Based on clinical experience and by using directed acyclic graphs, we identified a group of 20 confounders for the effect of exposure to OACs on both the chosen outcomes and the competing risk of death.[19] Multivariate competing risk regression adjusting for these 20 variables was performed according to the method of Fine and Gray,[20] to calculate subhazard ratios (SHR) describing associations between exposure to different OACs and the defined outcomes, treating death as a competing risk. The results were graphically presented by cumulative incidence functions.[21] To evaluate associations between OAC therapy and risk of all-cause mortality, multivariate Cox regression was performed. The proportional hazards assumption was checked using Schoenfeld residuals and by comparing the log-log transformation of the Kaplan-Meier survival curves for each variable. Robust sandwich estimates were calculated.[22] Estimating days of supply for warfarin, as well as anticoagulant effect of the dose taken, is difficult in registry-based studies. To elaborate on our findings, we performed post hoc analyses with NOAC–NOAC comparisons after the main analyses, which compared NOACs with warfarin. The variables adjusted for were gender, age, year of inclusion into the study, chronic kidney disease, hypertension, diabetes, ischaemic heart disease, peripheral artery disease, heart failure, dementia, thyroid disorders, active cancer (cancer diagnosis last 12 months), chronic lower respiratory tract disease, history of stroke/SE, history of bleeding-related hospitalisation, history of anaemia, use of cholesterol lowering drugs, use of antiplatelet drugs and use of NSAIDs during the last 12 months. Level of significance was set to 5%. Statistical analyses were performed using SAS V.9.4 (SAS Institute) and STATA V.16 (STATACorp LLC).

Sensitivity analyses
Four sensitivity analyses were performed for the outcomes stroke/SE, major bleeding and all-cause mortality: (1) allowing a longer gap period of 90 days between the calculated end of OAC supply and a new prescription dispensing before censoring; (2) analysing only truly OAC naive patients, by excluding patients with a dispensing of any anticoagulant for any indication from pharmacies during the last 5 years (12 months was used in the main analyses); (3) standardising follow-up time for all OACs to

Table 1 Baseline characteristics

	Dabigatran	Dabigatran	Rivaroxaban	Rivaroxaban	Apixaban	Apixaban	Warfarin
	150 mg two times per day	110 two times per day	20 mg once a day	15 mg once a day	5 mg two times per day	2.5 mg two times per day	2.5 mg
N	931	2926	3630	2478	7631	6155	6650
Year of inclusion into study							
2013	356 (38.2)	1 333 (45.6)	902 (24.8)	724 (29.2)	93 (1.2)	87 (1.4)	3131 (47.1)
2014	284 (30.5)	837 (28.6)	834 (23.0)	653 (26.4)	846 (11.1)	846 (13.7)	1868 (28.1)
2015	116 (12.5)	296 (10.1)	755 (20.8)	539 (21.8)	1780 (23.3)	1546 (25.1)	951 (14.3)
2016	88 (9.5)	224 (7.7)	680 (18.7)	362 (14.6)	2303 (30.2)	1916 (31.1)	485 (7.3)
2017	87 (9.3)	236 (8.1)	459 (12.6)	200 (8.1)	2609 (34.2)	1760 (28.6)	215 (3.2)
Age							
75–84	875 (94.0)	1867 (63.8)	2764 (76.1)	1279 (51.6)	6020 (78.9)	2643 (42.9)	4186 (62.9)
85–94	53 (5.7)	1020 (34.9)	845 (23.3)	1122 (45.3)	1560 (20.4)	3254 (52.9)	2379 (35.8)
95–105	3 (0.3)	39 (1.3)	21 (0.6)	77 (3.1)	51 (0.7)	258 (4.2)	85 (1.3)
Mean (SD)	78.0 (3.5)	83.0 (4.9)	81.0 (4.8)	84.4 (5.4)	80.8 (4.6)	85.6 (5.3)	82.9 (5.1)
Median (25th–75th percentile)	77 (76–79)	82 (79–86)	80 (77–84)	84 (80–88)	80 (77–84)	86 (82–89)	82 (79–87)
Female gender	386 (41.5)	1633 (55.8)	1812 (49.9)	1401 (56.5)	3744 (49.1)	3818 (62.0)	3316 (49.9)
Hypertension	619 (66.5)	2194 (75.0)	2566 (70.7)	1971 (79.5)	5521 (72.3)	4741 (77.0)	5235 (78.7)
Ischaemic heart disease	186 (20.0)	764 (26.1)	831 (22.9)	750 (30.3)	1874 (24.6)	1920 (31.2)	2511 (37.8)
Peripheral artery disease	73 (7.8)	289 (9.9)	366 (10.1)	267 (10.8)	796 (10.4)	722 (11.7)	898 (13.5)
Heart failure	160 (17.2)	902 (30.8)	830 (22.9)	982 (39.6)	1979 (25.9)	2490 (40.5)	2904 (43.7)
Chronic kidney disease	20 (2.1)	146 (5.0)	119 (3.3)	311 (12.6)	387 (5.1)	1065 (17.3)	1096 (16.5)
Diabetes mellitus	114 (12.2)	377 (12.9)	485 (13.4)	348 (14.0)	1117 (14.6)	962 (15.6)	1187 (17.8)
Thyroid disorders	32 (3.4)	151 (5.2)	146 (4.0)	143 (5.8)	321 (4.2)	333 (5.4)	385 (5.8)
Chronic lower respiratory tract disorder	234 (25.1)	707 (24.2)	944 (26.0)	600 (24.2)	2081 (27.3)	1639 (26.6)	1760 (26.5)
Active cancer (diagnosis last 12 months	91 (9.8)	283 (9.7)	375 (10.3)	277 (11.2)	823 (10.8)	715 (11.6)	745 (11.2)
Dementia	12 (1.3)	88 (3.0)	92 (2.5)	94 (3.8)	187 (2.5)	276 (4.5)	203 (3.1)
History of stroke/SE	136 (14.6)	528 (18.0)	600 (16.5)	411 (16.6)	1253 (16.4)	1117 (18.1)	1096 (16.5)
History of ischaemic stroke	134 (14.4)	512 (17.5)	588 (16.2)	394 (15.9)	1229 (16.1)	1087 (17.7)	1069 (16.1)
History of intracranial haemorrhage	3 (0.3)	27 (0.9)	21 (0.6)	23 (0.9)	50 (0.7)	67 (1.1)	45 (0.7)
History of bleeding	105 (11.3)	448 (15.3)	501 (13.8)	432 (17.4)	1106 (14.5)	1273 (20.7)	1225 (18.4)
History of gastrointestinal bleeding	23 (2.5)	131 (4.5)	143 (3.9)	143 (5.8)	297 (3.9)	372 (6.0)	399 (6.0)
History of anaemia	41 (4.4)	237 (8.1)	236 (6.5)	276 (11.1)	614 (8.0)	812 (14.8)	788 (11.8)
Use of antiplatelet drugs last 12 months	494 (53.1)	1789 (61.1)	2127 (58.6)	1581 (63.8)	4384 (57.4)	3830 (62.2)	3803 (57.2)
Use of NSAIDs last 12 months	242 (26.0)	590 (20.2)	770 (21.2)	451 (18.2)	1584 (20.8)	987 (16.0)	1128 (17.0)
Use of cholesterol lowering drugs	461 (49.5)	1463 (50.0)	1770 (48.8)	1264 (51.0)	4107 (53.8)	3174 (51.6)	3735 (56.2)
Mean CHA2DS2-VaSc score (SD)	3.9 (1.3)	4.4 (1.4)	4.2 (1.3)	4.6 (1.4)	4.3 (1.3)	4.7 (1.4)	4.7 (1.4)
Mean HAS-BLED score (SD)	2.6 (0.95)	2.8 (0.9)	2.7 (0.95)	3.0 (1.0)	2.8 (0.98)	3.0 (1.1)	2.9 (1.0)

Values are numbers (per cent), unless otherwise stated.

CHA2DS2-VaSc, congestive heart failure (or left ventricular systolic dysfunction), hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack or systemic embolism, vascular disease, age ≥65 years, sex category; HAS-BLED, hypertension, abnormal renal function/ abnormal liver function, prior stroke, prior major bleeding, labile international normalised ratio (INR), elderly age ≥65 years, prior alcohol or drug abuse/use of medications that predispose to bleeding (antiplatelet agents, NSAIDs); NSAIDs, non-steroidal anti-inflammatory drugs; SE, systemic embolism.

12 months; (4) an 'intention-to-treat'-like analysis, not censoring patients on switching between anticoagulants or discontinuation of therapy.

RESULTS

In total, 30 401 patients were included; 3857 patients initiating dabigatran (standard dose 931 patients; reduced dose 2926); 6108 patients initiating rivaroxaban (standard dose 3630 patients; reduced dose 2478 patients); 13 786 patients initiating apixaban (standard dose 7631; reduced dose 6155) and 6650 patients initiating warfarin. The median age for the total population was 82 years (IQR 78–86); the majority of patients were female (53.0%), and the mean CHA$_2$DS$_2$-VASC score was 4.5 (SD 1.4). Baseline characteristics of the study population in relation to treatment groups are shown in table 1. Initiators of standard doses of NOACs were likely to be younger than initiators of

warfarin, while initiators of reduced doses of NOACs were more likely to be of similar (dabigatran) or older age (rivaroxaban and apixaban) than initiators of warfarin. Users of dabigatran 150 mg two times per day had the lowest, and users of apixaban 2.5 mg two times per day, the highest median age (77 and 86 years, respectively). Median follow-up time was 24.4 months (standard dose) and 17.8 months (reduced dose) for dabigatran, 19.0 months (standard dose) and 16.2 months (reduced dose) for rivaroxaban, 12.7 months (standard dose) and 11.6 months (reduced dose) for apixaban and 19.9 months for warfarin. The proportion of patients who switched anticoagulants during the study period was 20.3% (standard dose) and 21.6% (reduced dose) for dabigatran, 11.8% (standard dose) and 11.9% (reduced dose) for rivaroxaban, 2.8% (standard dose) and 2.7% (reduced dose) for apixaban and 17.0% for warfarin. The crude incidence rate of stroke/SE (events per 100 person years) was
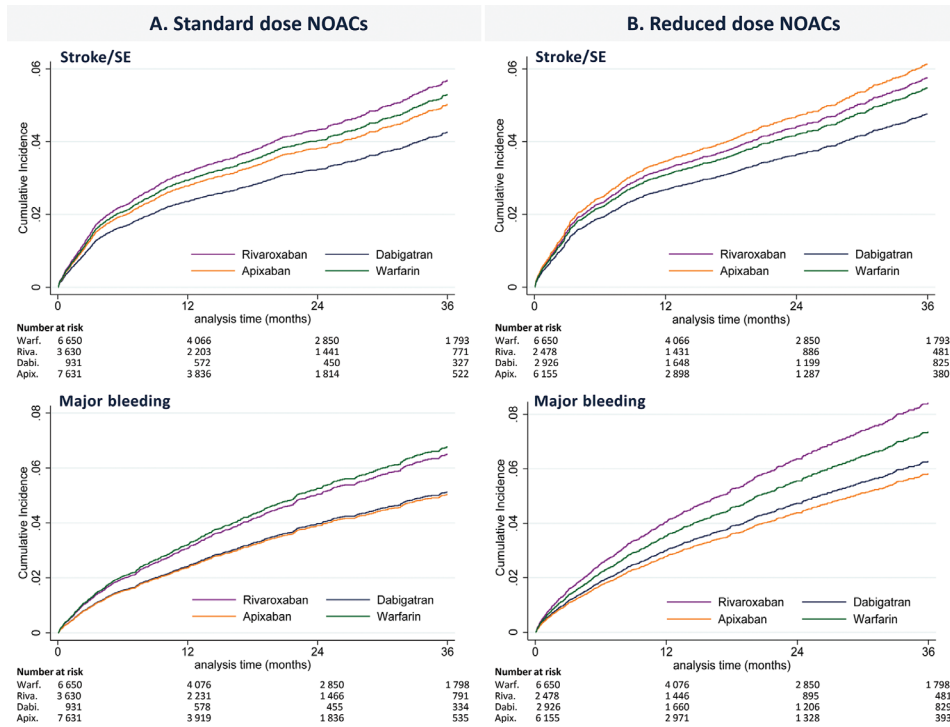
Figure 2 Cumulative incidence of main effectiveness and safety outcomes for warfarin, standard (A) and reduced (B) dose NOACs. NOAC, non-vitamin K antagonist oral anticoagulant; SE, systemic embolism.

Figure 3 Number of events, crude incidence rates[1] and subhazard ratios[2] between standard (A) and reduced (B) dose NOACs and warfarin for all outcomes. [1]Crude incidence rate, crude incidence/100 patient years; [2] competing risk regression, treating death as competing risk, adjusted for NOAC dose, gender, age, year of inclusion into the study, chronic kidney disease, hypertension, diabetes, ischaemic heart disease, peripheral artery disease, heart failure, dementia, thyroid disorders, active cancer (cancer diagnosis last 12 months), chronic lower respiratory tract disease, history of stroke/SE, history of bleeding-related hospitalisation, history of anaemia, use of cholesterol lowering drugs, use of antiplatelet drugs and use of NSAIDs during the last 12 months. *For risk of all-cause mortality multivariate Cox proportional regression adjusting for the same variables used in competing risk regression was performed. NOAC, non-vitamin K antagonist oral anticoagulant; NSAIDs, non-steroidal anti-inflammatory drugs; SE, systemic embolism.
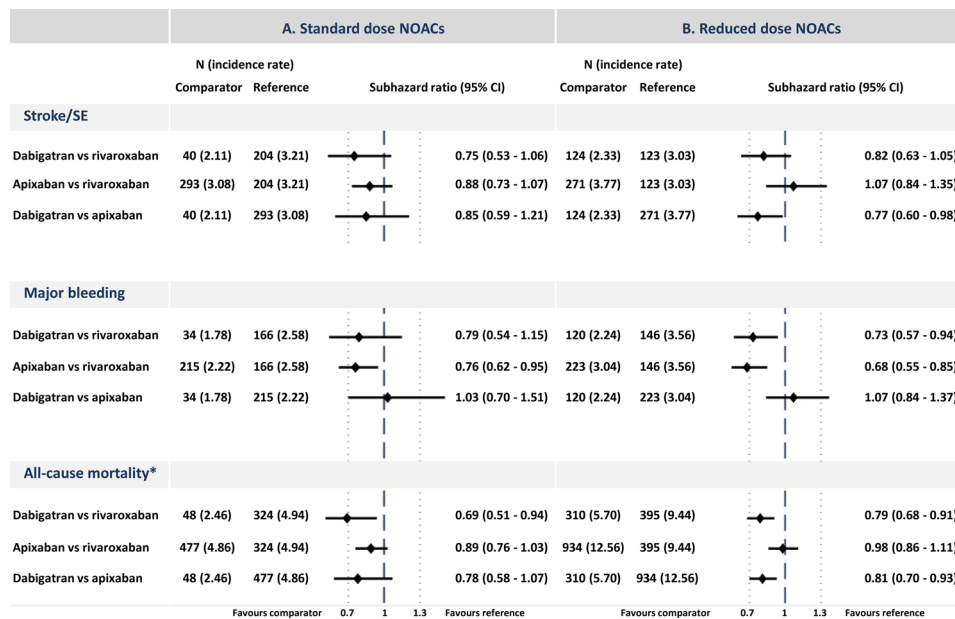
Figure 4 Number of events, crude incidence rates[1] and subhazard ratios[2] between standard (A) and reduced (B) dose NOACs for main outcomes and all-cause mortality. [1]Crude incidence rate, crude incidence/100 patient years; [2]competing risk regression, treating death as competing risk, adjusted for NOAC dose, gender, age, year of inclusion into the study, chronic kidney disease, hypertension, diabetes, ischaemic heart disease, peripheral artery disease, heart failure, dementia, thyroid disorders, active cancer (cancer diagnosis last 12 months), chronic lower respiratory tract disease, history of stroke/SE, history of bleeding-related hospitalisation, history of anaemia, use of cholesterol lowering drugs, use of antiplatelet drugs and use of NSAIDs during the last 12 months. *For risk of all-cause mortality, multivariate Cox proportional regression adjusting for the same variables used in competing risk regression was performed. NOAC, non-vitamin K antagonist oral anticoagulant; NSAIDs, non-steroidal anti-inflammatory drugs; SE, systemic embolism.

2.11 (standard dose) and 2.33 (reduced dose) for dabigatran, 3.21 (standard dose) and 3.03 (reduced dose) for rivaroxaban, 3.08 (standard dose) and 3.77 (reduced dose) for apixaban and 2.69 for warfarin. The crude incidence rate of major bleeding (events per 100 patient years) was 1.78 (standard dose) and 2.24 (reduced dose) for users of dabigatran, 2.58 (standard dose) and 3.56 (reduced dose) for rivaroxaban, 2.22 (standard dose) and 3.04 (reduced dose) for apixaban and 3.02 for warfarin. The cumulative incidence functions for stroke/SE and major bleeding for each OAC are shown in figure 2.

NOAC–warfarin comparisons

Results of the comparisons between NOACs and warfarin for the main outcomes stroke/SE and major bleeding, as well as ischaemic stroke, intracranial haemorrhage, gastrointestinal bleeding, any bleeding and all-cause mortality are shown in figure 3. We found similar risks of stroke/SE for both standard and reduced doses of all NOACs compared with warfarin. Both doses of apixaban were associated with lower risk of major bleeding compared with warfarin (standard dose SHR 0.74, 95% CI 0.60 to 0.91; reduced dose SHR 0.78, 95% CI 0.64 to 0.96), while use of both doses of dabigatran and rivaroxaban was associated with similar risks. For risk of all-cause mortality, no significant differences were found between standard dose of NOACs and warfarin, while reduced dose rivaroxaban (HR 1.42, 95% CI 1.25 to 1.61) and reduced dose apixaban (HR 1.38, 95% CI 1.22 to 1.56) were associated with significantly higher risk.

NOAC–NOAC comparisons

The results of NOAC–NOAC comparisons are shown in figure 4. No significant differences were found in risk of stroke/SE, except in the comparison between reduced dose of dabigatran

and reduced dose of apixaban (SHR 0.77, 95% CI 0.60 to 0.98). Standard dose of apixaban was associated with significantly lower risk of major bleeding compared with standard dose of rivaroxaban (SHR 0.76, 95% CI 0.62 to 0.95). Further, reduced doses of apixaban and of dabigatran were associated with significantly lower risk of major bleeding compared with reduced doses of rivaroxaban (figure 4).

Sensitivity analyses

The results of the sensitivity analyses (table 2) were in line with the main analyses with respect to the main outcomes stroke/SE and major bleeding. Regarding risk of all-cause death, the sensitivity analyses showed greater diversity in the results. Of particular interest is that in the 'intention-to-treat-analyses', the risk of all-cause death was lower or similar with reduced dose of NOACs compared with warfarin.

DISCUSSION

In this nationwide cohort study of elderly patients ≥75 years with AF, we investigated risk of thromboembolic and bleeding events associated with use of standard and reduced doses of NOACs compared with warfarin and NOACs compared with NOACs. Comparing NOACs with warfarin, we found comparable rates of stroke/SE for both standard and reduced dose NOACs and that both doses of apixaban were associated with significantly lower risks of major bleeding. In the NOAC–NOAC comparisons, reduced dose dabigatran was associated with a significantly lower risk of stroke/SE than reduced dose apixaban, while reduced dose dabigatran as well as both doses of apixaban were associated with lower risks of major bleeding compared with the corresponding doses of rivaroxaban. The median age of patients

Table 2 Sensitivity analyses

| | Main analysis* | Sensitivity analyses | | | |
		90-day gap period†	True OAC naive‡	Standardised to 12-month follow-up§	Intention to treat analysis¶
Standard dose NOACs vs warfarin					
Stroke/SE	**Subhazard ratio (95% CI)**				
Warfarin	Ref	Ref	Ref	Ref	Ref
Dabigatran	0.80 (0.57 to 1.13)	0.82 (0.58 to 1.15)	0.80 (0.56 to 1.14)	0.95 (0.62 to 1.43)	0.81 (0.62 to 1.08)
Rivaroxaban	1.07 (0.89 to 1.30)	1.08 (0.89 to 1.30)	1.02 (0.84 to 1.25)	1.02 (0.80 to 1.30)	0.97 (0.83 to 1.14)
Apixaban	0.95 (0.78 to 1.15)	0.95 (0.78 to 1.16)	0.92 (0.75 to 1.22)	1.00 (0.79 to 1.28)	0.88 (0.74 to 1.04)
Major bleeding	**Subhazard ratio (95% CI)**				
Warfarin	Ref	Ref	Ref	Ref	Ref
Dabigatran	0.75 (0.52 to 1.08)	0.73 (0.51 to 1.05)	0.77 (0.73 to 1.12)	0.86 (0.53 to 1.39)	0.67 (0.50 to 0.87)
Rivaroxaban	0.96 (0.78 to 1.16)	0.95 (0.78 to 1.15)	0.90 (0.58 to 0.90)	0.88 (0.67 to 1.16)	0.84 (0.72 to 0.99)
Apixaban	0.74 (0.60 to 0.91)	0.70 (0.57 to 0.87)	0.72 (0.58 to 0.90)	0.66 (0.50 to 0.86)	0.63 (0.53 to 0.75)
All-cause death	**HR (95% CI)**				
Warfarin	Ref	Ref	Ref	Ref	Ref
Dabigatran	0.77 (0.57 to 1.05)	0.79 (0.54 to 0.91)	0.75 (0.55 to 1.02)	0.76 (0.49 to 1.20)	0.66 (0.55 to 0.79)
Rivaroxaban	1.12 (0.97 to 1.28)	0.90 (0.80 to 1.02)	1.06 (0.91 to 1.23)	0.96 (0.78 to 1.18)	0.84 (0.77 to 0.92)
Apixaban	0.99 (0.85 to 1.15)	0.79 (0.70 to 0.91)	0.93 (0.79 to 1.08)	0.84 (0.69 to 1.03)	0.72 (0.65 to 0.80)
Reduced dose NOACs vs warfarin					
Stroke/SE	**Subhazard ratio (95% CI)**				
Warfarin	Ref	Ref	Ref	Ref	Ref
Dabigatran	0.87 (0.70 to 1.07)	0.86 (0.70 to 1.06)	0.83 (0.66 to 1.03)	0.91 (0.70 to 1.18)	0.87 (0.74 to 1.03)
Rivaroxaban	1.05 (0.85 to 1.30)	1.08 (0.87 to 1.33)	1.06 (0.85 to 1.32)	1.19 (0.92 to 1.54)	1.06 (0.89 to 1.26)
Apixaban	1.12 (0.92 to 1.38)	1.15 (0.94 to 1.41)	1.10 (0.89 to 1.35)	1.15 (0.90 to 1.47)	1.00 (0.84 to 1.18)
Major bleeding	**Subhazard ratio (95% CI)**				
Warfarin	Ref	Ref	Ref	Ref	Ref
Dabigatran	0.85 (0.69 to 1.05)	0.83 (0.68 to 1.03)	0.86 (0.68 to 1.07)	0.86 (0.65 to 1.14)	0.87 (0.74 to 1.01)
Rivaroxaban	1.15 (0.95 to 1.40)	1.14 (0.94 to 1.38)	1.16 (0.94 to 1.42)	1.15 (0.89 to 1.48)	0.95 (0.81 to 1.12)
Apixaban	0.78 (0.64 to 0.96)	0.79 (0.65 to 0.96)	0.81 (0.66 to 1.00)	0.77 (0.60 to 0.99)	0.67 (0.57 to 0.80)
All-cause death	**HR (95% CI)**				
Warfarin	Ref	Ref	Ref	Ref	Ref
Dabigatran	1.11 (0.97 to 1.27)	0.89 (0.79 to 1.00)	1.05 (0.91 to 1.21)	1.08 (0.89 to 1.30)	0.89 (0.82 to 0.96)
Rivaroxaban	1.42 (1.25 to 1.61)	1.14 (1.02 to 1.27)	1.35 (1.18 to 1.54)	1.14 (0.95 to 1.36)	0.98 (0.91 to 1.07)
Apixaban	1.38 (1.22 to 1.56)	1.09 (0.99 to 1.22)	1.34 (1.18 to 1.51)	1.24 (1.06 to 1.44)	0.96 (0.89 to 1.04)

*Multivariate competing risk regression, adjusted for NOAC dose, gender, age, year of inclusion into the study, chronic kidney disease, hypertension, diabetes, ischaemic heart disease, peripheral artery disease, heart failure, dementia, thyroid disorders, active cancer (cancer diagnosis last 12 months), chronic lower respiratory tract disease, history of stroke/SE, history of bleeding-related hospitalisation, history of anaemia, use of cholesterol lowering drugs, use of antiplatelet drugs and use of NSAIDs during the last 12 months, treating death as a competing risk.[2]

†Analyses of the risk of stroke/SE and major bleeding among users of different OACs, allowing a longer gap period of 90 days between the calculated end of OAC supply and a new prescription dispensing before censoring.

‡Analyses of the risk of stroke/SE and major bleeding among users of different OACs, excluding patients with a dispensing of any anticoagulant from pharmacies during the last 5 years (12 months was used in the main analyses).

§Analyses of the risk of stroke/SE and major bleeding restricting follow-up time for all OACs to 12 months.

¶An 'intention-to-treat'-like analysis: investigating risk of stroke/SE and major bleeding without censoring by treatment switch or discontinuation of NOACs.

NOACs, non-vitamin K antagonist oral anticoagulants; NSAIDs, non-steroidal anti-inflammatory drugs; OACs, oral anticoagulants; SE, systemic embolism.

included was 82 years and the mean CHA_2DS_2-VASc score was 4.5, implying that this was a truly high-risk population.

To our knowledge, this is one of the first studies of an all-comers nationwide cohort of patients with AF ≥75 years, investigating a less selected group of elderly patients than most previous observational studies.[12][13][23][24] Using high-quality nationwide registries with almost complete coverage[14] reduces selection bias and eliminates loss-to-follow-up; important limitations for studies based on insurance claims databases (eligibility for insurance required)[24] or prospective studies (healthy volunteer effect).[13]Also, using administrative health registries reduces information bias as all diagnoses are coded according to the ICD-10 system.

Our findings were generally in line with subgroup analyses[8–11] of the pivotal RCTs.[4–6] From the RE-LY trial,[4] subgroup analyses of the 7258 (40%) patients ≥75 years showed that the reduced risk of stroke/SE associated with dabigatran was maintained in the elderly population.[11] Subgroup analyses of the 6229 (44%) patients ≥75 years included in the ROCKET-AF trial[6] also showed a consistency in the effects of rivaroxaban versus warfarin regarding risk of stroke/SE across age groups, but a higher risk of major or clinically relevant non-major bleeding in patients >75 years.[8] From the ARISTOTLE trial,[5] subgroup analyses of the 5678 (31%) patients included ≥75 years showed that the benefits of apixaban in reducing risk of stroke/SE as well as major bleeding were maintained across all age groups.[9]

There are also some previous observational studies comparing NOACs versus warfarin in the elderly, with findings in line with our results.[12 13 23 24]

In a recent meta-analysis including 22 studies enrolling over 440 000 patients ≥75 years, indirect comparisons between NOACs (Bucher method) showed no significant differences between NOACs for risk of stroke/SE, but significant differences in risk of major bleeding; apixaban was associated with significantly lower risk of major bleeding compared with both dabigatran and rivaroxaban, while there was no significant difference between dabigatran and rivaroxaban.[25] Importantly, methods of indirect comparisons could systematically overestimate or underestimate treatment effect, warranting cautious interpretation.[26]

Regarding all-cause death, we found similar risks for standard doses of all three NOACs compared with warfarin, while reduced doses of rivaroxaban and apixaban were associated with a significantly higher risk of all-cause mortality. This was unexpected, as the RCTs on NOACs versus warfarin showed similar or favourable risks of all-cause mortality. We believe this discrepancy is due to unmeasured confounders. First, we did not have information about body mass index, estimated glomerular filtration rate and frailty—factors important in choice of anticoagulant dose and also affecting risk of death. Second, lack of knowledge of these factors made it impossible to assess appropriateness of dosage. A recent study from the Global Anticoagulant Registry in the FIELD-AF (GARFIELD-AF) investigated degree of recommended and non-recommended dosing of NOACs among 10 426 patients with AF and found that 23.2% were underdosed and 3.8% were overdosed.[27] Prescription of non-recommended doses was associated with a higher risk of all-cause mortality (HR 1.24, 95% CI 1.04 to 1.48). Patient characteristics leading clinicians to choose a non-recommended low dose are difficult to identify and adjust for, but influential for risk of all-cause mortality. Third, the sensitivity analyses showed consistency in all comparisons for stroke/SE and major bleeding, but great diversity for the risk of all-cause mortality, particularly when comparing reduced doses of NOACs with warfarin. This supports a stronger influence of residual confounding for this outcome, leading us to de-emphasise our findings.

A net clinical benefit of oral anticoagulation in elderly patients with AF has been shown in several studies,[2 28 29] but still many clinicians withhold anticoagulants due to fear of bleeding complications.[30] This study might increase physician confidence in prescribing OACs to this vulnerable high-risk group of patients.

Strengths and limitations

With the active-comparator design, we tried to reduce confounding by indication. However, unknown/unmeasurable confounders are inevitably present in observational studies, leading to residual confounding. Outcomes were not adjudicated, thus miscoding and under-reporting will be present, but likely equally for all NOACs. Information about the reason for dose reduction of NOACs was lacking, and some patients may have received non-recommended reduced doses. We therefore analysed standard and reduced dose NOACs separately. Furthermore, the criteria warranting dose reduction vary between NOACs, complicating comparisons. Perhaps most notably, in Europe the reduced dose dabigatran is recommended for all patients ≥80 years.[3] Accordingly, the reduced dose may be viewed as 'standard' for elderly patients using dabigatran. No subgroup analyses with respect to age were performed due to concern with statistical power. We studied use of OACs according to prescriptions dispensed, not drugs actually taken.

Finally, this study describes associations rather than drawing causal inferences.

CONCLUSION

In this real-world study of patients ≥75 years initiating oral anticoagulation for AF, standard and reduced dose NOACs were associated with similar risks of stroke/SE as warfarin and lower or similar risks of bleeding. The NOACs seem to be a safe option also in elderly patients.

Key messages

What is already known on this subject?
► Non-vitamin K antagonist oral anticoagulants (NOACs) are firmly established as the preferred class of drugs for stroke prophylaxis in atrial fibrillation (AF). No randomised controlled trials (RCTs) have specifically investigated the efficacy and safety of NOACs compared with warfarin or NOACs compared with NOACs, among elderly patients with AF.

What might this study add?
► This real-world study adds insight into the comparative effectiveness and safety of NOACs in the elderly population with AF compared with warfarin but also when compared with each other. It supports the findings from subgroup analyses of the pivotal RCTs comparing NOAC versus warfarin, that NOACs are an effective and safe option also for elderly patients with AF with their higher stroke and bleeding risk.

How might this impact on clinical practice?
► The results from this study could increase physician confidence in prescribing oral anticoagulants for elderly patients. It could also serve as a hypothesis generator for RCTs comparing NOAC versus NOAC.

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Supplementary material for

Paper III

Supplementary table S1

ICD-10 (International Classification of Diseases, 10th revision) and NOMESCO (Nordic Medico-Statistical Committee) codes used in definitions of co-morbidities and outcomes. Comorbidities were recognized either by ICD-10 diagnoses from hospital stays, or by a combination of hospital diagnoses and drugs dispensed. ATC (Anatomical Therapeutic Chemical system) codes from NorPD identified disease-specific drugs (e.g. anti-diabetics) and ICD-10 or International Classification for Primary Care 2 (ICPC-2) codes used as reasons for reimbursement of drugs for chronic illnesses for less specific drugs (e.g. beta blockers).

Conditions	ICD-10 code or procedure codes (NOMESCO) from NPR	ATC code or reimbursement code in NorPD
Atrial fibrillation	I48	Reimbursement code: I48 , K78 (ICPC)
Additional diagnoses to identify "valvular atrial fibrillation"	ICD10: I050, I052, I342, Z952 NOMESCO codes: FKD00, FKA, FMD00,	
Hypertension	I10, I11, I12, I13, I15	Reimbursement codes: I10-I13, I15 (ICD10) or K86, K87 (ICPC)
Chronic kidney disease	N00, N01, N02, N03, N04, N05, N06, N07, N08, N14, N15, N16, N181, N182, N183, N184, N185, N189, N19	
Ischemic heart disease	I20, I21, I22, I23, I24, I25	
Heart failure	I500, I501, I509	Reimbursement codes: I50 (ICD10) or K77 (ICPC)
Diabetes	E10, E11, E12, E13	ATC code A10A or A10B
Chronic lower respiratory tract disorders	J40 – J47	Reimbursement codes: J44 , J45 (ICD10) or R95 (ICPC
Active cancer	C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C44, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C77, C78, C79, C80, C81, C82, C83, C84, C85, C86, C88, C90, C91, C92, C93, C94, C95, C96, C97	
Thyroid disorders	Hypothyroidism: E010, E011, E012, E018, E030, E031, E032, E033, E034, E035, E038, E039 Hyperthyroidism: E050, E051, E052, E053, E054, E055, E058, E059	
Peripheral artery disease	I70, I71, I72, I73, I74, I77, I78, I79	
Inflammatory polyarthropathies	M05 – M14	
Ischaemic stroke	I630, I631, I632, I633, I634, I635, I636, I638, I639, I64	
Transient ischaemic attack (TIA)	G450, G451, G452, G453, G454, G458, G459, G46	

Conditions	ICD-10 code or procedure codes (NOMESCO) from NPR	ATC code or reimbursement code in NorPD
Ischaemic or haemorrhagic stroke	I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I612, I613, I614, I615, I616, I618, I619, I620, I621, I629, I630, I631, I632, I633, I634, I635, I636, I638, I639, I64,	
Major bleeding	K920, K921, I600-I609, I610-I619, I620-I629, I230, I312, M250, H431, H356, H313, H450, J942, K661 *Addition: A CRNM-bleeding diagnosis will be converted to a major bleeding diagnose if blood transfusion (NCMP REGG00, RXGG02) is coded within 10 days.*	
Systemic embolism	I74	
Intracranial bleeding	I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I612, I613, I614, I615, I616, I618, I619, I620, I621, I629	
Gastrointestinal bleeding	K920, K921, K922, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K228, K221, K290, K528, K625, I850	
CRNM bleeding	K922, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K228, K221, K290, K528, K625, I850, H113, R040, R041, R042, R048, R049, N836, N837, N920, N921, N922, N923, N924, N925, N926, N930, N938, N939, A985, N421, N857, N921, O721, S064, S065, S066, S068, T140, T141, T142, T143, T144, T145, T146, T147, T148, T149, D683, D698, D699, N02, R31, R58, D62	
Anaemia	D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D61, D62, D63,D64	
Alcoholism	E244, E52, G312, G621, G721, I426, K70, K860, O354, T51, Z714, Z721	
Use of NSAID		M01A
Use of antiplatelet drugs		B01A C
Use of cholesterol lowering drugs		C10A, C10B

NPR, Norwegian Patient Registry; NorPD,Norwegian Prescription Database; NCMP, Norwegian Classification of Medical Procedures; CRNM bleeding, clinically relevant non-major bleeding; NSAID, non-steroidal anti-inflammatory drug;

Supplementary table S2; ICD-codes used to calculate risk scores

	CHADS2-VASC	
Point	**Condition**	**Definition**
1	Heart Failure	use definition from baseline covariates (Table 1)
1	Hypertension	use definition from baseline covariates (Table 1)
1	Diabetes mellitus	use definition from baseline covariates (Table 1)
2	Stroke, TIA or systemic embolism	use definition from baseline covariates (Table 1)
1	Vascular Disease (myocardial infarction or peripheral arterial disease)	Combined definitions from baseline covariates "Ischaemic Heart Disease" , and "Vascular disease" in table 1.
1	Female gender	
1	Age 65-<75 years	
2	Age≥ 75 years	

	HAS-BLED	
Point	Condition	**Definition**
1	Hypertension	Use definition for "Hypertension" from baseline comorbidities
1	Abnormal kidney function	Use definition for "Chronic kidney disease" from baseline comorbidities
1	Abnormal liver function:	Use definition for "Liver disease" from baseline comorbidities
1	Stroke, TIA	use definition "History of stroke" from baseline comorbidities
1	Any bleeding other than haemorrhagic stroke	Use definition of Major and CRNM bleeding from baseline comorbidities, excluding codes for haemorrhagic stroke I60, I61, I690-I692
N/A	Labile INR	Not available
1	Age≥ 65 years	1 point for age 65 years or older
1	Alcohol/ Drug Therapy	Use definition of "Alcoholism" , "Use of NSAIDs last 12 months" and "Use of antiplatelet drugs last 12 months, from baseline comorbidities.

Values are numbers (percent) unless otherwise specified. TIA, transient ischaemic attack; NSAIDs, non-steroidal inti-inflammatory drugs; INR, International Normalised Ratio; CHA2DS2-VaSc, congestive heart failure (or left ventricular systolic dysfunction), hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack or systemic embolism, vascular disease, age ≥ 65 years, sex category; HAS-BLED, hypertension, abnormal renal function/ abnormal liver function, prior stroke, prior major bleeding, labile international normalised ratio (INR), elderly age ≥ 65 years, prior alcohol or drug abuse / use of medications that predispose to bleeding (antiplatelet agents, NSAIDs).