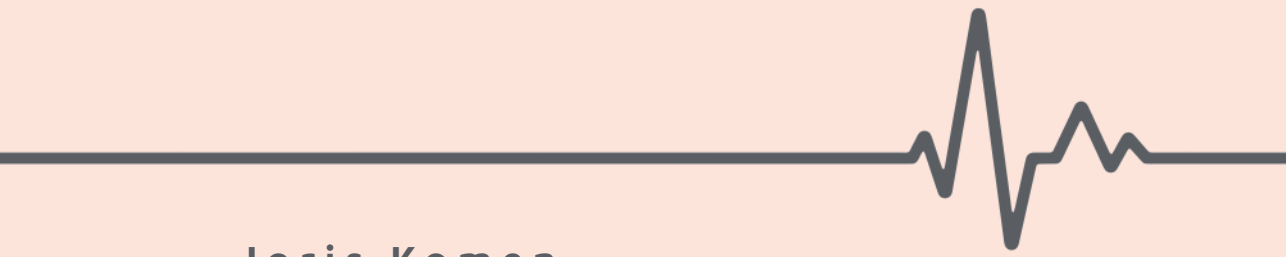
Advanced Pharmacoepidemiologic Approaches to Study the Utilization, Safety, and Effectiveness of NOAC Treatment in Patients with Atrial Fibrillation



Joris Komen

ADVANCED PHARMACOEPIDEMIOLOGIC APPROACHES TO STUDY THE UTILIZATION, SAFETY, AND EFFECTIVENESS OF NOAC TREATMENT IN PATIENTS WITH ATRIAL FIBRILLATION

Joris Jan Komen

Colophon

The research in this thesis was performed at the division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht, the Netherlands. The research in this thesis was a collaboration between Utrecht University, the Karolinska Institutet (Sweden), and the Stockholm County Council (Sweden). The research in this thesis was financially supported by the Stockholm County Council and the Swedish Heart Lung Foundation.

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ADVANCED PHARMACOEPIDEMIOLOGIC APPROACHES TO STUDY THE UTILIZATION, SAFETY, AND EFFECTIVENESS OF NOAC TREATMENT IN PATIENTS WITH ATRIAL FIBRILLATION

Geavanceerde farmaco-epidemiologische benaderingen om het gebruik, de veiligheid en de effectiviteit van NOAC-behandeling van patiënten met atriumfibrilleren te bestuderen

(met een samenvatting in het Nederlands)

Avancerade farmakoepidemiologiska tillvägagångssätt för att studera användning, säkerhet och effektivitet av NOAC-behandling hos patienter med förmaksflimmer

(med en sammanfattning på svenska)

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"Not because it is easy, but because it is hard"

e.w. Sjoerd J. Komen
Vrij naar John F. Kennedy, September 12, 1962
Address at Rice University on the Nation's Space Effort

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1

INTRODUCTION

RANDOMIZED TRIALS AND OBSERVATIONAL RESEARCH

Before a drug enters the market, the efficacy and safety of it is predominantly determined in randomized controlled trials (RCT). In an RCT the treating physician does not decide which treatment a patient receives, but this is allocated at random which ensures there is no link between patient characteristics and the treatment a patient receives [1]. In observational research, treatment allocation is not at random, and patient characteristics are, rightfully so, one of the key drivers when a physician decides about treatment. This phenomenon is also known as channelling and may lead to confounding bias when patient characteristics are risk factors for the outcome of interest [2]. One can imagine that if a group of patients prescribed with a new drug is, for example, older and sicker (i.e., has certain risk factors for the outcome of interest), this group is also more likely to develop certain outcomes such as adverse side effects, a disease, or even to die. If the group of older and sicker patients with this new drug then develops more side effects, it is difficult to tell whether this is due to the new drug, or because these patients were older and sicker to begin with. Randomization removes the link between treatment and risk factors, which makes it the golden standard to assess the efficacy of a new drug.

Besides this main advantage of an RCT, there are some limitations to it as well. First, RCTs are often conducted in a selected group of patients. Most RCTs have strict in- and exclusion criteria, which makes it questionable whether the results of the study are generalizable to the target population of the drug [3]. Halpin *et al*. applied the in- and exclusion criteria of 31 RCTs assessing bronchodilator therapy in chronic obstructive pneumatic disease (COPD) on a representative COPD population [4]. They found that the median eligibility of this population would be 23% after applying the in- and exclusion criteria. The study with the highest eligibility would select 58%, and the lowest only 3.5%. This could mean that, on average, the results of these trials are not certainly applicable to 77% of the COPD population, especially if those patients were excluded based on characteristics that can modify the treatment effect.

A second limitation of RCTs is that they often have a limited sample size and/or a relatively short duration of follow-up [5]. An RCT with a small sample size does not reveal potential rare adverse events of a drug, and a short follow-up gives no information regarding long-term effects of a drug. A third limitation is the costs of an RCT. Moore *et al*. reported in 2018 that the average cost of 59 trials that led to approval by the FDA in 2015 and 2016 was estimated at $19.0 million [6]. This ranged from $5 million for small uncontrolled trials, to $348.6 million for a large noninferiority trial. Besides the high costs of an RCT, they take a long time and much effort to perform. Therefore, some clinically relevant questions will never be answered with an RCT, as it is too expensive and laborious to perform. A fourth limitation is the circumstances of treatment in an RCT which may not reflect treatment circumstances in daily clinical practice, for example due to closer monitoring of the patients and more frequent visits to the physician.

A complementary approach to evaluate the safety and effectiveness of a drug is to use observational studies, which, in recent years, have gained popularity and are now also regularly demanded by regulators. Many disadvantages of the RCTs mentioned above can be remedied by observational research, which sometimes is also referred to as 'real-world evidence'. First, patient

populations from observational data can be fully unselected. If one uses data from a complete healthcare setting, such as the Stockholm Healthcare region [7], it is possible to include all patients with a certain disease or treatment. If the sample size is sufficient, this will yield results that are more generalizable compared to a clinical trial with numerous in- and exclusion criteria [8, 9]. Second, populations derived from observational data can be very large and data are often available for a long period of time, making it possible to study long-term effects of drugs. Third, if data are already collected in case of using routinely collected healthcare data, retrospective observational research is often cheap to perform and results can be delivered rapidly, as the data only need to be analysed to obtain results. While in a prospective study, such as an RCT, data still need to be collected by the time a study is planned, and thus it takes time to collect the data. On the other hand, when data is collected prospectively, researchers have the possibility to obtain data on all variables they deem necessary, while in routinely collected data one has to work with the data that happens to be routinely collected.

But, as mentioned, observational research will always be threatened by confounding bias, even though there are several epidemiological methods to handle confounding. This can be done, amongst others, by stratification, statistical adjustment, matching, or weighting [10]. With stratification, a cohort is split into groups that share a certain characteristic or not. The treatment-outcome association in a group of patients that share a certain characteristic is then not influenced by that characteristic. Adjusting through multivariate models is the mathematical process in which the association between the treatment and the outcome is calculated if all covariates (i.e., patient characteristics) would have been equal. Matching creates cohorts in which patient characteristics used for matching are equally distributed amongst the treated and untreated patients, and therefore these characteristics no longer affect the treatment-outcome association. Weighting puts larger weights on patients with characteristics that are underrepresented in either the treated or untreated group, which ultimately also yields cohorts in which patient characteristics are equally distributed.

One frequently used tool to handle confounding is the propensity score [11]. The propensity score is the probability of receiving the treatment, based on the patient characteristics. This score can be used for stratification, adjustment, matching, or weighting. Matching patients on the propensity score yields cohorts in which patient characteristics, at least those used to calculate the propensity score, are equally distributed. Similarly, weighting based on the inverse of the propensity score also yields comparable cohorts.

The goal of all approaches suggested above, stratification, adjusting, matching, or weighting, is to remove confounding. There are, however, some confounding factors that are impossible to directly adjust for with the aforementioned methods, so called unmeasured confounders [12]. In healthcare databases, which are often used in observational research, not all potential confounders are registered. For example, data is currently often not available for smoking, body mass index, or lifestyle factors. In addition, there are patient characteristics that are simply impossible to capture in databases which can play a large role in treatment decisions, for example frailty or the gut-feeling of physicians when they see a patient. And since these variables are not registered in databases, they will be impossible to directly adjust for through traditional methods. However, advances have been

made in developing methods that are capable of handling unmeasured confounding, such as case only designs or using instrumental variables, for example [13].

In addition, there are ways to test how likely it is that unmeasured confounding played a role in an observational study by applying sensitivity analyses. First, one can quantify how large an unmeasured confounder must have been in order to explain the association found in a study [14]. This depends on the prevalence of the potential unmeasured confounder, the association with the outcome, and the association with the treatment. Second, one can use falsification outcomes [15]. These are outcomes that are not associated with the treatment of interest but are associated with the potential unmeasured confounder. If these outcomes yield a neutral association with the treatment, it indicates that residual confounding is less likely.

OBSERVATIONAL RESEARCH AND NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS

After a drug receives market approval, usually based on the results of an RCT, numerous unanswered questions still remain to optimize the safe and effective use of a new medicine [3]. Some of them are inherent to the known disadvantages of an RCT, such as a limited sample size, a short follow-up, and a selected population. This yields questions about rare adverse side effects, long-term safety and efficacy, and the safety and effectiveness in clinical practice. Other questions can only be answered after a drug is on the market, such as early and long-term utilization patterns, and adherence and persistence to a treatment.

One recently introduced group of drugs that has gone through the phases of RCTs and market approval, followed by extensive observational research, is the non-vitamin K antagonist oral anticoagulants (NOACs) [16–19]. These drugs were introduced to the market for, amongst others, stroke prevention in patients with atrial fibrillation (AF), as an alternative to treatment with warfarin or other vitamin K antagonists (VKA). Besides AF, NOAC treatment is also indicated for the treatment and prevention of deep venous thromboembolism and pulmonary embolism, as well as primary prevention of thromboembolic complications after knee- or hip replacement surgery. In addition, rivaroxaban is indicated for the prevention of atherothrombotic events in patients with coronary artery disease or symptomatic peripheral artery disease. However, this thesis solely focusses on NOAC treatment for stroke prevention in AF.

Patients with AF suffer from a cardiac arrythmia which is characterized by the atria not contracting in sinus rhythm. This can either be short-term and temporary, called paroxysmal, or persistent (periods longer than seven days), or even permanent. AF is associated with, on average, a five-fold increased risk for an ischemic stroke [20]. Historically, it was hypothesized that through the poor contraction of the atria blood would stand still, and a thrombus could form, leading to a stroke. However, recent evidence coming from studies with implantable cardioverter-defibrillators have shown that AF patients are at an increased risk for stroke independently of whether the atria are in sinus rhythm at that time [21, 22]. This has led to abandoning the historical hypothesis, and it is currently hypothesized that AF is a marker for multiple underlying pro-embolic factors [23].

Treatment with oral anticoagulants reduces the risk for an ischemic stroke but increases the risk of suffering a hemorrhagic stroke and other bleeds. Over the past decades, warfarin, and other VKAs, have been the backbone of stroke prevention in patients with AF. Adequate therapy with VKAs reduces the risk for a stroke by 64% [24]. However, besides their effectiveness, treatment with VKAs comes with several impracticalities, such as drug-drug interactions, food-drug interactions, and high inter- and intraindividual variability in pharmacokinetics [25]. These impracticalities probably contributed to VKAs being one of the drugs most often causing hospitalization [26]. Because of this, treatment with VKAs needs to be monitored by measuring the patient's international normalized ratio (INR) and personalized dosing schedules are required to ensure adequate anticoagulation.

In April 2011, the first NOAC, the thrombin inhibitor dabigatran, received market approval by the European Medicines Agency for stroke prevention in patients with AF. After that, three other NOACs, the Factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, also received market approval in December 2011, December 2012, and June 2015, respectively. Contrary to VKAs, NOAC therapy does not require individual dosing schedules and INR measurements, as the pharmacokinetics of the drugs are much more stable [27]. Four pivotal clinical trials have shown that NOAC therapy is more efficacious compared to VKA in stroke prevention in patients with AF [28].

NOAC and VKA treatment inhibit different parts of the coagulation cascade [27]. Through this, they ultimately inhibit the forming of a thrombus and thus reduce the risk for a stroke. However, inherent to this mechanism of action, they both also increase the bleeding risk [29]. This can manifest as minor events such as increased bruising, but also as serious events like life-threatening gastro-intestinal bleeds or intracranial hemorrhages. The four pivotal clinical trials all showed that NOAC treatment, compared to warfarin treatment, resulted in a lower risk for intracranial hemorrhages, the most life-threatening bleed [28]. On the other hand, gastro-intestinal bleeds occurred, on average, more frequently with NOAC compared to warfarin treatment.

After the introduction of NOACs on the market, guidelines have adopted NOACs as the preferred oral anticoagulant treatment, both in Europe and the US [25,30]. However, given the increased bleeding risk with oral anticoagulants, not all AF patients should receive treatment. Only in patients where the stroke risk reduction outweighs the risk for a bleeding, treatment with an oral anticoagulant is recommended. Guidelines recommend using the CHA_2DS_2-VASc score, a stroke prediction score, to determine which patients should and should not receive treatment [31]. This score awards points based on the age (<65 = 0, 65 – 74 = 1, ≥75 = 2) and sex (female = 1, male = 0) of the patient and whether a patient has certain underlying diseases (congestive heart failure = 1, hypertension = 1, diabetes = 1, stroke/TIA/embolism = 2, vascular disease = 1). The risk that a patient suffers a stroke increases with each point. Treatment with an oral anticoagulant is recommended from a score of two and beyond for male patients, and three for female patients [25]. Treatment should be withheld in male patients with a score of zero and female patients with a score of one. However, in moderate risk patients, i.e. male patients with a score of one, and female patients with a score of two, the recommendations are less clear, and state that treatment *should be individualized based on net clinical benefit and consideration of patient values and preferences* [25].

After guidelines had adopted NOAC treatment for stroke prevention in AF and NOAC treatment was implemented in clinical practice, the first observational studies were conducted. These were

studies assessing the uptake of NOACs in clinical practice [32], and the first studies assessing the safety and effectiveness of NOAC treatment compared to VKA treatment [33–36]. These studies confirmed that the results from the RCTs also held true in clinical practice, but there were still many clinically relevant questions remaining, for example regarding the safety and effectiveness of NOACs in specific patient populations or in patients using potentially interacting comedication. In this thesis, we build on the existing evidence from the RCTs and further expand on the initial observational research performed.

THESIS OBJECTIVE AND CONTENT

The main aim of this thesis was to assess utilization patterns, safety, and effectiveness of NOAC treatment for stroke prevention in patients with AF, using advanced pharmacoepidemiologic methods.

Chapter 2 focuses on the introduction of NOACs in clinical practice. In chapter 2.1 we assess how policy interventions were associated with the uptake of NOACs in the Stockholm healthcare region. In chapter 2.2 we look at which factors were associated with different antithrombotic treatment options in this region. In chapters 2.3 and 2.4 we investigate how the introduction of NOACs changed antithrombotic treatment and clinical outcomes in both the Stockholm healthcare region (chapter 2.3) and four Western European countries (chapter 2.4). In chapters 2.5 and 2.6 we determine the persistence and adherence with NOAC treatment. In chapter 2.5 we do this in the Stockholm healthcare region and additionally also investigate how non-persistence and poor adherence were associated with the risk of stroke, and in chapter 2.6 we compare persistence and adherence with the different NOACs in five Western European countries.

Chapter 3 focuses on improving the clinical knowledge on the safety and effectiveness of NOAC treatment in patients with AF. In chapter 3.1, we assess the comparative effectiveness of NOAC treatment, VKA treatment, or no treatment in patients with AF at moderate risk for stroke. In chapter 3.2, we look at the risk for stroke and bleeding in patients with AF receiving oral anticoagulant treatment with or without concomitant antidepressant therapy. In chapter 3.3, we investigate the risk for upper gastrointestinal bleed (GIB) in patients with AF receiving NOAC treatment with or without concomitant proton pump inhibitor therapy. In chapter 3.4, we assess the risk for mortality after a patient with AF suffered from a stroke, an intracranial haemorrhage, or GIB, and whether this was associated with the antithrombotic treatment at the time of the event.

Chapter 4 focuses on improving the validity of propensity score matching. In chapter 4.1, we explore the random variability introduced by the random ordering in greedy matching. In chapter 4.2, we propose a new method to improve propensity score matching and test this using a Monte-Carlo simulation.

Finally, the general discussion in chapter 5 aims to unify the studies from this thesis, provide recommendations on how pharmacoepidemiologic studies can and, potentially, should be conducted, and summarize the clinical implications of the studies from this thesis.

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2

INTRODUCTION AND UTILIZATION OF NOAC THERAPY

2.1

EFFECTS OF POLICY INTERVENTIONS ON THE INTRODUCTION OF NOVEL ORAL ANTICOAGULANTS IN STOCKHOLM: AN INTERRUPTED TIME SERIES ANALYSIS

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Morten Andersen, Björn Wettermark

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ABSTRACT

Aims

To assess the effect of policy interventions, i.e. reimbursement decisions, guidelines, and regional recommendations, on the prescribing of oral anticoagulant treatment in patients with atrial fibrillation (AF).

Methods

Interrupted time series analyses using monthly data on all patients with a recorded diagnosis of AF newly initiated (both switchers and anticoagulant naïve patients) on either warfarin, dabigatran, rivaroxaban or apixaban in the Stockholm region from April 2011 until February 2016.

Results

A total of 34 165 initiations in 27 942 patients were included. The publication of the European Guidelines was associated with an increase in Novel Oral Anticoagulant (NOAC) initiations of 12.5% (95% confidence interval (CI): 7.3;17.7) after 5 months. The choice between the different NOACs was mainly associated with changes in the regional recommendations with apixaban initiations increasing by 19.5% (95% CI: 16.3;22.7) 5 months after the drug was recommended as a first-line alternative to warfarin. Dabigatran received a second-line recommendation but decreased by -9.5% (95% CI: -12.6;-6.4) and rivaroxaban which had no specific recommendation decreased by -9.2% (95% CI: -12.7;-5.7%). A steady decrease in warfarin and increase in NOAC initiations was seen throughout the study period and from November 2015, AF patients were more likely to receive apixaban than any other anticoagulant, while less than 20% of the initiations were with warfarin.

Conclusions

After reimbursement and inclusion in the European guidelines the NOACs started gaining popularity, while changes in regional recommendations were associated with the biggest change in the prescriber's choice between the different NOACs.

INTRODUCTION

For many years, warfarin and other vitamin K antagonists were the only oral anticoagulants (OACs) on the market used for prevention of thromboembolic complications in patients with atrial fibrillation (AF) [1, 2]. Despite the effectiveness of warfarin, there are some treatment-related drawbacks which may have contributed to underuse of this drug for stroke prevention in AF [3]. The need for continuous monitoring of coagulation, individualized patient dosing and several drug and food interactions have raised the need for the novel oral anticoagulants (NOACs) [4, 5]. NOACs have fewer treatment-related disadvantages and have been shown to be at least non-inferior to warfarin regarding efficacy and safety, and in some instances superior to warfarin in antithrombotic prophylaxis for patients with AF [6–8].

Besides the advantages of an apparent simplicity of treatment with the NOACs, there are certain concerns about them [9]. The main concern is the risk for poor adherence since there is no regular coagulation monitoring in patients treated with NOACs [10–12]. Other concerns have been the lack of specific antidotes before the first one recently became available for dabigatran [13], the possibilities of drug-drug interactions which so far are incompletely studied for NOACs, and the dependence on renal function for the elimination of especially dabigatran when considering that many high risk AF patients are elderly and have renal impairment [14–16].

In April 2011, dabigatran (Pradaxa®) was the first NOAC to get market approval from the European Medicines Agency (EMA) for the prevention of stroke and systemic embolism in adult patients with non-valvular AF [14]. Later, rivaroxaban (Xarelto®) and apixaban (Eliquis®) also got their market approvals [15, 16]. Health authorities in Europe have applied different approaches to optimize the introduction of these drugs [17]. In the Stockholm region, several policy interventions might over time have influenced the introduction of the NOACs, i.e., the European guidelines [12], the reimbursement decisions [18–20], the National guidelines [21], and the regional Drug and Therapeutic Committee (DTC) recommendations [22] (see box 1).

The DTC makes selections among therapeutic alternatives when several alternatives are available to increase the efficiency of pharmacotherapy in the whole healthcare system. In 2015, apixaban was recommended as the first-line NOAC along with warfarin, and dabigatran as a second-line alternative. The DTC motivated its choice which was based on a comparative evaluation of the pivotal studies and sub studies of the three NOACs on its homepage, but only in Swedish (www.janusinfo.se). Interestingly, Lip et al. later published a network meta-analysis of the major AF trials which concluded that apixaban offered the most favourable efficacy and safety profile [23].

Globally, there is a need for effective strategies to promote rational prescribing since healthcare expenditures are rising and budgets are limited [24]. Previous studies have shown that guidelines are slowly implemented in general, but with large variation between prescribers and between health care systems [25]. In Sweden, the implementation of regional DTCs was regulated by law in 1997, with the aim to improve the use of evidence-based and cost-effective medicines in healthcare [26]. The Swedish DTCs develop regional recommendations that are easily available for prescribers as booklets and through decision-support systems in the medical record, and they have various educational activities (see box 1). Multiple activities involving both research, media and marketing influence the prescribing

Intervention	Content of intervention	Date
2012 focused update of the ESC Guidelines for the management of atrial fibrillation [12]	Update of the 2010 European Society of Cardiology (ESC) guidelines for the management of atrial fibrillation. Prescribing a NOAC was preferred over a VKA when OAC treatment is indicated. No distinction between the NOACs was made, so even apixaban was recommended while it was still waiting for approval by the European Medicines Agency (EMA) and the American Food and Drug Administration (FDA).	August 2012
Reimbursement decision [18–20]	The Dental and Pharmaceutical Benefits Agency (TLV) decides which drugs are included in the Swedish Pharmaceutical Benefits Scheme (PBS), either for an entire patient population or only for defined subpopulations. Once a drug is included in the PBS, the regional health boards (county councils) covers costs for the medicine, after the patient has reached a certain cost-threshold in 12 months which they are responsible for themselves.	Dabigatran: December 2011 Rivaroxaban: October 2012 Apixaban: May 2013
National guidelines [21]	The National Board of Health and Welfare published a preliminary update of its National guidelines to include NOACs for the treatment of AF before issuing the final National guidelines. Many experts promoted these preliminary guidelines as if they were the final version of the guidelines. The final National guidelines were published almost two years later. The guidelines recommended either warfarin or any NOAC equally when OAC treatment is indicated. The National guidelines are not very actively disseminated.	Preliminary National guidelines: December 2013 Final National guidelines: October 2015
Regional DTC recommendations [22]	The Drug and Therapeutics Committee (DTC) in the Stockholm County publishes regional recommendations, called the Wise List, a yearly updated list consisting of approximately 200 medicines for common diseases, and additionally approximately 150 medicines for specialist care. The Wise List is actively implemented using several strategies, such as continuous medical education, active dissemination, both to prescribers and patients, and feedback of prescribing patterns to physicians. In 2015 apixaban and warfarin became the anticoagulation therapies of choice, while dabigatran was the preferred alternative NOAC for selected patients. Before the Wise List of 2015, warfarin was the only recommended oral anticoagulant for patients with AF, but either of the NOACs were suggested as alternatives for selected patients [27].	January 2015

Box 1. Policy interventions during the introduction of the NOACs.

of NOACs. However, it remains unknown to what extent different policy interventions have influenced the prescribing of anticoagulants in patients with AF. The aim of the present study was to analyse the effects of reimbursement decisions, European and National guidelines, and regional DTC recommendations, on prescriber's initiation of anticoagulant treatment in patients with AF in the Stockholm region.

METHODS

Data source

We conducted a retrospective, population based study using the administrative health registers of the Swedish capital region of Stockholm County, the Stockholm Healthcare Analysis Database (SHAD; Vårdanalysdatabasen). The SHAD contains encrypted patient-level data for all 2.2 million inhabitants in the Stockholm region (sex, age, diagnoses, prescription claims, hospitalizations and other healthcare consultations, migration and death) [28]. Diagnoses are available for secondary care since 1993 and for primary care since 2003. Prescription data, consisting of amounts, expenditures and reimbursement, the age and sex of the patient, co-payments and prescriber category, are available since July 2010. The study was approved by the Regional Ethical Review Board in Stockholm (EPN 2015/579-31/2).

Identification of patients

We identified all patients who claimed a first prescription, issued by any prescriber, of dabigatran (ATC-code: B01AE07), rivaroxaban (ATC-codes: B01AF01 or B01AX06), apixaban (ATC-code: B01AF02) and/or warfarin (ATC-code: B01AA03) from April 2011 until February 2016. A wash-out period of 9 months with no claims of the substance of inclusion was applied to identify newly initiated patients on each specific drug. Patients were excluded if they met one of the following criteria: no diagnosis-code for AF (ICD-code: I48) recorded by any healthcare provider in primary- or secondary care from 2003 until the first claim of the respective drug; a procedure code for mechanical valves or a diagnosis code for mitral stenosis (ICD-codes: I050, I052, I342).

We examined the proportion of newly initiated patients on each drug each month. A newly initiated patient could either be a patient who was anticoagulant naïve or a patient who had switched from another anticoagulant. Patients would be marked as switchers if they claimed a prescription for another anticoagulant during 6 months prior to inclusion, and thus patients could be included several times in the analysis.

Interventions

Using interrupted times-series (ITS) analyses, we linked time trends for new initiations with reimbursement decisions for the different NOACs, the inclusion of the NOACs in the regional DTC recommendations, and the adoption of NOACs in the European and National guidelines. The latter was analysed for two dates, i.e., when the preliminary and the final national guidelines were launched, respectively (see box 1). For apixaban, we decided to set the reimbursement date at June 2013, since the drug was reimbursed on the 29th of May 2013. For the European and

National guidelines and the regional DTC recommendations we analysed their effects on the total number of NOAC initiations. Since the regional DTC recommendations made a distinction between the three NOACs, we also analysed their effect on each NOAC separately. This was also done for the reimbursement decisions.

Statistical analysis

For the ITS, we used a segmented regression model with a step function to perform this [29, 30]. We fitted a least-squares regression line in each segment, with the assumption of a linear relationship between the time and the number of initiations in each month. With the Durbin-Watson test we tested the residuals of the models for first order autocorrelation [31]. To test for a shift in the proportions of the initiations before and after the different interventions, we included an indicator variable in the time series model [29]. This indicator variable had the value of 0 in the months before the intervention, and the value of 1 from the month of the intervention onwards.

In the segmented regression model we controlled for baseline levels and trends, and thereby estimated the numbers of initiations had the intervention not occurred [29]. We determined the effect of an intervention in two ways: the change in level and trend after the intervention from the predictions of the model; and the effect of the intervention after 5 months. All results are given as percentages of all new initiations with either warfarin or a NOAC in that month, including both switchers and anticoagulant naïve patients. The effect after 5 months is given as an absolute increase in percentages. The goodness of fit of the models used is provided with the R-squared value, which is the proportion of variation explained by the statistical model, ranging from 0 to 1 [32].

We analysed every intervention one year (12 data points) before and one year after zvvthe intervention with monthly intervals if data were available and when no other intervention occurred within this time frame. If it was visually clear that a time frame shorter or longer than a year fitted the data better, we used this time frame. Initially we looked for a change in level after one month but when the level effect clearly lasted longer, the models were adapted to better fit the data. The statistical package IBM SPSS Statistics version 23.0 was used for all statistical analyses. Data extraction was done using SAS EG 6.1 (SAS Institute Inc., Cary, NC).

RESULTS

Patients

Of the 53 740 claims of a first prescription of the anticoagulant drugs in question, 34 165 were included for 27 942 different patients. A total of 19 090 claims were excluded since no previous diagnosis of AF was recorded for these patients and a further 485 because the patient had recorded codes for a mechanical valve or mitral stenosis. Of the 34 165 initiations in non-valvular AF patients, 17 559 were with warfarin, 5 181 with dabigatran, 7 131 with apixaban and 4 294 with rivaroxaban (appendix 1). For warfarin, 630 (3.6%) patients were switched from another anticoagulant treatment, for dabigatran this was 1 493 (28.8%) patients, for apixaban 2 474 (34.7%), and for rivaroxaban 1 626 (37.9%).

Time trends

During the study period, a steady decrease in initiations of warfarin and increases with NOACs was observed. This seemed to commence with the European guidelines and be strengthened by the national reimbursement decisions. From May 2014, patients with AF were more likely to be initiated on a NOAC instead of on warfarin (figure 1). Very few patients were switched to warfarin, while switches to NOACs increased continuously. Every July and August there was a decrease in the total number of initiations, which coincides with the summer holidays in Sweden. The biggest change in the choice between individual NOACs occurred after apixaban was included in the regional DTC recommendations (figure 2). The European and the preliminary National guidelines did not favour any particular NOAC and did not seem to have influenced choices between the NOACs, while the final National guidelines seemed to have caused a small further increase in apixaban initiations. At the end of the study period, patients with AF were more likely to be initiated on apixaban than on any other OAC and fewer than 20% of the patients were initiated on warfarin.

Interrupted time series analyses

The European guidelines caused both a significant positive level effect and an increase in trend, while the number of NOAC initiations was stable in the months before the intervention (figure 3A, table 1). This resulted in a 12.5% increase in NOAC initiations 5 months after the European guidelines

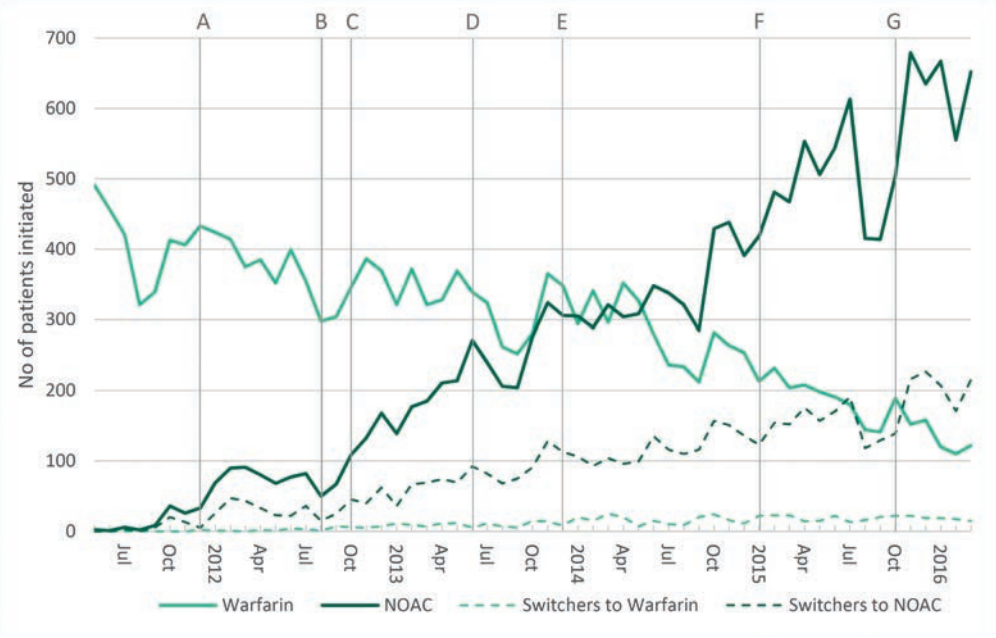

Figure 1. Numbers of patients with atrial fibrillation initiated on a novel oral anticoagulant (NOAC) or warfarin per month, and of patients who switched from another anticoagulant treatment. Dates of policy interventions are indicated as A: reimbursement of dabigatran; B: European guidelines; C: reimbursement of rivaroxaban; D: reimbursement of apixaban; E: preliminary national guidelines; F: regional Drug and Therapeutics Committee recommendations; G: final national guidelines

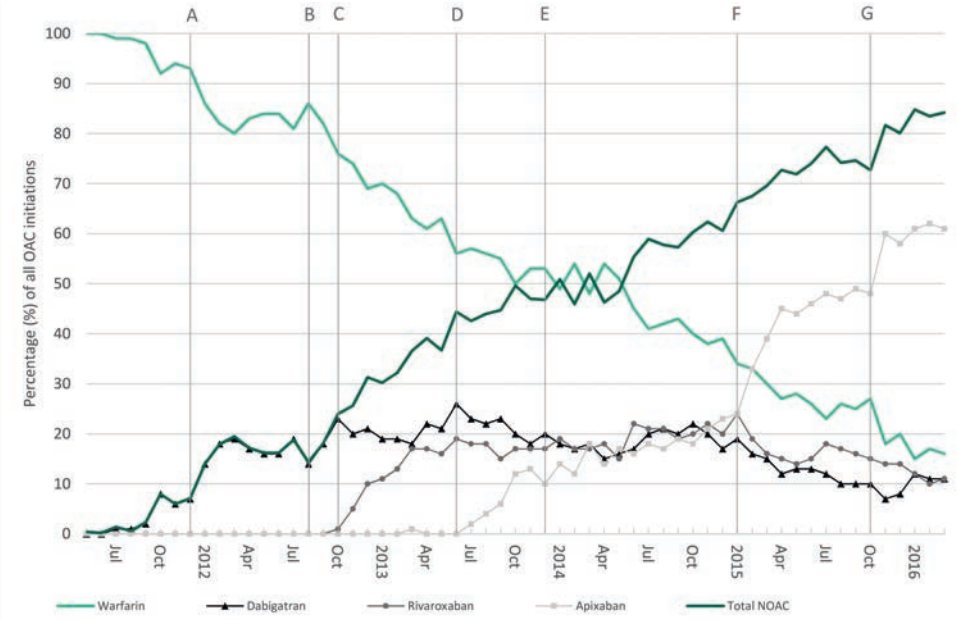

Figure 2. Proportions of all patients with atrial fibrillation initiated with any novel oral anticoagulant (NOAC) or warfarin per month (green curves) and those initiated with each NOAC (grey curves). Dates of policy interventions are indicated as A: reimbursement of dabigatran; B: European guidelines; C: reimbursement of rivaroxaban; D: reimbursement of apixaban; E: preliminary national guidelines; F: regional Drug and Therapeutics Committee recommendations; G: final national guidelines. OAC, oral anticoagulant

were issued. The National guidelines, both preliminary and final, and the regional recommendations did not result in any significant changes in total NOAC initiations after 5 months (figure 3B-3D).

Before reimbursement, only 5 and 11 patients were initiated on apixaban and rivaroxaban, respectively (figure 3A and figure 2), whereas 109 patients were initiated on dabigatran. Therefore, the effect of the reimbursement of dabigatran was non-significant after 5 months (table 2). Apixaban and rivaroxaban had increased significantly 5 months after they were reimbursed. Inclusion of apixaban as the recommended first-line NOAC together with warfarin in the DTC recommendations in the Stockholm region was associated with an increase in the proportion of patients initiated on apixaban and decreases in rivaroxaban and dabigatran initiations (figure 3C). After 5 months, there was an increase of 19.5% for apixaban, and a decrease of 9.2% for rivaroxaban. Even though dabigatran was also included in the regional DTC recommendations as an alternative for selected patients, the drug showed a significant decrease of 9.5% after 5 months.

Sensitivity analyses

If switched patients were excluded, the effect of the different interventions might have been different and therefore sensitivity analyses were conducted throughout, using only the anticoagulant naïve initiations (supplementary figure 2). This resulted in no appreciable differences (data not shown).

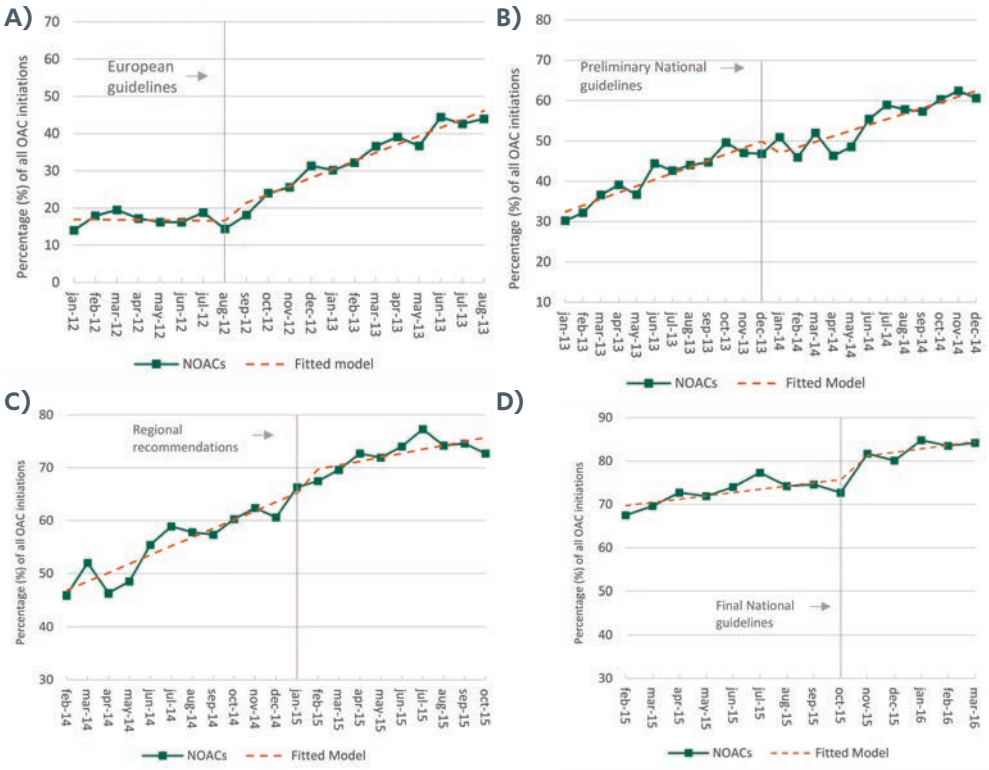

Figure 3A-D. Association between the different policy interventions and novel oral anticoagulant (NOAC) initiations. (A) European guidelines; (B) preliminary national guidelines; (C) regional recommendations; D) final national guidelines. OAC, oral anticoagulant

Table 1. Associations between the launch of European guidelines, the preliminary and final national guidelines and the regional Drug and Therapeutic Committee recommendations and the increase in total novel oral anticoagulant (NOAC) initiations as a percentage of all OAC initiations

	European guidelines	Preliminary National guidelines	Regional recommendations	Final National guidelines
Model fit (R-squared)	0.965	0.903	0.948	0.900
Pre-trend (%/month)	-0.05	1.46	1.67	0.74
Length of level effect (months)	1	1	1	1
Level effect (%)	4.82 (p=0.034)	-4.48 (p=0.054)	2.89 (0.194)	4.72 (p=0.053)
Effect on trend (%)	2.29 (p<0.001)	-0.19 (p=0.555)	-0.93 (p=0.025)	0.10 (p=0.888)
Effect after 5 months (% (95%-CI))	12.5 (7.3;17.7)	-5.2 (-10.7;0.2)	-0.8 (-5.9;4.3)	5.1 (-1.5;11.7)

Table 2. Associations between reimbursement decisions and changes in the regional Drug and Therapeutic Committee recommendations and increases for each novel oral anticoagulant (NOAC) as percentages of all OAC initiations.

	Dabigatran	Apixaban	Rivaroxaban
Reimbursement decisions			
Model fit (R-squared)	0.918	0.977	0.992
Pre-trend (%/month)	1.67	0.02	0.02
Length of level effect (months)	3	4	5
Level effect (%)	3.20 (p=0.449)	11.13 (p<0.001)	17.04 (p<0.001)
Effect on trend (%)	-1.18 (p=0.161)	0.66 (p=0.002)	-0.10 (p=0.506)
Effect after 5 months (% (95%-CI))	0.8 (-11.2;12.8)	11.7 (9.2;14.2)	17.0 (15.0;19.1)
Regional recommendations			
Model-fit (r-squared)	0.863	0.991	0.690
Pre-trend (%/month)	0.33	0.81	0.533
Length of level effect (months)	1	3	1
Level effect (%)	-5.1 (p=0.001)	19.69 (p=0<0.001)	-6.47 (p=<0.001)
Effect on trend (%)	-1.09 (p<0.001)	-0.09 (p=0.764)	-0.67 (p=0.019)
Effect after 5 months (% (95%-CI))	-9.5 (-12.6;-6.4)	19.5 (16.3;22,7)	-9.2 (-12.7;-5.7)

DISCUSSION

In this population-based interrupted time series analysis we found that the actively implemented regional DTC recommendations, the Wise List [33], were associated with the biggest change in AF treatment during the introduction of the NOACs. The regional DTC recommendations clearly influenced decisions between the three NOACs but did not seem to have any direct effect on the decision whether to prescribe a NOAC or warfarin. After reimbursement and after the European guidelines were launched, the numbers of patients with non-valvular AF initiated on warfarin decreased in favour of more patients being treated with a NOAC; from May 2014 onwards patients were more likely to be initiated on a NOAC than on warfarin, and at the end of the study period patients were more likely to be initiated on apixaban than any other OAC. Neither the preliminary nor the final National guidelines influenced this trend.

Dabigatran was the only NOAC that was prescribed before it was reimbursed. This may be attributable to the fact that it was the first NOAC to be launched and many clinicians expressed an urgent need for alternatives to warfarin [5, 34] and therefore did not wait for the reimbursement decision. Also patients could be eager to start using the NOACs. Thus, dabigatran showed the strongest increase among all NOACs in number of users during the first few months on the market. This is in concordance with a study in Canada also finding that dabigatran was used before reimbursement and rivaroxaban and apixaban only after reimbursement [35].

The increase in NOAC initiations and decrease in warfarin initiations was steady throughout the study period, and commenced after the publication of the European guidelines, which is in line with previous studies in Denmark and in Ontario, Canada [36, 37]. Other studies have shown differences in the adoption of dabigatran, where the uptake in the US was the fastest and the uptake in the UK was the slowest, with Stockholm being intermediate [38–41].

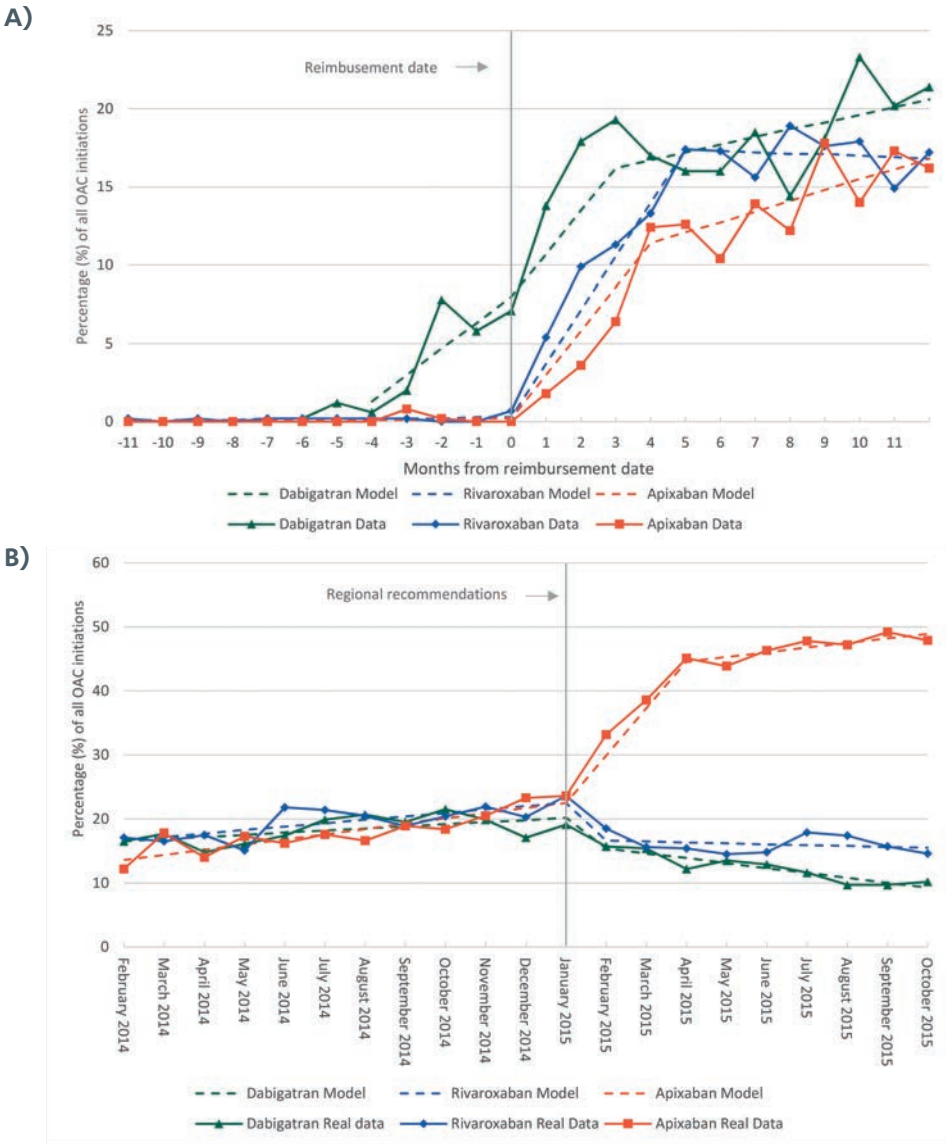

Figure 4A-B. Association between the reimbursement decisions (A) and the regional recommendations (B), and initiations of each oral anticoagulant (OAC)

The European Guidelines were published two months before the reimbursement of rivaroxaban and eight months after the reimbursement of dabigatran. With the current study design, it is not possible to distinguish which intervention caused the biggest increase, and therefore it is likely that it is caused by the combination of the three interventions happening close in time. During the rest of the study period neither the National guidelines, both preliminary and final, nor the regional DTC recommendations seemed to influence the steady increase in NOAC initiations, but it is not unlikely that these guidelines have added to the increase indirectly.

To our knowledge this is the first study that used an ITS design to investigate the effect of all reimbursement decisions and guidelines on the introduction of the NOACs. Numerous factors can influence prescriber choices concerning NOACs, including research, media and marketing, but the biggest changes seem to have been captured within the models used. However, other factors such as the market approval for Praxbind® (idarucizumab), the antidote for dabigatran, in November 2015 [13] may also have influenced the trends. This probably contributed to the increase of dabigatran, and the total NOAC increase, after the final National guidelines were published, one month before the market approval of the antidote.

The regional DTC recommendations caused a large change in the prescriber´s choice of NOAC; after 5 months, the increase in apixaban, the recommended NOAC, was even larger than the increase 5 months after it was reimbursed. This may be explained by the active implementation strategies used by the regional DTC [33], including education, financial incentives, and prescription feedback to prescribers, all of which are proven to be effective [42–45]. The present analyses thus show that the regional implementation strategies are effective in influencing the prescriber's therapeutic choices regarding anticoagulant treatment in patients with AF. These findings are in line with previous studies which have shown that there is high adherence to the regional DTC recommendations in Stockholm, i.e., approximately 87% in primary care and 77% in secondary care for drugs overall [33]. We may thus conclude that regional recommendations are a useful tool to influence the prescribing of newly arriving drugs, despite all other influences when they are introduced on the market.

An ITS design has been shown to be appropriate for investigations of the effects of policy interventions, and the effects of reimbursement decisions and guidelines have been studied numerous times with this design [46, 47]. However, the use of an ITS design in this study has some limitations. First of all, the interventions happened close in time and the effect of one intervention may influence the other, as is the case with the European guidelines and the reimbursement of dabigatran and rivaroxaban. Therefore, it is difficult to tell which intervention was most important for the early increase of NOAC initiations. This can also be seen in the effect of the preliminary National guidelines on the NOAC prescriptions. Because apixaban was reimbursed six months before these guidelines, it looked like the preliminary National guidelines decreased the growth of apixaban, and with that also the NOACs in total. However, a few months after reimbursement the growth of dabigatran and rivaroxaban diminished as well, and therefore it is unlikely that this decrease for apixaban was caused by the preliminary National guidelines. It looks like the reimbursements of rivaroxaban and apixaban influenced the trend for dabigatran (figure 2), but since these interventions happened in a short time period, it is not possible to separate the effects. Besides the limitations in the ITS method, there are some other study limitations. Firstly, the study relies on diagnoses in health care records which might be missing in some cases. This might have led to an underestimation of the total amount of patients diagnosed with AF. However, since for the main analyses the proportions of patients initiated with each treatment were used, it is unlikely that this underestimation caused any bias in the results. The secondary care database is well validated [48], but validation studies for the primary care database are limited [28]. Secondly, some diagnoses from private specialists in the Stockholm region are not included since data for these caregivers are not available.

The strength of this study compared to previous studies of the adoption of NOACs is the use of ITS analyses which is considered to be the strongest quasi-experimental design in intervention research [29]. We also included all patients with a non-valvular AF diagnosis in an entire healthcare system, including both primary and secondary care, and we analysed the different NOACs separately. With this study design we can show that the regional DTC recommendations had a large influence on the prescriber's choice of anticoagulant therapy in the Stockholm County, which supports its usefulness in influencing the prescribing also of other newly arriving drugs.

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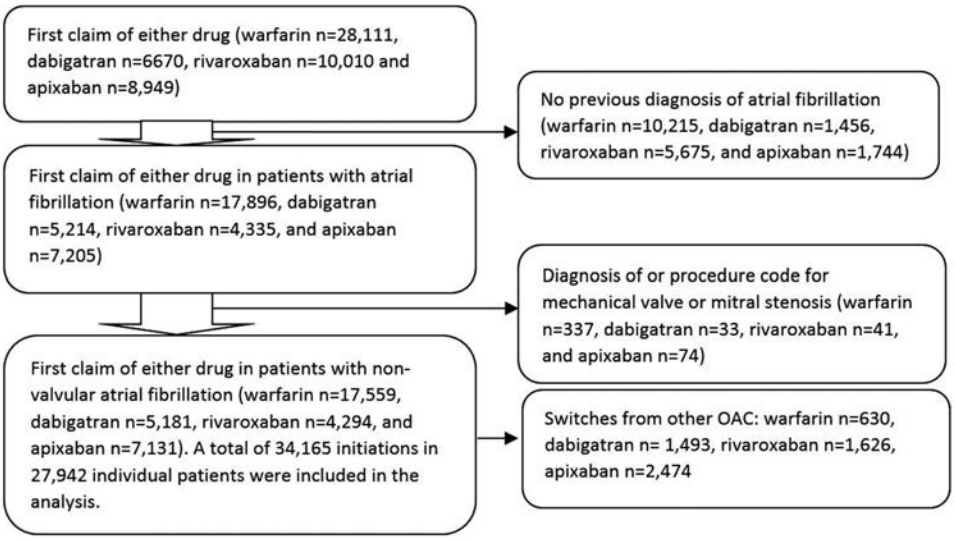
SUPPLEMENTARY DATA

2.1



Supplementary figure 1. Flow chart of patient selection

Supplementary figure 2. Sensitivity analysis showing proportions of all patients with atrial fibrillation initiated with any NOAC or warfarin per month. Dotted lines are used for the main analysis, and the solid lines show results for anticoagulant naïve patients. No differences in trends were measurable when comparing this to the total cohort including switchers.

2.2

FACTORS ASSOCIATED WITH ANTITHROMBOTIC TREATMENT DECISIONS FOR STROKE PREVENTION IN ATRIAL FIBRILLATION IN THE STOCKHOLM REGION AFTER THE INTRODUCTION OF NOACS

Joris Komen, Tomas Forslund, Paul Hjemdahl, Björn Wettermark

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ABSTRACT

Purpose

2.2

To investigate the influence of patient characteristics such as age, and stroke and bleeding risks on decisions for antithrombotic treatment in patients with atrial fibrillation (AF).

Methods

A retrospective, population based study including AF patients initiated with either warfarin, dabigatran, rivaroxaban, apixaban or low-dose aspirin (ASA) between March 2015 and February 2016. Multivariate models were used to calculate adjusted odds ratios (aOR) for factors associated with treatment decisions.

Results

A total of 6 765 newly initiated patients were included, most with apixaban (46.4%) and least with ASA (6.7%). There were more comorbidities in patients initiated with ASA or warfarin compared to the cohort average. Patients with high stroke risks had higher chances of receiving ASA (CHA_2DS_2-VASc ≥5 vs 0; aOR 2.01; 95% confidence interval (CI) 1.12-3.33). Among patients receiving oral anticoagulants, patients with high bleeding risks more often received warfarin (ATRIA-score 5-10 vs 0-3; aOR 1.40; CI 1.20-1.64). Among NOACs, apixaban was preferred for patients with higher stroke risks (aOR 1.78; CI 1.31-2.41), high bleeding risks (aOR 1.54; CI 1.26-1.88) and high age (age group ≥ 85 vs 0-65; aOR 1.84; CI 1.44-2.35). Conversely, dabigatran treatment was associated with lower ages and lower risks.

Conclusions

High stroke and bleeding risks favored choices of warfarin or ASA. Among patients receiving NOACs apixaban was favored for elderly and high risk patients whereas dabigatran was used in lower risk patients. The inadvertent use of ASA, especially among those with high stroke risks, should be further discouraged.

INTRODUCTION

Patients with atrial fibrillation (AF) on average have a five-fold increased risk for stroke compared to the general population [1]. Treatment with oral anticoagulants reduces this risk by two thirds [2]. With a prevalence of more than 3% in the total adult population in Sweden, AF is the most common arrhythmia, with more than 80% of the patients having risk factors motivating chronic oral anticoagulant therapy [3].

In 2011, the first of the presently available non-vitamin K oral anticoagulants (NOACs), dabigatran, was registered in Europe for the prevention of thromboembolic complications in patients with AF [4]. Rivaroxaban and apixaban [5, 6]were registered for thromboembolic prophylaxis in patients with AF and reimbursed on the Swedish market in 2012 and 2013, respectively. NOACs are effective alternatives to the traditional treatment with vitamin K antagonists like warfarin and are now extensively used [7].

The efficacy and safety of these NOACs compared to warfarin have been demonstrated in one pivotal phase III clinical trial for each drug [8–10], but the effectiveness and safety of drugs may differ substantially between clinical trials and clinical practice [11]. The risk-benefit ratio of treatment with a NOAC or warfarin may, e.g., depend on the population treated, with important discrepancies between the trial populations and real-life users of these drugs [12].

Low-dose aspirin (ASA), has been shown to be much less effective than oral anticoagulant therapy for stroke prevention in AF without being safer from the standpoint of bleeding [2, 13, 14], and several guidelines recommend ASA only for AF patients who are unwilling or unable to take oral anticoagulation treatment [15, 16]. Nonetheless, ASA is still used by a substantial number of AF patients [17] for reasons which are not fully understood but may reflect physicians´ reluctance to change therapeutic traditions or misperceptions regarding the benefit and safety of ASA treatment.

Previous studies have shown important factors associated with the prescribing of either warfarin or a NOAC [12, 18–21], but there is limited knowledge regarding predictors for prescribing ASA or for decisions between the three NOACs. The aim of the current study was to investigate the influence of patient characteristics such as stroke risk, bleeding risk and age on decisions regarding antithrombotic treatment in patients with atrial fibrillation.

METHODS

Patient selection

For this retrospective, population based study, we used the administrative health register of the Stockholm County (Vårdanalysdatabasen, the VAL database). Pseudonymized data regarding patient sex, age, diagnoses, prescription claims, hospitalizations and other healthcare consultations, migration and death for all 2.2 million inhabitants in the Stockholm region are available in the database [22], and may be linked through the Personal Identity Number [23]. All diagnosis codes from primary care, hospitalizations and specialist consultations in ambulatory care are included. Since July 2010, the VAL database also includes data on claims of prescriptions from any pharmacy in Sweden corresponding to the information available in the National Swedish Prescribed Drug register, i.e., amounts, expenditures and reimbursement, the age and sex of the patient, co-payments and prescriber category [24].

The analyses were conducted in VAL, which is the administrative health care register of the Stockholm region. The data in VAL is pseudonymized and individual patients cannot be identified. The research was approved by the Regional Ethical Review Board in Stockholm and personal data permit was obtained from the Public Healthcare Services Committee, Department of Healthcare Development of the Stockholm County Council.

We included all first claimed prescriptions from March 2015 to February 2016, of either warfarin (ATC: B01AA03), low-dose ASA (ATC: B01AC06), or a NOAC (ATC: B01AE07, B01AF01 or B01AF02) after a 9 month wash out period to identify newly initiated patients. Patients were excluded if there was no registered diagnosis code for AF (see appendix Table 1 for ICD-codes) from 2003 until the date of the first claim of the antithrombotic agent selected for the patient. Initiations were also excluded if the patient had a recorded procedure code for mechanical valves, or a diagnosis code for mitral stenosis. Patients were then excluded if they had been treated with any oral anticoagulant 6 months prior to initiation. Comorbidities and prescriber information were linked to the initiations using ICD-10 codes recorded at each consultation and prescriber codes recorded at the first prescription, respectively [23].

From this cohort, we created three subgroups of patients initiated on the drugs included in the analyses (Figure 1). The first subgroup was created to analyze predictors for treatment with ASA versus any oral anticoagulation treatment, the second subgroup was created for analyses comparing warfarin and NOAC and the third subgroup to analyze predictors for decisions of the three NOACs separately. In the first subgroup, we excluded patients who had been treated with ASA 6 months prior to inclusion to avoid including patients twice in the same analyses. In the second and third subgroups, patients could be treated with ASA prior to inclusion.

For the patient's comorbidities, we searched for registered diagnostic codes by any caregiver in the region from 2003 until the date of inclusion. Ischemic stroke risks were evaluated by calculating the CHA_2DS_2-VASc-scores [25] (congestive heart failure +1, hypertension +1, age [65-74 +1; ≥75 years +2], diabetes mellitus +1, previous ischemic stroke +2, vascular disease +1, and female sex +1). Bleeding risks were calculated using the ATRIA-score (anemia +3, severe renal disease +3, age ≥75 +2, any prior hemorrhage diagnosis +1 and hypertension +1) [26]. The age of each patient was determined at the date of inclusion. Other comorbidities included in the models, defined in Table 1 as complicating comorbidities, were chosen based on previous knowledge and standards from published studies.

Statistical analyses

Descriptive statistics were used to describe the baseline characteristics of the treatment groups. One-way analyses of variance (ANOVA) were used to calculate p-values for differences between mean values. For variables with proportional values, a chi-square test was used. We analyzed factors associated with ASA treatment compared to oral anticoagulant treatment, warfarin compared to NOAC, and one NOAC compared to the two other NOACs. In a multivariate model, we calculated adjusted odds ratios (aOR) with 95%-confidence intervals (CI) for treatment decisions for different stroke risk, bleeding risk and age categories. Variables in the multivariate model were chosen based on previous knowledge and standards from published literature. To investigate the effects

of the CHA_2DS_2-VASc score and the ATRIA score on treatment decisions, we adjusted for gender and all comorbidities presented in Table 1, except for the qualifying risk factors of the scores. For the effect of the age group on the treatment decision we adjusted for gender and all comorbidities presented in Table 1, and with this model we could therefore investigate each qualifying comorbidity from the stroke and bleeding risk calculation. We checked all models for statistically significant interactions between the covariates. The statistical package IBM SPSS Statistics version 23.0 was used for all statistical analyses. Data extraction was performed using SAS EG 6.1 (SAS Institute Inc., Cary, NC).

RESULTS

Patient selection

A total of 6 765 patients were included in the cohort (see Appendix Figure 1). The first subgroup comparing ASA with oral anticoagulant therapy consisted of 4 316 patients previously not treated with ASA, the second subgroup comparing warfarin versus NOACs of 6 312 patients and the third subgroup comparing the three NOACs consisted of 4 621 patients.

Baseline characteristics

Among the patients initiated with oral anticoagulant treatment, 27.8% received warfarin and 72.2% received a NOAC (Table 1). Among patients treated with a NOAC, 15.5% received dabigatran, 16.7% rivaroxaban and 67.8% apixaban. The mean age of the cohort was 74.3 years and 54.7% were males. The proportions of patients with the highest risks for stroke and bleeding were higher in patients initiated with ASA or warfarin; the group initiated with ASA had the highest proportion of very old patients as well (Table 1). The mean CHA_2DS_2-VASc and ATRIA scores were the lowest for patients initiated with dabigatran, while patients initiated with apixaban and rivaroxaban differed little from the cohort average. The proportions of patients with renal disease and anemia were the lowest among dabigatran initiated patients. The baseline characteristics of patients in the different treatment groups did not differ between 2014 (Appendix Table 2), i.e. before regional recommendations regarding NOACs were issued, and the study period (Table 1).

Warfarin was preferentially prescribed in primary care, while ASA was prescribed more often by geriatricians and dabigatran by cardiologists. Regarding comorbidities, dementia was less common in patients initiated with warfarin or dabigatran, VTE was more common in patients with rivaroxaban, and all comorbidities, except VTE and obesity, were more common than average in patients initiated with ASA.

The prevalence of vascular disease (i.e. angina pectoris, myocardial infarction, atherosclerosis and peripheral vascular disease) was higher among patients treated with ASA compared to oral anticoagulation in the elderly (34.7 vs. 28.0 %) and among patients with a CHA_2DS_2-VASc score ≥5 (51.8 vs. 41.8 %).

Of the patients initiated with warfarin, 45,9% had been treated with ASA in the six months prior to inclusion, 8.9% with clopidogrel and 6.5% with both ASA and clopidogrel. For patients initiated with a NOAC, this was 36.2%, 4.0% and 1.5%, respectively.

Table 1. Baseline characteristics of patients newly initiated with treatment from March 2015 until February 2016. All numbers are percentages unless otherwise stated

Variable	Overall	ASA	Warfarin	Dabigatran	Rivaroxaban	Apixaban	p-value
Number of patients	6 765	453	1 691	717	770	3 134	
Male sex	54.7	54.1	54.9	60.4	54.4	53.4	0.022
Age							
Mean age (years)	74.3	75.1	74.9	70.4	73.7	74.8	<0.001
0-65	20.3	24.9	17.9	29.7	20.9	18.6	
66-75	32.2	20.1	30.5	37.7	35.2	32.8	
76-85	30.1	28.3	33.9	22.7	29.6	30.1	
≥86	17.5	26.7	17.6	9.9	14.3	18.5	
CHA_2DS_2-VASc-score							
CHA_2DS_2-VASc (mean)	3.67	3.77	3.89	3.17	3.56	3.69	<0.001
0	4.4	4.4	4.1	8.6	4.0	3.7	<0.001
1	9.9	10.6	7.2	14.4	11.6	9.9	
2-4	52.5	47.9	52.5	51.2	53.9	53.2	
≥5	33.2	37.1	36.3	25.8	30.5	33.2	
Comorbidities included in CHA_2DS_2-VASc-score							
Chronic heart failure	26.4	30.5	30.7	17.0	25.8	25.8	<0.001
Hypertension	70.2	65.6	73.9	63.7	69.1	29.4	<0.001
Age ≥ 75	50.6	56.5	54.9	34.5	47.7	51.9	<0.001
Age 65-74	31.8	20.5	29.2	38.9	34.8	32.5	<0.001
Diabetes mellitus	19.2	17.0	23.1	15.3	19.1	18.3	<0.001
Stroke or embolism	22.4	24.7	20.8	26.2	19.5	22.8	0.007
Vascular disease	28.3	35.5	35.2	21.2	27.5	25.3	<0.001
Female sex	45.3	45.9	45.1	39.6	45.5	46.6	0.022
ATRIA-score							
ATRIA (mean)	2.6	2.9	2.9	1.9	2.4	2.6	<0.001
0-3	76.7	70.4	72.0	85.5	79.9	77.3	<0.001
4	6.2	7.9	6.8	6.7	6.0	5.6	
≥5	17.1	21.6	21.2	7.8	14.2	17.1	
Comorbidities included in ATRIA-score							
Anemia	17.3	21.4	20.4	11.3	15.7	16.9	<0.001
Renal disease	8.7	11.7	13.2	3.2	6.4	7.7	<0.001
Age ≥ 75	50.6	56.5	54.9	34.5	47.7	51.9	<0.001
Serious bleeding	9.8	12.1	9.7	8.9	7.8	10.2	0.106
Hypertension	70.2	65.6	73.9	63.7	69.1	29.4	<0.001
Prescriber category							
Primary care	31.8	28.0	48.8	18.7	30.9	26.5	<0.001
Cardiology	26.5	14.3	17.8	33.2	29.4	30.7	<0.001
Internal medicines	19.4	14.6	13.8	19.2	19.1	23.3	<0.001
Geriatrics	7.6	15.5	8.2	5.2	4.5	7.5	<0.001
Other/unknown	14.7	27.6	11.4	23.7	16.1	12.0	<0.001
Complicating comorbidities							
Liver disease	2.1	4.6	2.5	1.3	2.9	1.6	<0.001
Dementia	5.0	11.3	2.8	2.5	6.1	5.5	<0.001
VTE	9.6	5.7	10.6	6.8	15.5	8.8	<0.001
Alcoholism	6.3	8.6	5.8	7.5	6.5	5.8	0.097

Table 1. (continued)

Variable	Overall	ASA	Warfarin	Dabigatran	Rivaroxaban	Apixaban	p-value
Cancer	24.8	26.7	25.6	19.4	23.2	25.6	0.005
COPD	10.7	11.3	10.9	7.8	9.7	11.4	0.069
Frequent falls	15.7	19.2	15.1	12.1	17.4	15.9	0.010
Obesity	9.8	7.9	10.4	11.2	10.3	9.3	0.290

Factors associated with treatment decisions

A high stroke risk increased the probability of receiving ASA instead of oral anticoagulant treatment, while stroke risk did not influence the probability of receiving warfarin compared to a NOAC (Figures 1A+B). A high bleeding risk drove the decision from a NOAC towards warfarin while the bleeding risk did not influence the decision for ASA. Age did not play a substantial role in the decision between warfarin or a NOAC. Patients in the age group 66-75 years had a decreased probability of receiving ASA compared to an oral anticoagulant, but this probability was increased among the very old.

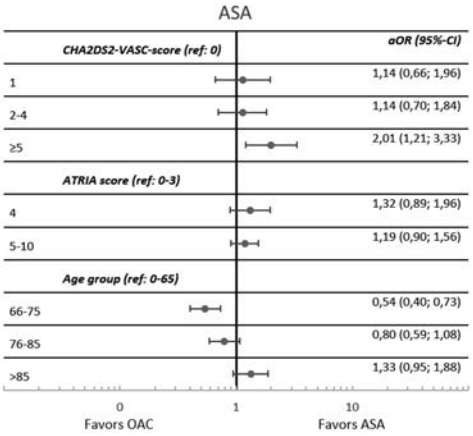
Comorbidities associated with an increased use of ASA were liver disease, dementia and vascular disease, while VTE drove the decision towards oral anticoagulant treatment (Appendix Figure 2A). Renal disease and vascular disease favored warfarin, and dementia favored NOAC treatment (Appendix Figure 2B).

Among patients treated with a NOAC, the chances of being treated with apixaban were higher for patients with higher risks for stroke and bleeding and in higher age groups (Figure 1E), while the chances of receiving dabigatran were lower for patients in these groups (Figure 1C). Initiations of rivaroxaban were not specifically associated with either stroke risk, bleeding risk or age group (Figure 1D). In the age-category models, the probability of receiving dabigatran was increased if patients had a previous stroke or thromboembolism, while renal disease and dementia decreased the probability (Appendix Figure 2C). Liver disease and VTE increased the probability of receiving rivaroxaban and renal disease favored apixaban (Appendix Figures 3D and 3E).

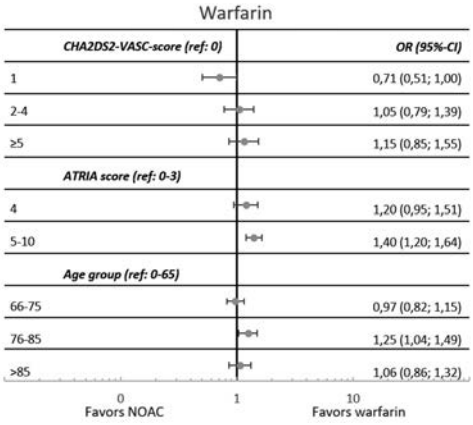
DISCUSSION

In this retrospective population-based study, we found that stroke risk, bleeding risk and age category influenced the prescribers' treatment decision for stroke prevention in AF patients in a manner which was not always in accordance with the evidence base and recommendations. Patients with the highest stroke risk had an increased probability of receiving ASA treatment, while bleeding risk did not influence this decision. The probability of receiving ASA was decreased in patients aged 66-75 but increased in the very old. For warfarin, the decision was driven by higher bleeding risks, while stroke risk and age did not influence the probability of prescribing warfarin. Among patients initiated on a NOAC, higher stroke risk, higher bleeding risk and higher age drove decisions towards apixaban and away from dabigatran, while the probability of receiving rivaroxaban was not influenced by these variables. The pattern of choices between NOACs did not seem to be

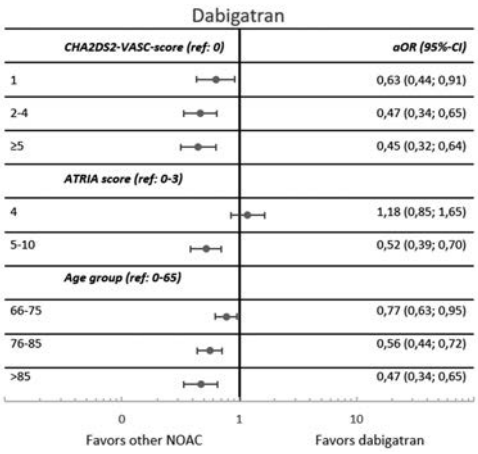
A)


ASA
CHA2DS2-VASC-score (ref: 0)
aOR (95%-CI)
1
1,14 (0,66; 1,96)
2-4
1,14 (0,70; 1,84)
≥5
2,01 (1,21; 3,33)
ATRIA score (ref: 0-3)
4
1,32 (0,89; 1,96)
5-10
1,19 (0,90; 1,56)
Age group (ref: 0-65)
66-75
0,54 (0,40; 0,73)
76-85
0,80 (0,59; 1,08)
>85
1,33 (0,95; 1,88)
0
1
10
Favors OAC
Favors ASA

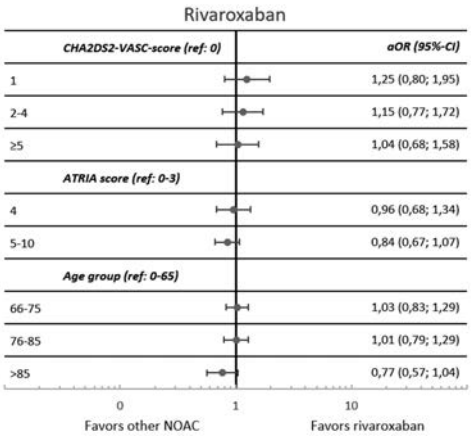
B)


Warfarin
CHA2DS2-VASC-score (ref: 0)
OR (95%-CI)
1
0,71 (0,51; 1,00)
2-4
1,05 (0,79; 1,39)
≥5
1,15 (0,85; 1,55)
ATRIA score (ref: 0-3)
4
1,20 (0,95; 1,51)
5-10
1,40 (1,20; 1,64)
Age group (ref: 0-65)
66-75
0,97 (0,82; 1,15)
76-85
1,25 (1,04; 1,49)
>85
1,06 (0,86; 1,32)
0
1
10
Favors NOAC
Favors warfarin

D)


Dabigatran
CHA2DS2-VASC-score (ref: 0)
aOR (95%-CI)
1
0,63 (0,44; 0,91)
2-4
0,47 (0,34; 0,65)
≥5
0,45 (0,32; 0,64)
ATRIA score (ref: 0-3)
4
1,18 (0,85; 1,65)
5-10
0,52 (0,39; 0,70)
Age group (ref: 0-65)
66-75
0,77 (0,63; 0,95)
76-85
0,56 (0,44; 0,72)
>85
0,47 (0,34; 0,65)
0
1
10
Favors other NOAC
Favors dabigatran

C)


Rivaroxaban
CHA2DS2-VASC-score (ref: 0)
aOR (95%-CI)
1
1,25 (0,80; 1,95)
2-4
1,15 (0,77; 1,72)
≥5
1,04 (0,68; 1,58)
ATRIA score (ref: 0-3)
4
0,96 (0,68; 1,34)
5-10
0,84 (0,67; 1,07)
Age group (ref: 0-65)
66-75
1,03 (0,83; 1,29)
76-85
1,01 (0,79; 1,29)
>85
0,77 (0,57; 1,04)
0
1
10
Favors other NOAC
Favors rivaroxaban

E)

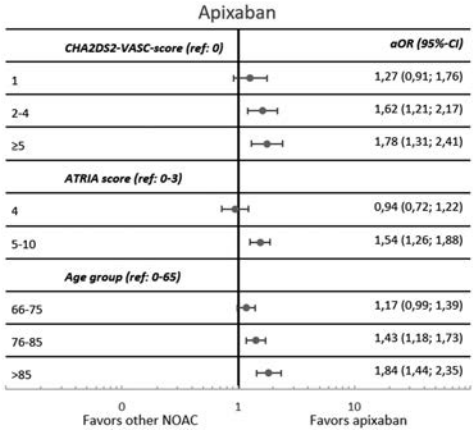

Apixaban
CHA2DS2-VASC-score (ref: 0)
aOR (95%-CI)
1
1,27 (0,91; 1,76)
2-4
1,62 (1,21; 2,17)
≥5
1,78 (1,31; 2,41)
ATRIA score (ref: 0-3)
4
0,94 (0,72; 1,22)
5-10
1,54 (1,26; 1,88)
Age group (ref: 0-65)
66-75
1,17 (0,99; 1,39)
76-85
1,43 (1,18; 1,73)
>85
1,84 (1,44; 2,35)
0
1
10
Favors other NOAC
Favors apixaban

Figure 1. Adjusted Odds Ratios (aOR) of factors associated with treatment decisions for (A) ASA compared to an oral anticoagulant, (B) warfarin compared to a NOAC, (C) dabigatran compared to apixaban and rivaroxaban, (D) rivaroxaban compared to dabigatran and apixaban, and (E) apixaban compared to dabigatran and rivaroxaban. Three multivariate models were used to calculate how stroke risk, bleeding risk and age group influenced treatment decisions.

influenced by the introduction of regional NOAC recommendations in 2015 but there was a large increase in apixaban prescribing after 2014.

Especially ASA, and to a lesser extent warfarin, continued to be chosen for more severely ill patients after the introduction of the NOACs. Thus, almost all comorbidities were more common among ASA and warfarin initiated patients compared to the cohort average. This indicates that prescribers tend to stay with well-known old drugs for the treatment of more vulnerable patients. Despite clear-cut recommendations since several years to favor oral anticoagulant over ASA treatment, 6.7% of all patients were still initiated with ASA. It is especially remarkable that patients with the highest risks for stroke, to a large part driven by high age, more often received ASA compared to patients with lower risks, since ASA is much less effective than oral anticoagulation treatment for the prevention of stroke without offering significant benefits regarding safety [2, 13, 14]. However, the higher prevalence of vascular disease among the elderly and high-risk patients could have contributed to this decision. We have no data on stent placements which to some extent could contribute to ASA treatment. Patients could potentially be treated with single or dual antiplatelet therapy plus oral anticoagulation at the time of inclusion. However, there is a difficulty in correctly identifying patients who switched and those actually receiving this combination therapy. Still it seems as if the combination occurred more often in patients treated with warfarin, indicating again that this was the preferred therapy for the more severely ill patients.

Among geriatricians, the proportions initiated on ASA or warfarin were larger than the cohort average. This could in part be due to uncertainty about still poorly investigated drug-drug interactions with NOACs among elderly frail patients with many drugs [27]. Warfarin was the preferred alternative for initiation of oral anticoagulation in primary care indicating that the uptake of NOACs, as for other new drugs, is dependent on acceptance in secondary care before becoming established in primary care [28].

The ROCKET-AF trial included only patients with a $CHADS_2$ score of 2 or above (equivalent to CHA_2DS_2-VASc scores well above 3), which resulted in a mean $CHADS_2$ score of 3.5 and the oldest patient population among the pivotal NOAC trials [9]. However, in our real-life users the average $CHADS_2$ score for rivaroxaban treated patients was only 2.1 (data not shown). Instead, apixaban was the favored NOAC for older patients with higher risks for stroke. This suggests that factors other than trial characteristics guide the prescribers in their choice of NOAC for high-risk patients. Local recommendations in the Wise List prioritized apixaban among the NOACs during the study period [7] but the patient characteristics in the different treatment groups were similar the year before this recommendation (Appendix Table 2). Previous studies report similar results with rivaroxaban being initiated in patients with average $CHADS_2$ scores of 2.7 [21], and 1.7 [29]. Due to the lack of randomized clinical trial data for rivaroxaban in patients with $CHADS_2$ scores 0-1, further investigation of the risk-

benefit ratio for this drug in low risk AF patients is of interest. Similarly, since the ARISTOTLE trial included a substantially smaller proportion of elderly patients than that found among real-life users, close follow-up of elderly high risk patients is needed [10].

To our knowledge, this is the first study of patient characteristics associated with decisions between the available NOACs as well as decisions to resort to ASA instead of an oral anticoagulant. Some studies have determined predictors for NOAC compared to warfarin treatment [12, 18–21], and found that higher stroke and bleeding risks often are associated with warfarin use. In the present, more recent study a higher stroke risk did not channel the selection towards warfarin, indicating that the experience gained by prescribers has enabled the use of NOACs also in higher risk patients. This is in accordance with guidelines either favoring NOACs over warfarin (ESC) or giving them equal priority (US & Swedish). However, warfarin treatment was still favored for patients with higher bleeding risks, most likely due to the possibility to personalize warfarin treatment and the availability of well-established drugs and routines for reversal of bleeds related to warfarin treatment, whereas specific NOAC antidotes were still lacking.

Dabigatran was preferentially used among younger, low-risk patients. The dependence on renal function for the elimination of dabigatran [4], has apparently been an important factor when choosing an oral anticoagulant for elderly AF patients. Dabigatran is the recommended second-line NOAC in the regional recommendations in Stockholm but should be used with caution for elderly and frail patients who often have renal impairment [15]. Dabigatran drug levels can be measured in routine care in Stockholm but the possibility to monitor if the dosage is adequate is seldom used; it appears to be simpler for the prescribers to choose another drug which is thought to be safer for vulnerable patients than to individualize the dose. Apixaban is the NOAC which is least dependent on renal function for its elimination [4–6]. This might explain why elderly patients who often have renal impairment were more likely to receive apixaban and less likely to receive dabigatran.

Our study has some limitations. Firstly, previous studies have found predictors for treatment decisions for which we have no data, for example the ethnicity of the patient and the preference of the patient and/or the prescriber [12, 18, 21]. Other studies have also found regional differences in the odds for receiving NOACs or warfarin, whereas our study was confined to one region; cross-regional and cross-national comparisons would be of interest as local recommendations and routines may differ. Of interest is that patterns in NOAC prescribing changed after the introduction of regional NOAC recommendations in Stockholm in 2015 [7, 15] whereas the patient characteristics in the different treatment groups did not change after the recommendation. A limitation in the broad application of the present findings may have been created by the regional recommendations. Our previous work has shown that the regional recommendations increased apixaban prescribing and thus to some extent choices between NOACs but not other treatment decisions [7]. However, the pattern of patient characteristics did not change from the period before the recommendations were issued and there is no limitation on the broad application of the findings for ASA versus OAC treatment or warfarin versus NOAC treatment. Secondly, when calculating the ATRIA score, we probably underestimated renal impairment, since only limited data on renal impairment (no creatinine levels, only diagnostic codes) are available in the VAL database [30]. However, the same underestimation occurred for all patients and treatment alternatives; we believe that this possible bias is limited and

that the available data allow us to interpret how bleeding risks influence prescriber decisions. Lastly, since patients were included in this cohort after being newly initiated with a treatment, we lack patients who received no treatment at all, which in some cases might be the appropriate action.

The strengths of the present study compared to previous ones are that it has been undertaken in all patients with AF in an entire healthcare system, including both primary and secondary care. This is the first study which compares predictors for all treatment alternatives, and for the three NOACs separately. Large changes have occurred in NOAC utilization in the last few years. We only investigated patients initiated from March 2015 until February 2016, since the utilization patterns and factors influencing them were relatively stable during this period [7].

In conclusion, we found that high stroke and bleeding risks favored treatment with warfarin or ASA, the latter being at odds with the available evidence and recommendations. Among NOACs apixaban use was channeled towards high risk patients, while dabigatran was mainly prescribed for low risk patients. Even though rivaroxaban was tested in and marketed for high-risk patients, this did not influence the prescriber's decision between the NOACs. Thus, post-marketing surveillance is needed to follow how patient characteristics influence prescriber's decisions and the outcomes achieved with the treatments chosen. Increased efforts to reduce ASA treatment instead of oral anticoagulant treatment are warranted, as well as improved education and further evidence regarding the treatment of high risk AF patients.

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APPENDICES

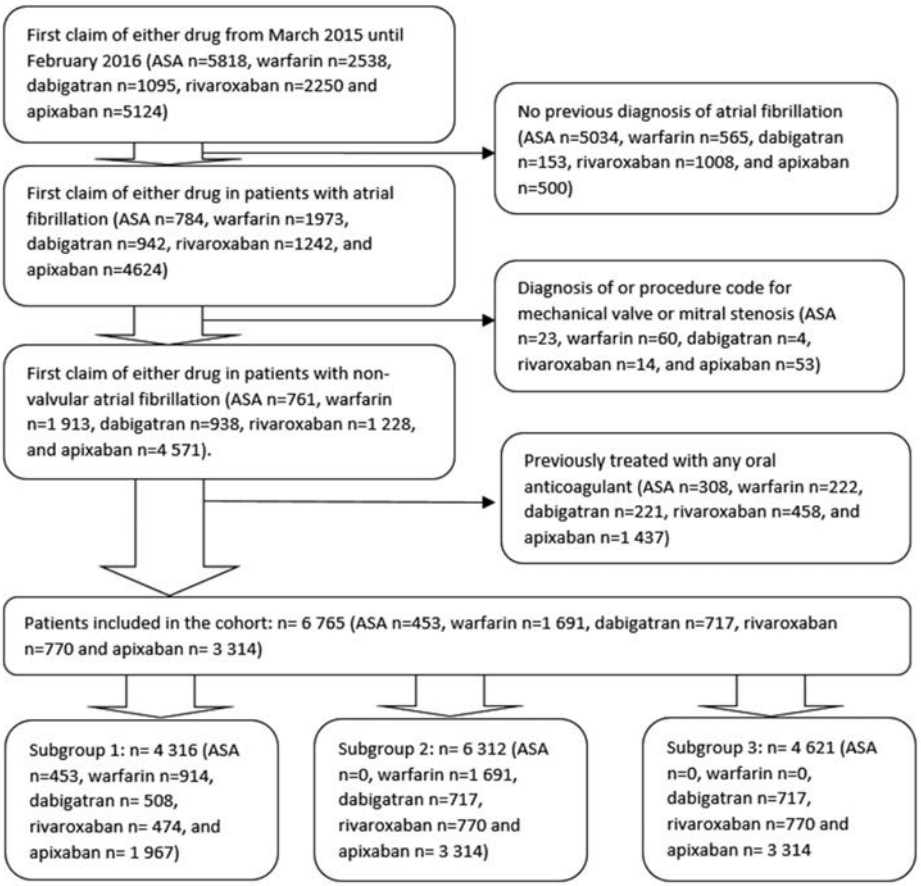
2.2

Appendix table 1. ICD-10 codes used for defining comorbidities in the database

Diagnosis	ICD-code beginning with
Anemia	D50-64
Atrial fibrillation	I48
Cancer	entire C-series
Chronic heart failure	I50
COPD	J43-44
Dementia	F00-F03
Diabetes mellitus	E10-E14
Frequent falls (more than one registration)	W00-19
Hypertension	I10-I15
Liver disease	K70-77
Mechanical valve	Procedure codes FCA60, FCA70, FDC10, FGE00, FGE10, FGE20, FGE96, FJF00, FJF10, FJF12, FJF20, FJF96, FKD00, FKD10, FKD20, FKD96, FMD00, FMD10, FMD12, FMD13, FMD20, FMD30, FMD40, FMD96
Mitral stenosis	I050, I052, I342
Obesity	E65-66
Renal disease	N17-19
Serious bleeding	I60-62, I690-I692, S064-S066, I850, I983, K25-28 (subcodes 0-2 and 4-6 only), K625, K922, D629
Stroke or embolism	I63, I64, I679, I693, I694, I698, I67-, I69-, Z866, Z867, G450, G451, G452, G453, G458, G45.9, G45-, I74
Vascular disease	I20-I25, I70, I739
Venous thromboembolism	I26, I80-I82

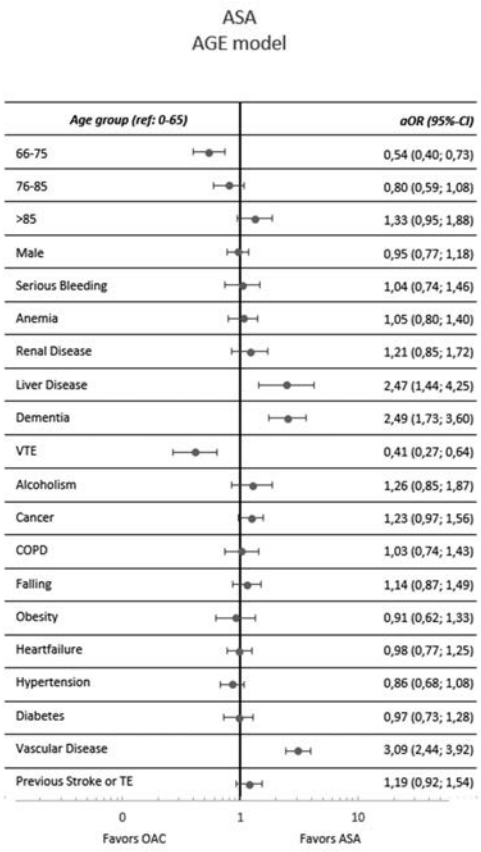
Appendix table 2. Comparing patient characteristics of the population in the cohort to those initiated in 2014, the year before the local Stockholm recommendation, the Wise List, advised apixaban as the preferred NOAC.

Variable	Overall	ASA	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Patients initiated in 2014						
Number of patients	6 576	713	3 099	1 036	924	795
Male sex	55.6	53.9	54.4	61.3	53.9	56.2
Age						
Mean age (years)	74.2	75.5	74.8	69.8	74.6	75.5
CHA_2DS_2-VASc-score						
CHADS-VASc (mean)	3.64	3.64	3.79	2.96	3.73	3.82
ATRIA-score						
ATRIA (mean)	2.5	2.8	2.7	1.8	2.4	2.7
Population in the cohort						
Number of patients	6 765	453	1 691	717	770	3 134
Male sex	54.7	54.1	54.9	60.4	54.4	53.4
Age						
Mean age (years)	74.3	75.1	74.9	70.4	73.7	74.8
CHA_2DS_2-VASc-score						
CHADS-VASc (mean)	3.67	3.77	3.89	3.17	3.56	3.69
ATRIA-score						
ATRIA (mean)	2.6	2.9	2.9	1.9	2.4	2.6



Appendix figure 1. Flow chart of patient selection.

A)



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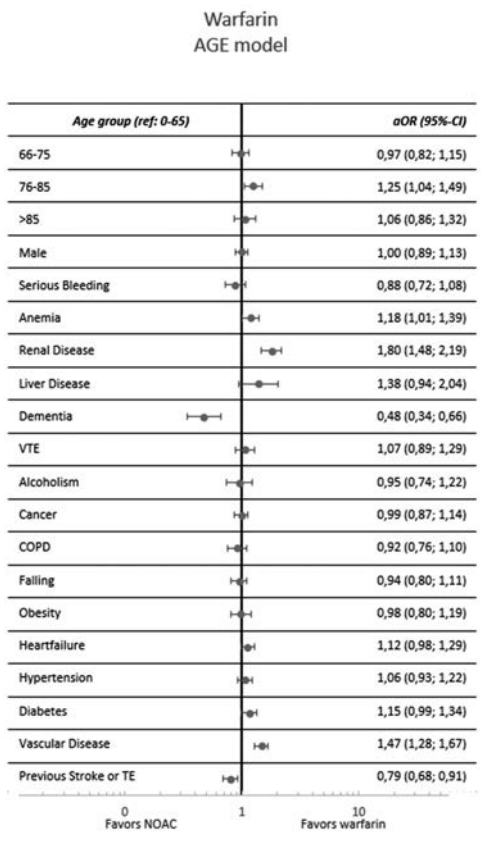
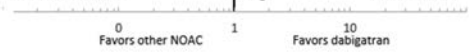


Appendix figure 2. Adjusted Odds Ratios (aOR) of all comorbidities associated with treatment choises for (A) ASA compared to an oral anticoagulant, (B) warfarin compared to NOAC, (C) dabigatran compared to apixaban and rivaroxaban, (D) rivaroxaban compared to dabigatran and apixaban, and (E) apixaban compared to dabigatran and rivaroxaban. In this Figure the multivariate model for analyzing the effects of age on treatment decisions is shown. This model includes all complicating comorbidities as defined in Table 1.

C)

Dabigatran
AGE model

Age group (ref: 0-65)	aOR (95%-CI)
66-75	0,77 (0,63; 0,95)
76-85	0,56 (0,44; 0,72)
>85	0,47 (0,34; 0,65)
Male	0,90 (0,75; 1,07)
Serious Bleeding	1,11 (0,82; 1,50)
Anemia	0,85 (0,65; 1,11)
Renal Disease	0,58 (0,37; 0,91)
Liver Disease	0,64 (0,32; 1,32)
Dementia	0,55 (0,33; 0,90)
VTE	0,73 (0,53; 1,00)
Alcoholism	1,24 (0,89; 1,71)
Cancer	0,86 (0,70; 1,06)
COPD	0,79 (0,58; 1,06)
Falling	0,83 (0,65; 1,06)
Obesity	1,21 (0,92; 1,59)
Heartfailure	0,73 (0,59; 0,92)
Hypertension	0,88 (0,73; 1,05)
Diabetes	0,89 (0,70; 1,12)
Vascular Disease	1,00 (0,81; 1,23)
Previous Stroke or TE	1,71 (1,41; 2,09)



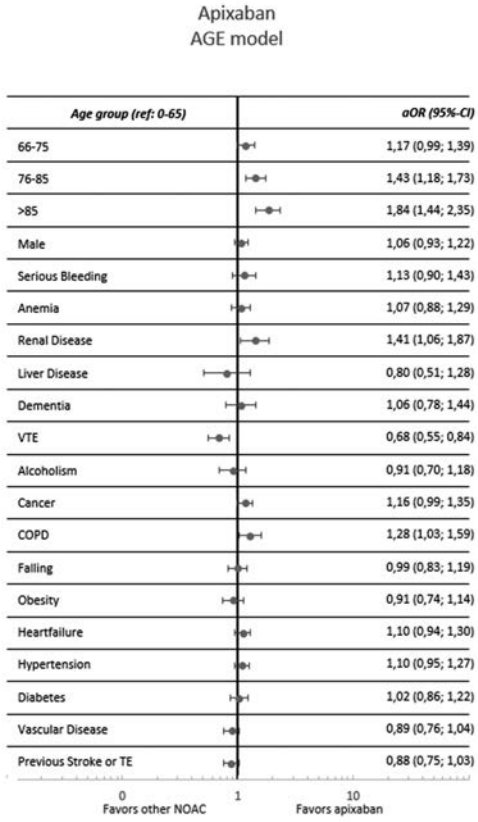
D)

Rivaroxaban
AGE model

Age group (ref: 0-65)	aOR (95%-CI)
66-75	1,03 (0,83; 1,29)
76-85	1,01 (0,79; 1,29)
>85	0,77 (0,57; 1,04)
Male	1,00 (0,85; 1,18)
Serious Bleeding	0,76 (0,56; 1,02)
Anemia	1,04 (0,82; 1,31)
Renal Disease	0,86 (0,61; 1,20)
Liver Disease	1,85 (1,11; 3,08)
Dementia	1,36 (0,96; 1,92)
VTE	2,08 (1,65; 2,63)
Alcoholism	0,95 (0,68; 1,33)
Cancer	0,92 (0,76; 1,11)
COPD	0,84 (0,64; 1,09)
Falling	1,19 (0,96; 1,47)
Obesity	0,97 (0,74; 1,28)
Heartfailure	1,11 (0,91; 1,35)
Hypertension	0,99 (0,83; 1,19)
Diabetes	1,07 (0,87; 1,33)
Vascular Disease	1,19 (0,99; 1,44)
Previous Stroke or TE	0,73 (0,60; 0,90)

Appendix figure 2. (continued)

E)



Appendix figure 2. (continued)

2.3

IMPROVED STROKE PREVENTION IN ATRIAL FIBRILLATION AFTER THE INTRODUCTION OF NOACS – THE STOCKHOLM EXPERIENCE

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ABSTRACT

Background and purpose

To study the impact of improved antithrombotic treatment in atrial fibrillation (AF) after the introduction of Non-vitamin K antagonist oral anticoagulants (NOACs) on the incidence of stroke and bleeding in a real-life total population including both primary and secondary care.

Methods

Using the Stockholm County Healthcare database (VAL) all resident and alive patients with a recorded diagnosis for AF during the preceding five years were followed for clinical outcomes during 2012 (n=41008) and 2017 (n=49510).

Results

Pharmacy claims for OACs increased from 51.6% to 73.8% (78.7% amongst those with CHA_2DS_2-VASc ≥2). NOAC claims increased from 0.4% to 34.4%. Ischemic stroke incidence rates (IR) decreased from 2.01 per 100 person years in 2012, to 1.17 in 2017 (IRR 0.58, 95% CI; 0.52–0.65). The largest increases in OAC use and decreases in ischemic strokes were seen in patients aged 80 years or above who had the highest risk of stroke and bleeding. The IR for major bleeding (2.59) remained unchanged (IRR 1.00; 95% CI; 0.92–1.09) even in those with a high bleeding risk. Poisson regression showed that 10% of the absolute ischemic stroke reduction was associated with increased OAC treatment, while 27% was related to a generally decreased risk for all stroke.

Conclusion

Increased OAC use contributed to a marked reduction of ischemic strokes without increasing bleeding rates between 2012 and 2017. The largest stroke reduction was seen in elderly patients with the highest risks for stroke and bleeding. These findings strongly support the adoption of current guideline recommendations for stroke prevention in AF in both primary and secondary care.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a prevalence of at least 3% in the adult population of Sweden [1]. AF is a major risk factor for stroke, giving patients with this condition a five-fold increased risk of suffering a stroke [2]. Both the prevalence of AF and the related stroke risk increase markedly in the elderly [2]. Treatment with an oral anticoagulant (OAC) reduces the risk for stroke effectively [3–5]. Vitamin K antagonists such as warfarin have been the mainstay for stroke prevention in AF patients since several decades [6]. However, many patients, especially the elderly and frail, have received less efficient but not safer acetylsalicylic acid (ASA) or no antithrombotic treatment at all [7]. Previous studies in Sweden indicated that the largest preventable stroke burden was among elderly patients not receiving warfarin treatment [8, 9].

Four pivotal trials have shown the efficacy and safety of the non-vitamin K antagonist oral anticoagulants (NOACs) dabigatran, rivaroxaban, apixaban, and edoxaban compared to warfarin [10–13]. Numerous observational studies have corroborated their safety and effectiveness in clinical practice [14, 15]. The accumulating evidence has resulted in revisions of guideline recommendations [17,18,19] and has been associated with substantial increases in the utilization of NOACs in clinical practice all over the world [20], as well as in the Stockholm healthcare region [21]. However, particularly in AF patients with a high stroke risk, in whom also bleeding concerns are common [8], OACs have continued to be underused resulting in preventable strokes [20,22].

In addition to the early warfarin and ASA trials [5], two relatively recent randomized studies have shown superiority of OAC compared to ASA treatment in AF patients. However, these patients were relatively young and without serious co-morbidities in one study [6], and the majority of fragile patients were not considered eligible in the other [23]. The American AF guidelines recommend either warfarin or a NOAC for patients with CHA_2DS_2-VASc ≥2 with careful consideration to balance the benefits and risks of bleeding in each individual patient [19]. The European AF guidelines prioritized NOACs over warfarin already 2012 and have recently abandoned the recommendation to use the HAS-BLED scale to evaluate bleeding risk in favor of reducing modifiable risk factors and treating also patients with a high bleeding risk with OACs [20]. Both guidelines recommend strongly against prescribing ASA unnecessarily. Thus, the question remains what risks and benefits can be seen with increasing OAC and decreasing ASA treatment in an entire non-selected AF population, which includes treatment of old and fragile patients in primary care.

The present study aims to investigate how antithrombotic treatment strategies and ischemic stroke and bleeding rates have changed following the adoption of recommendations for increased anticoagulant treatment and decreased utilization of ASA in AF. We compared these clinical outcomes in the entire AF populations of the Stockholm County during 2012 and 2017.

METHODS

Data source

We conducted a retrospective cohort study, using the Stockholm Healthcare Analyses Database (Vårdanalysdatabasen, VAL) [7]. VAL contains pseudonymized individual-level data for all inhabitants in the region (2.09 million in 2011 and 2.27 million in 2016), from both primary and secondary care,

giving the unique possibility of complete healthcare data for follow-up of virtually all inhabitants [7]. Demographic information prescription claims, diagnoses, and healthcare consultations are linked using the Personal Identity Number of each inhabitant [24]. Data on secondary care (outpatient visits and hospitalizations) have been registered since 1993, primary care data since 2003, and pharmacy claims data since July 2010. Pharmacy data cover claims anywhere in the country, and consist of amounts dispensed, expenditures and reimbursement, the age and sex of the patient, co-payments, and prescriber category [25].

The study was approved by the Regional Ethical Review Board in Stockholm (EPN 2015/579-31/2). Data available on request from the authors.

Patient selection

We created two cohorts for follow-up of clinical outcomes during 2012 and 2017, respectively. For ICD-10 and ATC codes see Appendix Table 1. All patients, alive and residents of the Stockholm County on 31 December 2011 and 31 December 2016 with a recorded diagnosis code for AF in the previous five years, were identified. Patients were excluded if they had a code for mechanical valves or mitral stenosis [20], or if they moved into the region during the five years before the index date.

Treatment, risk, and outcome definition

Treatments were assessed based on a claim of any OAC in 2011 and 2016, respectively. Sensitivity analyses were conducted by defining treatment based on a claim in the last six months of 2011 and 2016. An additional analysis investigated patients switching and stopping treatment in the year of outcome.

The stroke risk was estimated with the CHA_2DS_2-VASc score [26]. Bleeding risk was assessed using a modified HAS-BLED score, since INR values were not available [27] (hypertension +1, abnormal liver function +1, abnormal renal function +1, previous stroke +1, prior bleeding and/or anemia +1, age >65 +1, alcohol misuse +1, medication use predisposing to bleeding +1). A HAS-BLED score of 3-8 was considered high risk. Comorbidities were based on diagnoses recorded during the five years before the inclusion date.

The primary effectiveness outcome was ischemic stroke in acute somatic inpatient care as a primary or secondary diagnosis [14]. For safety, the primary outcome was a major bleed in acute somatic inpatient or outpatient care, including hemorrhagic stroke, intracranial bleeding, bleeding requiring hospitalization, and gastrointestinal bleeding [14]. Outcomes were assessed with censoring for death and migration. Rates of TIA/ ischemic and unspecified stroke; and total mortality are also reported [14].

In addition, exploratory comparisons of ischemic stroke and severe bleed in 2017 in patients with prevalent NOAC or warfarin treatment are presented. Patients who switched treatment during 2016 were excluded.

Statistical analysis

Basic descriptive statistics were used to describe the cohorts. With a Poisson regression, we calculated incidence rates (IR) and 95% confidence intervals (CIs) to compare outcomes between 2012 and 2017. Predefined stratified analyses were made for age, stroke, and bleeding risk groups.

To examine the influence of changed OAC-treatment strategies on ischemic stroke and major bleeds, we used stepwise adjustment for changes in demographic characteristics, baseline stroke and bleeding risks, and finally for OAC treatment.

RESULTS

Clinical characteristics

A total of 41 008 and 49 510 patients with non-valvular AF were included in the 2012 and 2017 cohorts, respectively (Appendix Figure 1). This corresponds to 2.6% and 2.9% of the total adult populations of the Stockholm County. The demographics, clinical characteristics, CHA_2DS_2-VASc and HAS-BLED scores of the two cohorts were similar (Table 1).

Antithrombotic treatment

In the 2012 cohort, 51.6% of the patients received treatment with any OAC, while there was a substantial increase to 73.8% in the 2017 cohort (see Table 2). A corresponding decrease could be seen in the number of patients with ASA monotherapy, from 32.1% to 10.4%. In the 2017 cohort 39.3%% had claimed only warfarin and 34.4% claimed a NOAC. The proportion of patients receiving no antithrombotic treatment (i.e., neither OAC nor ASA) was similar. In the 2017 cohort, a larger proportion of the patients remained on OAC treatment in the year of outcome, and more patients switched from no OAC treatment to OAC treatment, compared to 2012 (Appendix Table 2).

The proportion of patients treated with an OAC increased in all age groups (Table 2). Notably, the largest increase was among the elderly (≥80 years of age), from 47.0% to 74.1%; as well as among potentially frail patients with simultaneously high CHA_2DS_2-VASc and HAS-BLED scores (Table 2).

Ischemic stroke, major bleeding and total mortality

Ischemic stroke incidence rates (IR) decreased from 2.01 per 100 person years in 2012, to 1.17 in 2017 (IRR 0.58, 95% CI; 0.52 – 0.65) (Table 3). The reduction of ischemic stroke was to a large extent driven by fewer strokes among elderly and high-risk patients (Figures 1A and 1B). The total mortality (death as a non-competing outcome) was significantly lower in the AF population in 2017 (IRR 0.90, 95% CI; 0.86-0.95).

Regarding safety outcomes, there was no significant change in major bleeding, with an IR of 2.59 in both cohorts, resulting in a crude IRR of 1.00, 95% CI; (0.92 – 1.09) (Table 3). The results were similar for all secondary bleeding endpoints, except hospitalized bleeding rates which had decreased in 2017 (Table 3). Stratified analyses showed no differences between age-groups (Figure 1A) or CHA_2DS_2-VASc scores (Figure 1B).

The stroke reduction was most pronounced in patients with the largest relative increase of OAC treatment (i.e., with HAS-BLED 3+ and increasing with the CHA_2DS_2-VASc score) (Figure 2). The rates of major bleeds were high in these high-risk individuals, but did not increase over the years.

Association between treatment and ischemic stroke and major bleeding

The crude IRR for ischemic stroke comparing the two cohorts, was 0.58 (95%-CI: 0.52 – 0.65) (Table 4). Adding the CHA_2DS_2-VASc score into the model resulted in an IRR of 0.63 (95% CI;

Table 1. Patient characteristics in the 2012 and 2017 cohort. SD: standard deviation; TIA: transient ischemic attack

	2012 (n= 41 008)	2017 (n= 49 510)
Male (%)	22 818 (55.6%)	28 424 (57.4%)
Age, mean (SD), y	74.6 (12.5)	75.0 (11.9)
0-39 years	574 (1.4%)	509 (1.0%)
40-64 years	7 115 (17.4%)	7 545 (15.2%)
65-74 years	10 808 (26.4%)	14 344 (29.0%)
75-79 years	6 150 (15.0%)	8 327 (16.8%)
≥80 years	16 361 (39.9%)	18 785 (37.9%)
CHA_2DS_2-VASc score, mean (SD)	3.62 (1.9)	3.66 (1.9)
0	2 368 (5.8%)	2 560 (5.2%)
1	3 875 (9.5%)	4 183 (8.5%)
2-4	21 320 (52.0%)	26 594 (53.7%)
5-9	13 445 (32.8%)	16 173 (32.7%)
HAS-BLED score, mean (SD)	2.37 (1.24)	2.28 (1.22)
0	2 543 (6.2%)	3 289 (6.6%)
1-2	20508 (50.0%)	26 680 (53.9%)
≥3	17957 (43.8%)	19 541 (39.5%)
Heart failure	13 408 (32.7%)	14 979 (30.3%)
Hypertension	25 990 (63.4%)	34 372 (69.4%)
TIA/stroke/systemic embolism	8 007 (19.5%)	10 398 (21%)
Vascular disease	11 545 (28.2%)	11 862 (24.0%)
Diabetes	7 891 (19.2%)	10 034 (20.3%)
Abnormal renal function	2 866 (7.0%)	5 524 (11.2%)
Abnormal liver function	555 (1.4%)	791 (1.6%)
Previous bleeding	2 979 (7.3%)	4 479 (9.1%)
Anaemia	6 497 (15.8%)	9 897 (20.0%)
Alcohol misuse	1 562 (3.8%)	1 865 (3.8%)
Cancer	7 783 (19.0%)	10 630 (21.5%)
Falls	3 662 (8.9%)	6 770 (13.7%)
Chronic obstructive pulmonary disease	3 921 (9.6%)	5 043 (10.2%)
Dementia	2 589 (6.3%)	3 462 (7.0%)
Obesity	2 375 (5.8%)	3 097 (6.3%)
Rate control drugs	29 839 (72.9%)	37 356 (75.5%)
Rhythm control drugs	3 674 (8.9%)	3 094 (6.3%)
Low molecular weight heparins	2 369 (5.8%)	2 505 (5.1%)
Clopidogrel	1 221 (3.0%)	1 319 (2.7%)
Ticagrelor	9 (0.0%)	155 (0.3%)
Prasugrel	18 (0.0%)	11 (0.0%)
Antihypertensive drugs	37 067 (90.4%)	44 891 (90.7%)
Lipid-lowering drugs	15 201 (37.1%)	19 791 (40.0%)
Insulin	2 743 (6.7%)	3 496 (7.1%)
Oral antidiabetic drugs	3 811 (9.3%)	5 079 (10.3%)
Proton pump inhibitors	10 148 (24.8%)	13 258 (26.8)

Table 2. Antithrombotic treatment strategies per cohort. The first 26 rows present the proportion of patients receiving OAC treatment stratified per risk score.

Treatment	2012 (n= 41 008)	2017 (n= 49 510)
OAC	21 152 (51.6%)	36 515 (73.8%)
0-39 years, n (%)	61 (10.6%)	76 (14.9%)
40-64 years, n (%)	2 874 (40.4%)	3 759 (49.8%)
65-74 years, n (%)	6 682 (61.8%)	11 701 (81.6%)
75-79 years, n (%)	4 002 (65.1%)	7 031 (84.4%)
≥80 years, n (%)	7 533 (46.0%)	13 948 (74.3%)
CHA_2DS_2VASc 0, n (%)	559 (23.6%)	544 (21.3%)
HAS-BLED 0	412 (25.9%)	475 (22.0%)
HAS-BLED 1-2	145 (18.9%)	68 (17.7%)
HAS-BLED 3+	2 (20.0%)	1 (8.3%)
CHA_2DS_2VASc 1, n (%)	1 599 (41.3%)	2 303 (55.1%)
HAS-BLED 0	274 (32.8%)	339 (34.0%)
HAS-BLED 1-2	1 296 (45.2%)	1 930 (62.9%)
HAS-BLED 3+	29 (17.0%)	34 (28.3%)
CHA_2DS_2VASc 2-4, n (%)	11 913 (55.9%)	21 131 (79.5%)
HAS-BLED 0	83 (71.6%)	96 (74.4%)
HAS-BLED 1-2	9 376 (67.8%)	16 338 (85.7%)
HAS-BLED 3+	2 454 (33.3%)	4 697 (63.6%)
CHA_2DS_2VASc 5-9, n (%)	7 081 (52.7%)	12 537 (77.5%)
HAS-BLED 0	0	0
HAS-BLED 1-2	2 494 (81.9%)	3 817 (91.9%)
HAS-BLED 3+	4 587 (44.1%)	8 720 (72.6%)
Warfarin	21 050 (51.3%)	21 323 (43.1%)
NOAC	178 (0.4%)	17 040 (34.4%)
Only warfarin	20 974 (51.2%)	19 475 (39.3%)
ASA	16 491 (40.0%)	7 931 (16.0%)
No OAC	12 992 (31.7%)	5 112 (10.3%)
No ASA or OAC	6 864 (16.7%)	7 883 (15.9%)

0.58 – 0.69). Adjusting for OAC treatment resulted in an IRR of 0.73 (95% CI: 0.66 – 0.80), indicating that an absolute 10% reduction of ischemic strokes was associated with the increased OAC treatment.

The crude IRR for major bleeding comparing the two cohorts, was 1.00 (95%-CI: 0.92 – 1.09). Further adjustments did not result in any significant changes regarding major bleeding rates (Table 4).

Comparisons of prevalent treatment with NOAC or warfarin revealed similar rates of ischemic stroke in 2017 after adjustment for the CHA_2DS_2-VASc score: NOAC vs warfarin IRR 0.89 (95% CI: 0.71 – 1.11). The rate of severe bleeding after adjustment for the HAS-BLED score was lower with NOAC: IRR 0.74 (95% CI: 0.65 – 0.85). The results were similar in patients with a high risk for both stroke and bleeding (Appendix Figure 3).

Table 3. All safety and effectiveness outcomes for the whole AF population in 2012 and 2017IR: incidence rate per 100 person years; IRR: incidence rate ratio; TIA: transient ischemic attack.

	2012 (n= 41 008)	2017 (n= 49 510)	IRR (95% CI)
Effectiveness, (IR)			
Ischemic Stroke	2.01	1.18	0.58 (0.52 – 0.65)
TIA/ischemic stroke/unspecified stroke	2.70	1.72	0.64 (0.58 – 0.70)
Safety, (IR)			
Major bleeds	2.59	2.59	1.00 (0.92 – 1.09)
Hospitalized bleeds	1.98	1.74	0.88 (0.79 – 0.97)
Intracranial bleeds	0.78	0.85	1.09 (0.94 – 1.27)
Hemorrhagic stroke	0.31	0.28	0.90 (0.70 – 1.15)
Gastrointestinal bleeds	1.12	1.18	1.05 (0.93 – 1.20)

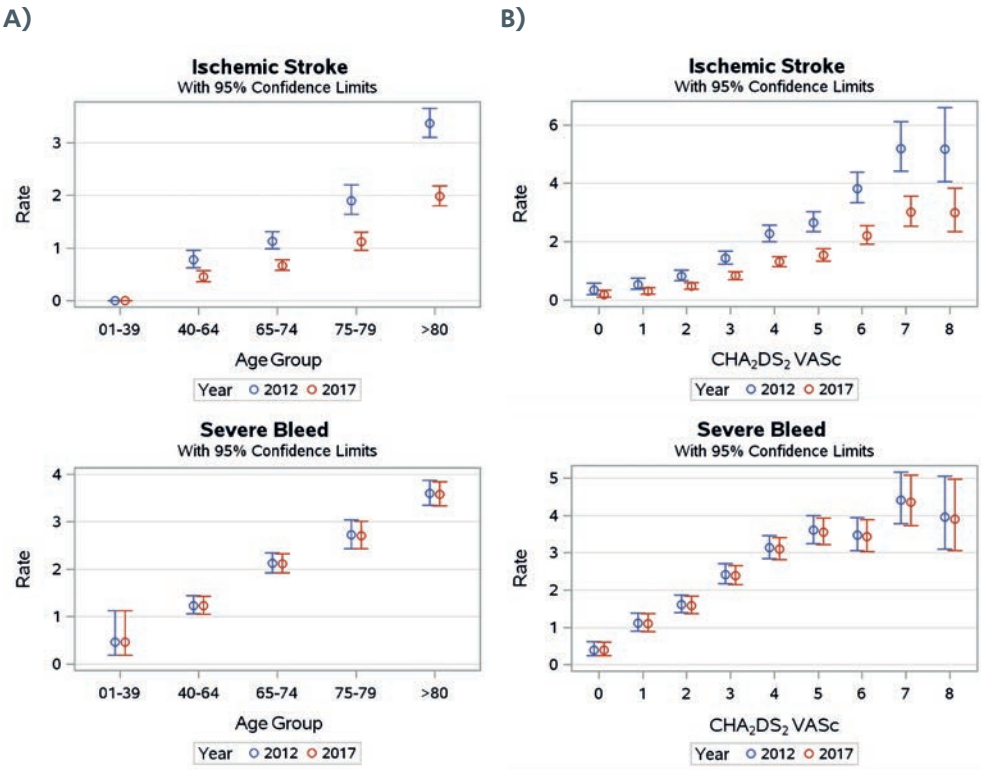

Figure 1. Incidence rates of ischemic stroke and major bleeding in 2012 and 2017, stratified by: 1A) Age group 1B) CHA_2DS_2-VASc score

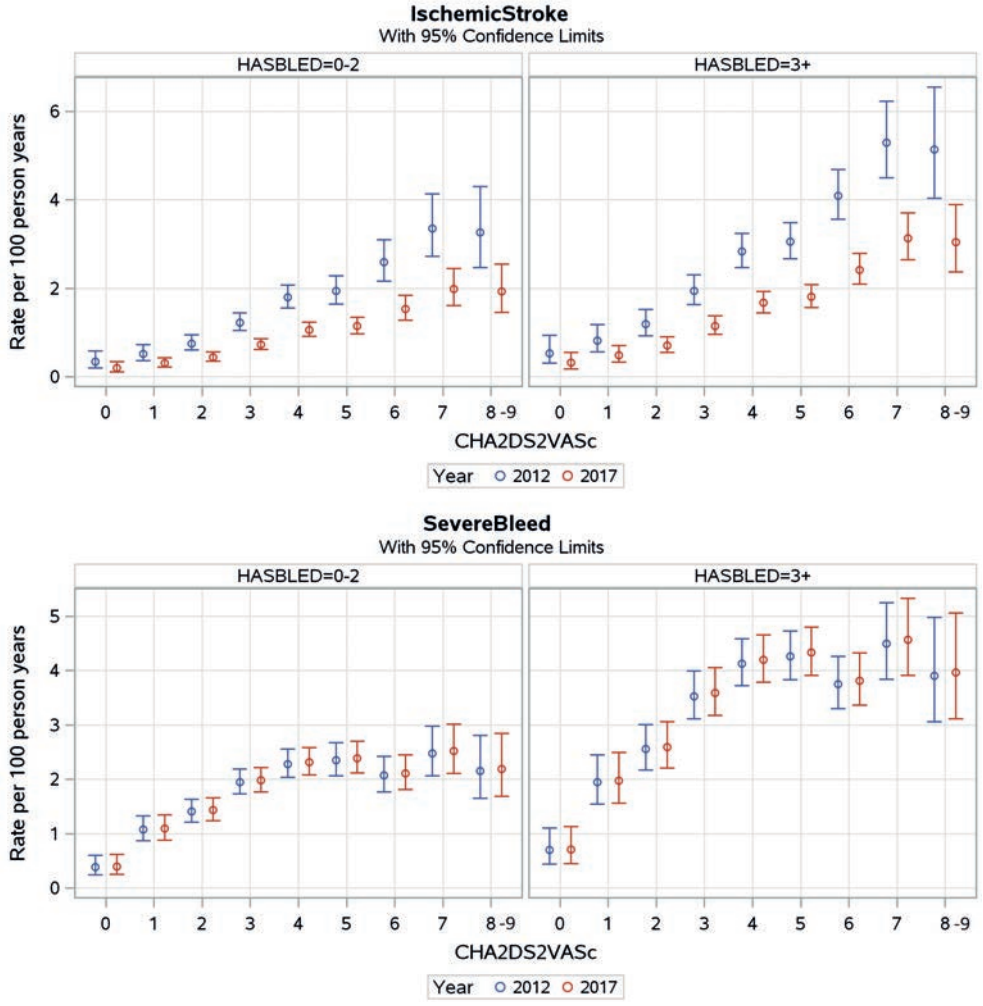

Figure 2. Incidence rates of ischemic stroke and major bleeding in 2012 and 2016, stratified by CHA_2DS_2-VASc and HAS-BLED score

Table 4. Incidence Rates per 100 person years and Incidence Rate Ratios with 95% confidence intervals for ischemic stroke and major bleeding IR: Incidence rate per 100 person years; IRR; incidence rate ratio; CI: 95% confidence interval. OAC: oral anticoagulant.

			Calculated IRR (CI 95%)			
	2012 IR	**2017 IR**	**Crude**	**Adjusted for age-group and sex**	**Adjusted for CHA_2DS_2VASc or HAS-BLED -score**	**Adjusted for CHA_2DS_2VASc or HAS-BLED -score and OAC treatment**
Ischemic stroke	2.01	1.18	0.58 (0.52 – 0.65)	0.64 (0.58 – 0.70)	0.63 (0.58 – 0.69)	0.73 (0.66 – 0.80)
Major bleeding	2.59	2.59	1.00 (0.92 – 1.09)	0.99 (0.91 – 1.08)	1.04 (0.95 – 1.13)	0.99 (0.91 – 1.08)

DISCUSSION

In this population-based comparative cohort study, we compared antithrombotic treatment patterns and clinical outcomes among patients with non-valvular AF in an entire healthcare region with more than 2 million inhabitants. We found a considerable increase in the number of patients with AF. In the 2017 cohort, AF patients received OACs, in particular NOACs, much more frequently while ASA treatment decreased correspondingly compared to the 2012 cohort. NOAC use increased from 1% to 47% of OAC treated patients and ASA monotherapy decreased from 31.7% to 10.3%. This is in line with international as well as Swedish Guidelines [17,18,19]. The largest increases in OAC treatment were seen among potentially frail patients with high stroke risk, and a simultaneously high bleeding risk. The changed treatment pattern was associated with a lower incidence rate for ischemic stroke. Bleeding rates remained unchanged and this was consistent throughout age groups and at different levels of baseline stroke and bleeding risks. All effectiveness outcomes occurred less frequently in 2017, while none of the bleeding outcomes increased.

Poisson-regression models indicated that the increase in the proportion of patients treated with OACs played a significant role in the reduction of stroke incidence. Adjusting for age, sex, and CHA_2DS_2-VASc scores influenced the IRRs little, due to comparable characteristics of the populations in the two cohorts. Adjusting for OAC treatment provided an explanation for 10% of the absolute reduction in ischemic stroke. This is consistent with results from randomized trials [5,6,23], given the observed 22.2% absolute increase in OAC treated patients and a corresponding decrease of ASA treatment.

Comparison of NOAC or warfarin in 2017 indicates advantages with NOAC treatment, consistent with results from clinical trials [11-13]. The risk of ischemic stroke was similar to the comparison in our previous observational study, which only included new initiations in previously OAC naïve AF patients [15]; but bleeding rates were more favorable in the prevalent NOAC users of the present study. These results add to the knowledge that NOACs can be used in a beneficial and safe way in frail and elderly AF patients.

After adjustment for OAC treatment, an absolute decrease in ischemic stroke of approximately 27% remained unexplained. An important factor could be the growing AF population as the increased awareness of AF with earlier detection of patients with a low AF burden might explain part of the observed decrease in the risk for ischemic stroke [28,29]. Other explanations could be better quality of anticoagulation with NOACs, but more switches and/or persistence to OAC treatment might also contribute (Appendix Table 2). In the total population of the Stockholm region there was a 21% reduction of ischemic strokes (mainly non-AF related) between 2012 and 2017, with the largest reductions seen among the elderly (Appendix Figure 2). Potential explanations for this general improvement in stroke incidence could be an overall healthier population, with lower blood pressure levels, healthier lifestyles, and better managed preventive drug treatment in the elderly [30,31].

Both the American and European guidelines for stroke prevention in AF emphasize the value of increased OAC treatment [17,19], and the European guidelines have abandoned the use of bleeding risk scores to withhold OAC treatment [20]. Presently, the treatment goal recommended by the Swedish national board of health and welfare is to treat at least 80% of the AF patients with an OAC when a clear indication (e.g., CHA_2DS_2-VASc ≥2) is present [25]. In the 2017 cohort, this goal was essentially

reached, with 78.9% of patients with CHA_2DS_2-VASc scores 2-9 being treated. Yet, in selected patients OACs may not be indicated despite a high risk of stroke and the optimal proportion of AF patients gaining a net benefit from OAC treatment remains unknown. However, our findings clearly demonstrate the clinical effectiveness and safety of achieving at least 80% on OAC treatment. In fact, the greatest stroke reduction associated with OAC use was seen in those patients with the highest stroke and bleeding risks who in previous years often were left untreated or received less effective treatment with ASA.

Our study has some limitations. First, some diagnoses might be missing in the healthcare records. This might yield slight underestimation of stroke risks evaluated by the CHA_2DS_2-VASc score as well as of both safety and effectiveness outcomes. However, we have data also from primary care which increases the availability of comorbidities used for CHA_2DS_2-VASc scoring [7], and they were similar in the two cohorts. Therefore, we do not believe this has biased the results. Second, we did not include stopping or switching treatment strategy in our main analysis. To address this, we conducted additional analyses, which indicated an increased persistence and a larger portion of untreated patients switching to OAC treatment in later years (Appendix Table 2). Using a 6-month time interval to define OAC exposure yielded almost identical results. Since the main aim of the present study was not to compare the effectiveness of different antithrombotic treatments, we believe the exposure definitions were sufficient.

One major strength of this study lies in the data used. The VAL database contains ICD-10 codes for diagnoses and procedures from both primary and secondary care, as well as other data which provide comprehensive information about the patient. Previous work has investigated the value of primary care records for risk stratification [7], and 14% of the AF patients in the present cohorts could only be identified in primary care records. Secondly, we have contributed to the difficult but clinically important question whether or not to treat frail and elderly patients with OACs. Further research is, however, needed to address the question which OAC treatment is best for the frail and elderly, and to better characterize high-risk populations in whom withholding OAC treatment should be the preferred strategy. The large reduction of ischemic stroke within and outside of the AF population also merits further exploration.

In conclusion, increasing OAC treatment due to the availability of NOACs in a complete, non-selected population of patients with non-valvular AF was associated with a marked reduction of ischemic stroke, while bleeding rates remained similar. The greatest clinical improvements were seen among elderly patients with elevated risks for both stroke and bleeding. These findings strongly support the adoption of current guideline recommendations for stroke prevention in AF in both primary and secondary care.

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APPENDICES

Appendix table 1. ICD-10 codes and ATC-codes used to define comorbidities, outcomes, and treatments in the present study

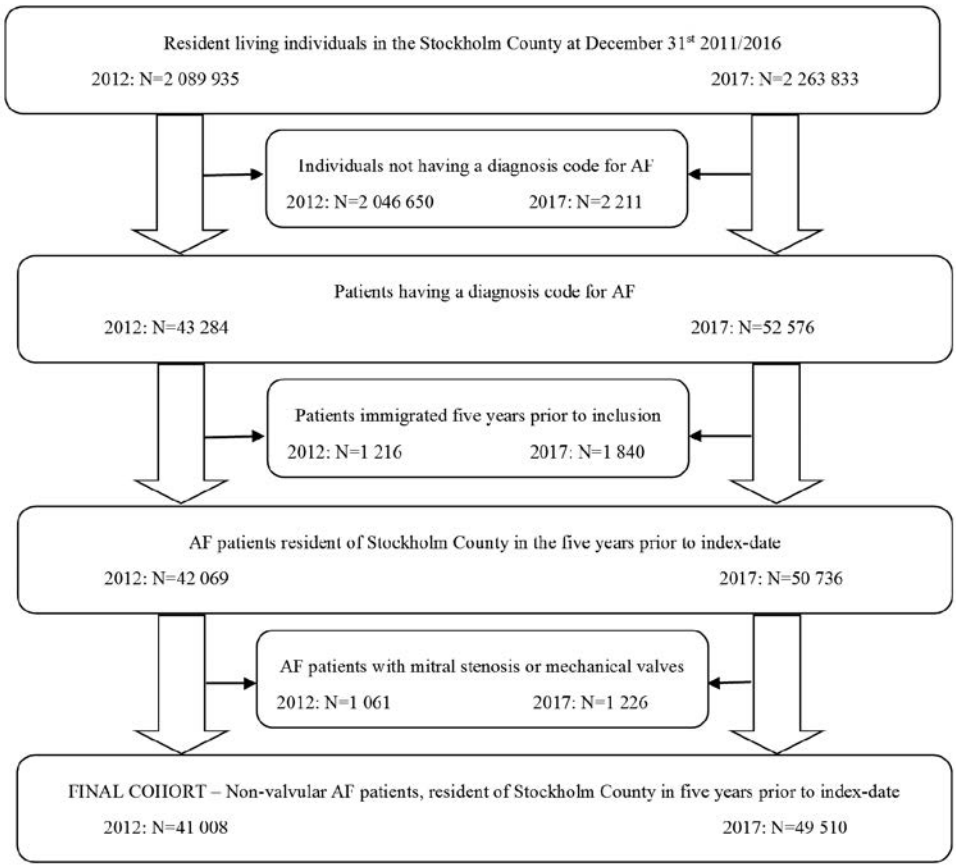
Comorbidities	ICD-code beginning with
Alcohol abuse	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714
Anemia	D50-64
Any severe bleed	I60-62, I690-I692, S064-S066, I850, I983, K25-28 (subcodes 0-2 and 4-6 only), K625, K922, D500, D629, J942, I312, H431, H356
Atrial fibrillation	I48
Cancer	entire C-series
COPD/Emphysema	J43-44
Dementia	F00-F03
Diabetes	E10-E14
Frequent falls (more than one registration)	W00-19
Gastric duadenal bleeding	K25-28 (subcodes 0-2 and 4-6 only)
Heart failure	I50
Hypertension	I10-I15
Ischemic stroke, arterial embolism, and stroke, unspecified	I63, I64, I679, I693, I694, I698, I67-, I69-, Z866A, Z866B, Z867, G450, G451, G452, G453, G458, G45.9, G45-, I74
Intracranial bleeding	I60-I62, I690-I692, S064-S066
Liver disease	K70-77
Mechanical valve	Z952 Procedure codes: FCA60, FDC10, FGE00, FGE96, FJF00, FJF96, FKD00, FKD96, FMD00, FMD96
Mitral stenosis	I050, I052, I342
Obesity	E65-66
Renal disease	N17, N183, N184, N185, N189
Vascular disease	I20-I25, I70, I739
Venous thromboembolism	I26, I80-I82
Outcomes	**ICD-code beginning with**
Any severe bleed	I60-62, S064-S066, I850, I983, K25-28 (subcodes 0-2 and 4-6 only), K625, K922, D500, D629, J942, I312, H431, H356
Gastrointestinal bleed	K25-28 (subcodes 0-2 and 4-6 only), K625, K922
Hemorrhagic stroke	I60-I61
Intracranial bleed	I60-I62, S064-S066
Ischemic stroke	I63
Other intracranial bleed	I62, S064-S066
TIA/ischemic stroke/stroke unspecified	I63, I64, G450, G451, G452, G453, G458, G459
Treatment	**ATC-code beginning with**
Acetylsalicylic acid (aspirin)	B01AC06
Apixaban	B01AF02
Dabigatran	B01AE07
Edoxaban	B01AF03

Appendix table 1. (continued)

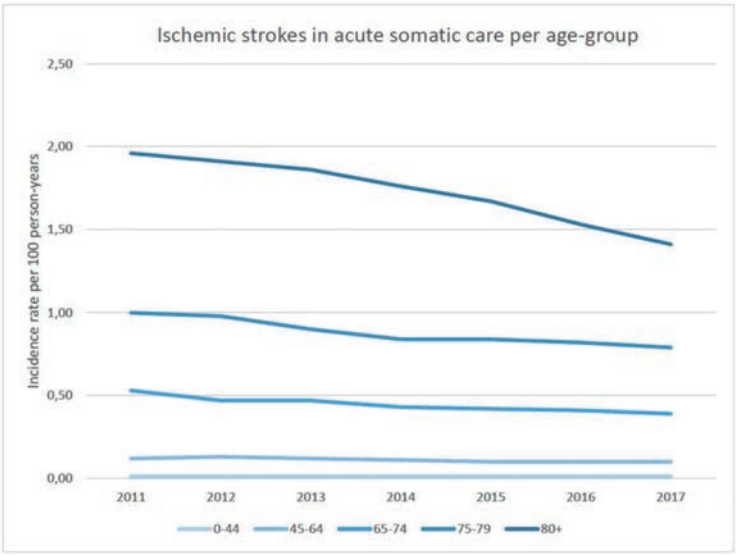
Treatment	ATC-code beginning with
Rivaroxaban	B01AF01, B01AX06
Warfarin	B01AA
Concomitant drug use	**ATC-code beginning with**
Antihypertensive drugs	C03, C07, C08, C09
Clopidogrel	B01AC04
Insulin	A10A
Lipid lowering drugs	C10
Low Molecular Weight Heparin	B01AB04, B01AB05
Oral diabetic drugs	A10B
Prasugrel	B01AC22
Proton pump inhibitors	A02BC
Rate control drugs	C07AB, C08D
Rhythm control drugs	C07AA07, C01B
Ticagrelor	B01AC24

Appendix table 2. Proportion of patients on oral anticoagulant treatment (OAC) in the outcome year

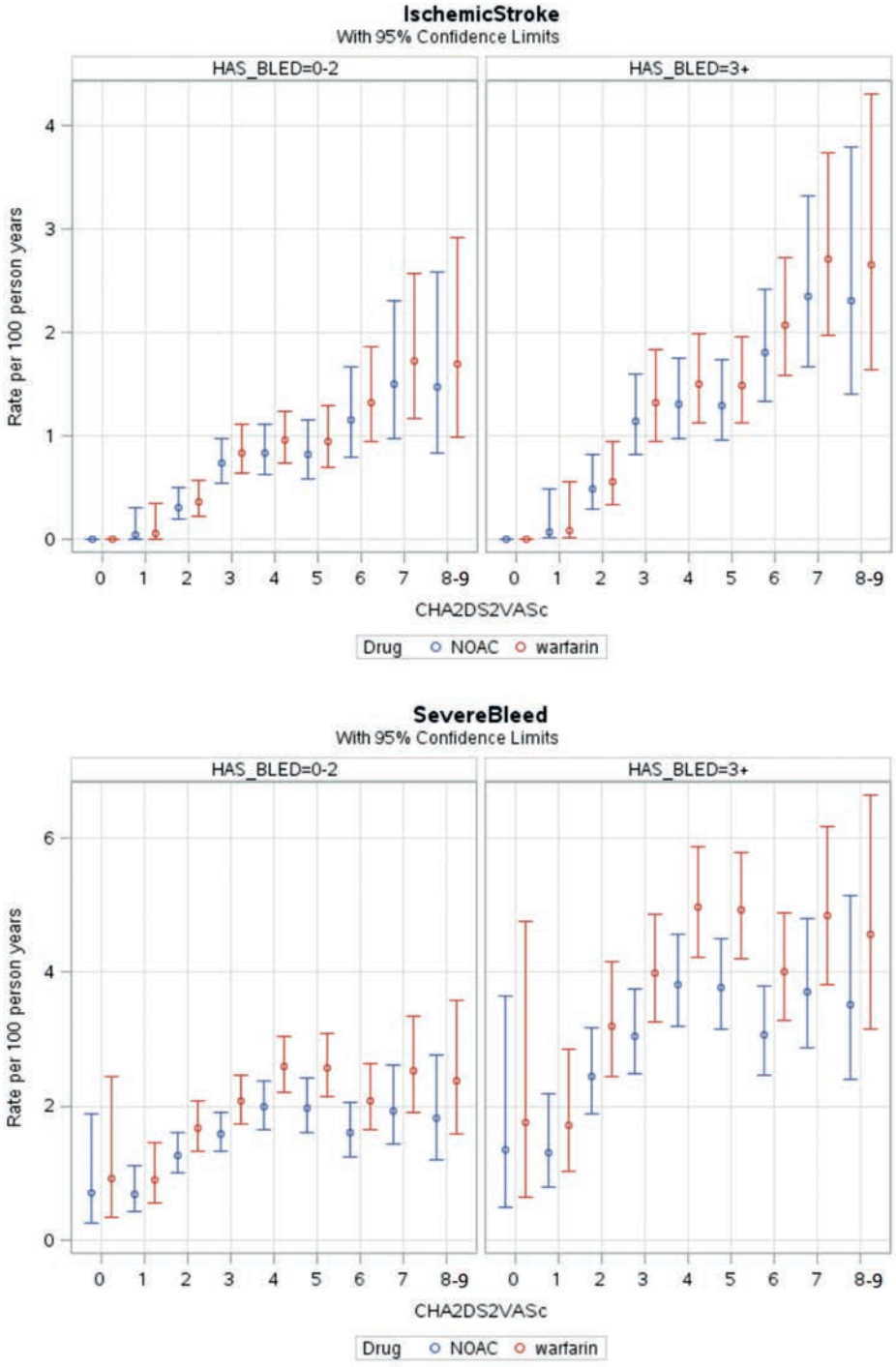
Baseline treatment	2012 N = 41 008	Claim of OAC during 2012	2017 N = 49 510	Claim of OAC during 2017
OAC	21 152	19 388 (91.7%)	36 515	34 581 (94.7%)
No OAC	19 856	1 924 (9.7%)	12 995	1 805 (13.9%)



Appendix figure 1. Flow-chart of patient selection



Appendix figure 2. Overall ischemic stroke rates in the Stockholm region in inpatient acute somatic care per age group



Appendix figure 3. Exploratory comparison of ischemic stroke and severe bleed in 2017 in atrial fibrillation patients with NOAC (n=15 192) or warfarin (n=19 475), stratified by CHA2DS2-VASc and HAS-BLED scores. Patients having switched between NOAC and warfarin in 2016 have been excluded

2.4

STROKE PREVENTION THERAPY AND OUTCOMES IN ATRIAL FIBRILLATION BEFORE AND AFTER THE INTRODUCTION OF NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS IN FOUR WESTERN EUROPEAN COUNTRIES

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Manuscript ready for submission

ABSTRACT

Background

It is unknown how the effectiveness and safety of stroke prevention in atrial fibrillation (AF) has changed since the introduction of non-vitamin K antagonist oral anticoagulants (NOACs) regarding changes in the incidence of stroke and bleeding.

Methods

Using data from Stockholm, Denmark, Scotland, and Norway, we created two calendar-time based cohorts, 2012 and 2017. Patients were included in each cohort if they had a diagnosis for AF in the five years preceding the 1-year cohort window. We assessed treatment with NOACs, vitamin K antagonists (VKAs), and aspirin in the six months prior to the start of each year and assessed strokes and bleeds during the year. We used Poisson regression to contrast outcomes in 2012 and 2017 and to adjust for changes in baseline characteristics other than OAC treatment.

Results

We included 280 359 patients in the 2012 cohort and 356 779 patients in the 2017 cohort. Treatment with oral anticoagulants increased in each country from approximately 45% to 65%, while treatment with aspirin decreased from approximately 30% to 10%. In all countries except Scotland, there was a decreased stroke rate in 2017, while the bleeding rates were unchanged, after adjustment for changes in baseline characteristics. The absolute stroke reduction was largest in the elderly and high-risk patients.

Conclusion

After the introduction of NOACs on the market, more AF patients were receiving treatment with an oral anticoagulant, and this was accompanied by a reduction in stroke rate without increasing the bleeding rate.

BACKGROUND

Since 2011, four non-vitamin K oral anticoagulants (NOACs) have been introduced on the market for stroke prevention in patients with atrial fibrillation (AF). Randomized clinical trials have proven the efficacy and safety of the drugs compared to vitamin K antagonists (VKAs) [1–5]. After the introduction, NOACs have gained in popularity and are now widely used in clinical practice, driven by guidelines recommending these drugs over VKAs [6, 7]. In addition, these guidelines no longer recommend aspirin monotherapy for stroke prevention. After the uptake of NOACs in clinical practice, many observational studies have confirmed the safety and effectiveness in daily clinical practice [8].

Data from the worldwide prospective GLORIA-AF registry have shown that the proportion of AF patients treated with an oral anticoagulant (OAC) in selected centres increased from 33% prior to the NOAC introduction to 80% after the introduction [9, 10]. During the same period, the proportion of AF patients treated with low dose aspirin decreased from 42% to 11%. In the Stockholm healthcare region, it was recently shown that a similar improvement in antithrombotic therapy for stroke prevention was accompanied by a reduction in stroke from 2.01%/year to 1.18%/year, while bleeding rates remained unchanged at 2.59%/year [11].

Large-scale international studies assessing whether the introduction of this new treatment option for stroke prevention in AF has been associated with changes in OAC utilization, stroke rate, and bleeding rate in an unselected AF population are lacking. Therefore, the aim of the current study was to assess and compare how OAC utilization, stroke rates, and bleeding rates have changed among AF patients after the introduction of NOACs in four Western European healthcare settings: Stockholm (Sweden), Denmark, Scotland, and Norway.

METHODS

Databases

We used data from four Western European healthcare settings: Stockholm, Denmark, Scotland, and Norway. All databases are described in detail elsewhere and an overview is provided in Appendix Table 1 [12–17] In short, each database contains prescription claims data from community pharmacies and diagnoses from secondary care. Diagnostic data from primary care is available for the Stockholm healthcare region only. We extracted and analyzed data locally using a common protocol and common data model and the same analytical coding script in all centers, which ensured identical data analysis across centres. In this approach, all data can remain local and only the final analytical results are transferred. Although similar analyses have been published based on data from the Stockholm region [11], due to changes in the methodology these data have been re-analyzed and included in the present study to allow for cross-country comparisons.

Patient selection

We created two cohorts of AF patients, the 2012 and the 2017 cohort (see Appendix Figure 1 for a graphical study presentation) and sought to exclude as few patients as possible. For the 2012 cohort, we included all patients with a recorded AF diagnosis from January 2007 (January 2008 for

Norway due to data availability) until December 2011. Patients were excluded if they migrated in or out of the region or were in- or excluded from the data source in that period, and patients had to be alive on 1 January 2012. Patients were also excluded if they had mechanical valves or mitral stenosis in the five-year period prior to inclusion. We defined antithrombotic treatment on 1 January 2012 by looking for a prescription claim of a VKA, a NOAC, or aspirin from July to December 2011. Patients without any of those treatments were defined as untreated. For the 2017 cohort, we applied the same criteria, but looked for an AF diagnosis from January 2012 until December 2016, patients had to be alive on 1 January 2017, and we defined treatment by prescriptions claims in July – December 2016.

Patients were mutually exclusively assigned to one of the four treatment groups: NOAC, VKA, aspirin, or no treatment. If a patient filled both an aspirin and a VKA or a NOAC prescription, the patient was assigned to the VKA or NOAC group. If a patient claimed both a VKA and a NOAC prescription, the patient was assigned to the drug they filled last in the treatment-assessment period.

Baseline characteristics

For baseline comorbidities, we assessed both the CHA_2Ds_2-VASc and a modified HAS-BLED score; a stroke risk and bleeding risk predictor score, respectively [18, 19]. We looked for components of both scores in the 5 years prior to 2012 and 2017 (see Appendix Table 2 for ICD-10 codes). Besides age and sex, the components of the CHA_2DS_2-VASc score are heart failure, hypertension, stroke/transient ischemic attack (TIA)/systemic embolism, vascular disease, and diabetes. The components of the modified HAS-BLED score are hypertension, renal disease, liver disease, stroke, prior bleeding, and medication usage predisposing to bleeding (i.e., non-steroidal anti-inflammatory drugs (NSAIDs), P2Y12-inhibitors, or oral corticosteroids).

For baseline medication, we assessed prescription claims in the six months prior to 2012 and 2017 (see Appendix Table 2 for ATC codes). Comedication included NSAIDs, P2Y12-inhibitors, oral corticosteroids, diuretics, beta-blockers, calcium-channel blockers, RAAS-inhibitors, statins, oral antidiabetic drugs, insulin, proton pump inhibitors, and antidepressants.

Outcome definition

For the 2012 cohort, we looked for the occurrence of the outcome of interest in 2012, and for the 2017 cohort in 2017. We looked for both ischemic and haemorrhagic events (see Appendix Table 2 for ICD-10 codes). The primary ischemic event was the occurrence of an ischemic stroke. The secondary ischemic event was a composite of ischemic stroke, unspecified stroke, and TIA. The primary haemorrhagic event was a composite of any severe bleed. Secondary haemorrhagic events were the occurrence of a gastrointestinal bleed (GIB) or an intracranial haemorrhage (ICH). We looked for a registration of the events in secondary inpatient care, to only include severe events. Patients were censored at the first occurrence of an outcome of interest, emigration, death, or the end of the study period.

Statistical analysis

We used descriptive statistics to describe baseline characteristics in both cohorts for each country and to present incidence rates (IR) of outcomes per 100 person years (%/year) in both cohorts.

We used Poisson regression to calculate incidence rate ratios (IRR), contrasting outcomes in 2012 to 2017. We stratified our analysis on predefined subgroups according to age groups, CHA_2DS_2-VASc score and HAS-BLED score. We used different Poisson regression models. We started with a crude model, including only outcome and year of inclusion. We then added age and sex to this model, followed by either the CHA_2DS_2-VASc score for ischemic events, or the HAS-BLED score for haemorrhagic events, to account for potential changes in stroke or bleeding risk that may have acted as the driver for a change in event rates.

Supplementary analysis

Since we only had access to data starting in 2008 in the Norwegian database, we performed a sensitivity analyses to see how this affected our results. For all other countries, we performed an analysis where we only included patients from 2008 to 2011 for the 2012 cohort, to mimic the patient selection in Norway, and assessed how this affected the patient selection and outcome rates.

To assess how treatment and event rates changed over time, we performed an additional analysis where we looked at the treatment and event rate per year, starting in 2004 and ending in 2017. For each year, we created a cohort of patients diagnosed with AF in maximum five years prior to that year, even though data was not available that far back for all countries. For each year-cohort, we assessed treatment and outcomes in the same manner as the main analysis, looking for treatment in the last year of the AF diagnosis window and for outcomes in the year after the AF diagnosis window. We created graphs to assess the trends in treatment over time with the proportion of patients treated with an OAC, aspirin monotherapy, and the proportion of patients untreated (no aspirin or OAC). In addition, we created similar graphs to assess the trends in outcomes over time with the proportion of patients suffering from a stroke and the proportion of patients suffering from a bleed.

RESULTS

In total, we included 637 138 patients with AF, 280 359 in the 2012 cohort and 356 779 in the 2017 cohort representing an increase of 27%. Most patients were from Norway (N=205 169), followed by Denmark (N=201 525), Scotland (N=139 613), and least from Stockholm (N=90 831). In all countries, more patients were included in the 2017 cohort. Baseline characteristics in terms of age, sex, stroke risk, and bleeding risk were similar, both amongst the different countries as well as when comparing the full 2012 with the 2017 cohort (Table 1, Appendix Table 3).

In all countries, the proportion of AF patients on OAC treatment increased substantially from 2012 to 2017, mainly driven by more patients being treated with a NOAC (Table 2). In Stockholm, OAC use increased from 47.9% in 2012 to 68.9% in 2017, in Denmark from 50.2% to 73.2%, in Scotland from 42.0% to 59.4%, and in Norway from 50.4% to 64.4%. The proportion of patients receiving aspirin alone decreased from approximately 30% to approximately 10% in all countries. The proportion of patients that was untreated remained almost unchanged at approximately 22% in all countries. Stratifying treatment by age groups showed that in the elderly (age of 85 or higher), treatment changed the most from 2012 to 2017 in all countries; more patients were receiving an

Table 1. Summary of baseline characteristics per database and per year. The full baseline characteristics are in appendix table 3.

	Stockholm		Denmark		Scotland		Norway	
	2012	**2017**	**2012**	**2017**	**2012**	**2017**	**2012**	**2017**
n patients	40898	49933	87179	114346	63597	76016	88685	116484
Age (mean)	74.54 (12.68)	75.18 (12.04)	72.95 (12.83)	73.93 (12.20)	74.50 (12.24)	75.35 (11.95)	74.35 (13.30)	73.97 (13.36)
Sex (% female)	17888 (43.7%)	21003 (42.1%)	37898 (43.5%)	48547 (42.5%)	29377 (46.2%)	34619 (45.5%)	37263 (42.0%)	47818 (41.1%)
CHA_2DS_2-VASc (mean)	3.64 (2.01)	3.62 (1.92)	3.13 (1.84)	3.11 (1.77)	3.38 (1.82)	3.36 (1.76)	3.31 (1.88)	3.21 (1.84)
HAS-BLED (mean)	2.21 (1.30)	2.31 (1.30)	1.93 (1.26)	1.93 (1.23)	2.13 (1.27)	2.23 (1.30)	1.95 (1.25)	2.01 (1.31)

Table 2. Treatment of AF patients per database and per year. OAC: oral anticoagulant; VKA: vitamin K antagonist; NOAC: non-vitamin K antagonist oral anticoagulant

	Stockholm		Denmark		Scotland		Norway	
	2012	**2017**	**2012**	**2017**	**2012**	**2017**	**2012**	**2017**
OAC	19590 (47.9%)	34385 (68.9%)	43726 (50.2%)	83665 (73.2%)	26702 (42%)	45163 (59.4%)	44717 (50.4%)	75061 (64.4%)
VKA	19430 (47.5%)	18449 (36.9%)	40633 (46.6%)	37100 (32.4%)	26657 (41.9%)	25444 (33.5%)	43953 (49.6%)	26728 (22.9%)
NOAC	160 (0.4%)	15936 (31.9%)	3093 (3.5%)	46565 (40.7%)	45 (0.1%)	19719 (25.9%)	764 (0.9%)	48333 (41.5%)
Aspirin	11582 (28.3%)	3980 (8%)	22869 (26.2%)	7645 (6.7%)	23933 (37.6%)	12068 (15.9%)	22565 (25.4%)	14289 (12.3%)
None	9726 (23.8%)	11568 (23.2%)	20584 (23.6%)	23036 (20.1%)	12962 (20.4%)	18785 (24.7%)	21403 (24.1%)	27134 (23.3%)

OAC and the proportion of elderly on aspirin monotherapy more than halved in all countries (see Appendix Table 4).

In Stockholm, Denmark, and Norway, the crude ischemic stroke rate decreased from 2012 to 2017 (Table 3). The largest relative decrease was found in Stockholm and Norway, in which the crude rates were approximately 40% lower in 2017. In Scotland, the stroke rate remained unchanged. However, both in Scotland and in Denmark, the stroke rate was already the lowest of the four countries in 2012, at 1.21 events/100 person years (%/py). In all countries, the crude bleeding rate was approximately the same in 2017 as in 2012, including the rates of GIB and the rates of ICH.

The results from the Poisson regression show that the crude stroke rates were statistically significantly lower in 2017 than in 2012 in all countries but Scotland (Table 4). They remained statistically significantly lower after adjusting for age and sex and after adjusting for the CHA_2DS_2-VASc score. The fully adjusted IRRs were lowest in Stockholm and Norway, both at 0.63. The bleeding rates were not statistically different in 2012 and 2017 in any country but Scotland. In Scotland, the bleeding rates were statistically increased in 2017 compared to 2012, mainly driven by a higher ICH rate in 2017 (IRR: 1.31; CI: 1.13 – 1.52).

When stratifying the stroke rates by CHA_2DS_2-VASC score, there was a higher stroke rate in patients with higher scores in each country (Figure 1). In Stockholm and Norway, the stroke rate reduced even more in 2017 compared to 2012 at higher CHA_2DS_2-VASc scores, while this was not visible in Denmark and Scotland. When stratifying the bleeding rates by HAS-BLED score, we observed a higher bleeding risk at higher HAS-BLED scores, however, the bleeding rate was similar in 2012 and 2017 at all HAS-BLED scores in all countries (Figure 2). Stratifying by age-group showed similar results as stratifying by stroke risk score, both for stroke and bleeds (Appendix Figure 3).

Supplementary analyses

When removing the data from 2007 to mimic the Norwegian setting, we included slightly less patients in Denmark, Stockholm, and Scotland. However, the patient characteristics were no different, just as the stroke and bleeding rates were unchanged (see Appendix Table 5).

Looking at the trends over time, the proportion of patients receiving an OAC increased starting in 2012 and continuing until 2017 (see Appendix Figure 4). Before 2012, there was no clear increase or decrease in the trend. Looking at the trend of patients receiving aspirin monotherapy, this was stable before 2012 and started decreasing from 2012 onwards, while the untreated group remained at approximately 20% and did not change over time (see Appendix Figure 5 and 6). The stroke rate was already declining before 2012 and continued to decline throughout the study period, while the bleeding rate remained stable over time (see Appendix Figure 7 and 8).

DISCUSSION

In 637 138 patients from Stockholm, Denmark, Norway, and Scotland, we found that the number of AF patients as well as the proportion treated with oral anticoagulants has increased from 2012 to 2017 in all countries, while the proportion treated with aspirin in monotherapy reduced. In all countries but Scotland, there was a significantly lower ischemic stroke rate in 2017 compared to

Table 3. Number of events and incidence rate per 100 person-years for each outcome per database and year. The Stroke/TIA outcome consists of ischemic stroke, unspecified stroke, and TIA. TIA: transient ischemic attack; GIB: gastrointestinal bleed; ICH: intracranial haemorrhage

	Stockholm		Denmark		Scotland		Norway	
	2012	**2017**	**2012**	**2017**	**2012**	**2017**	**2012**	**2017**
Ischemic stroke	812	619	987	1099	712	829	1476	1195
	(2.11)	(1.32)	(1.21)	(1.02)	(1.21)	(1.19)	(1.79)	(1.09)
Stroke/TIA	1106	876	1930	2061	1480	1595	2194	1863
	(2.88)	(1.86)	(2.36)	(1.92)	(2.52)	(2.29)	(2.66)	(1.7)
Major bleed	829	1025	1758	2197	1060	1424	2230	2973
	(2.16)	(2.18)	(2.15)	(2.05)	(1.81)	(2.04)	(2.7)	(2.72)
GIB	407	466	1066	1272	725	852	907	1166
	(1.06)	(0.99)	(1.3)	(1.19)	(1.23)	(1.22)	(1.1)	(1.07)
ICH	277	366	435	647	277	446	499	625
	(0.72)	(0.78)	(0.53)	(0.6)	(0.47)	(0.64)	(0.61)	(0.57)

Table 4. Incidence rate ratios per outcome and database, contrasting 2017 to 2012. Incidence rate ratios were crude, adjusted for age and sex, and adjusted for risk score. The ischemic outcomes were adjusted for the CHA_2DS_2-VASc score and the bleeding outcomes for the HAS-BLED score. TIA: transient ischemic attack; GIB: gastrointestinal bleed; ICH: intracranial haemorrhage; IRR: incidence rate ratio

		Crude IRR	**Age sex IRR**	**Score IRR**
Stockholm	Ischemic stroke	0.62 (0.56 - 0.69)	0.61 (0.55 - 0.68)	0.63 (0.57 - 0.70)
	Stroke/TIA	0.65 (0.59 - 0.71)	0.64 (0.58 - 0.69)	0.66 (0.60 - 0.72)
	Major bleed	1.01 (0.92 - 1.11)	0.99 (0.90 - 1.08)	0.96 (0.88 - 1.06)
	GIB	0.94 (0.82 - 1.07)	0.91 (0.80 - 1.04)	0.89 (0.78 - 1.01)
	ICH	1.08 (0.92 - 1.26)	1.05 (0.90 - 1.23)	1.04 (0.89 - 1.22)
Denmark	Ischemic stroke	0.85 (0.78 - 0.92)	0.82 (0.75 - 0.89)	0.86 (0.79 - 0.93)
	Stroke/TIA	0.81 (0.76 - 0.87)	0.79 (0.74 - 0.84)	0.82 (0.77 - 0.88)
	Major bleed	0.95 (0.89 - 1.01)	0.92 (0.86 - 0.98)	0.95 (0.90 - 1.02)
	GIB	0.91 (0.84 - 0.99)	0.88 (0.81 - 0.95)	0.91 (0.84 - 0.99)
	ICH	1.13 (1.00 - 1.28)	1.09 (0.96 - 1.23)	1.13 (1.00 - 1.28)
Scotland	Ischemic stroke	0.98 (0.89 - 1.08)	0.95 (0.86 - 1.05)	0.99 (0.90 - 1.09)
	Stroke/TIA	0.91 (0.85 - 0.97)	0.88 (0.82 - 0.94)	0.92 (0.86 - 0.99)
	Major bleed	1.13 (1.04 - 1.23)	1.1 (1.02 - 1.19)	1.09 (1.00 - 1.18)
	GIB	0.99 (0.90 - 1.09)	0.97 (0.88 - 1.07)	0.95 (0.86 - 1.05)
	ICH	1.36 (1.17 - 1.58)	1.31 (1.13 - 1.52)	1.31 (1.13 - 1.52)
Norway	Ischemic stroke	0.61 (0.57 - 0.66)	0.62 (0.57 - 0.67)	0.63 (0.59 - 0.68)
	Stroke/TIA	0.64 (0.60 - 0.68)	0.65 (0.61 - 0.69)	0.66 (0.62 - 0.71)
	Major bleed	1.01 (0.95 - 1.06)	1.02 (0.97 - 1.08)	0.97 (0.92 - 1.02)
	GIB	0.97 (0.89 - 1.06)	0.98 (0.90 - 1.07)	0.92 (0.85 - 1.01)
	ICH	0.94 (0.84 - 1.06)	0.95 (0.85 - 1.07)	0.92 (0.82 - 1.04)

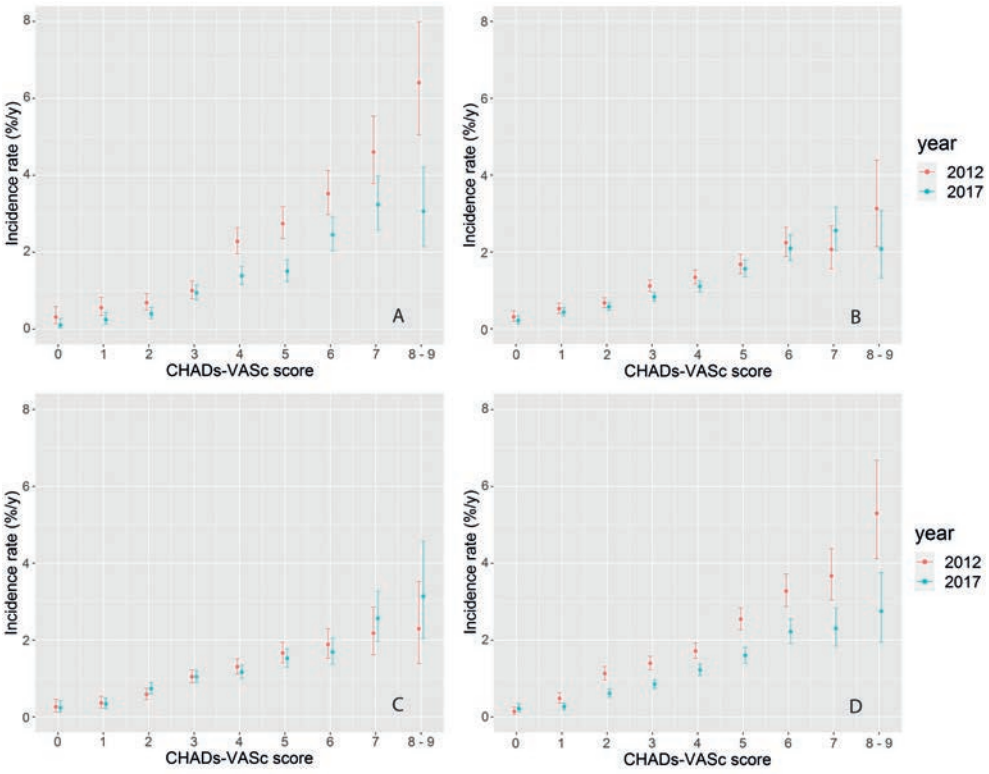

Figure 1. Stroke rates per CHA_2DS_2-VASc score for each country. A (top left panel): Stockholm; B: Denmark; C: Scotland; D: Norway

2012, after adjustment for the CHA_2DS_2-VASC score. In addition, the bleeding rate was unchanged in all countries, but Scotland, in which the bleeding rate increased with approximately 9%, mainly driven by an increased risk for ICH which was 31% higher. In general, the highest absolute stroke risk reduction was observed in high-risk patients, which were also the patients in which the proportion of patients treated with an oral anticoagulant increased the most during the study period.

With the current study design, we were unable to make any causal interpretation on why stroke and bleeding rates were different in some countries. However, there were two patterns in the results that may have contributed to the fact that there was no stroke rate reduction and an increased bleeding rate in Scotland. First, the stroke rate was already the lowest in Scotland in 2012, at 1.21 %/py, meaning there was less potential for reduction, although this rate was similar in Denmark in which the rate did decrease even further in 2017. Second, the proportion of patients receiving an OAC was lowest in Scotland in 2017, at 59.4%, which also may have contributed to a lesser reduction of the stroke rate. In addition, in the other countries there was a shift of VKA and aspirin treatment towards NOAC treatment, and this shift was less pronounced in Scotland. As NOAC treatment has a lower risk for ICH compared to VKA treatment [5], this could be part of the higher ICH rate in 2017 in Scotland.

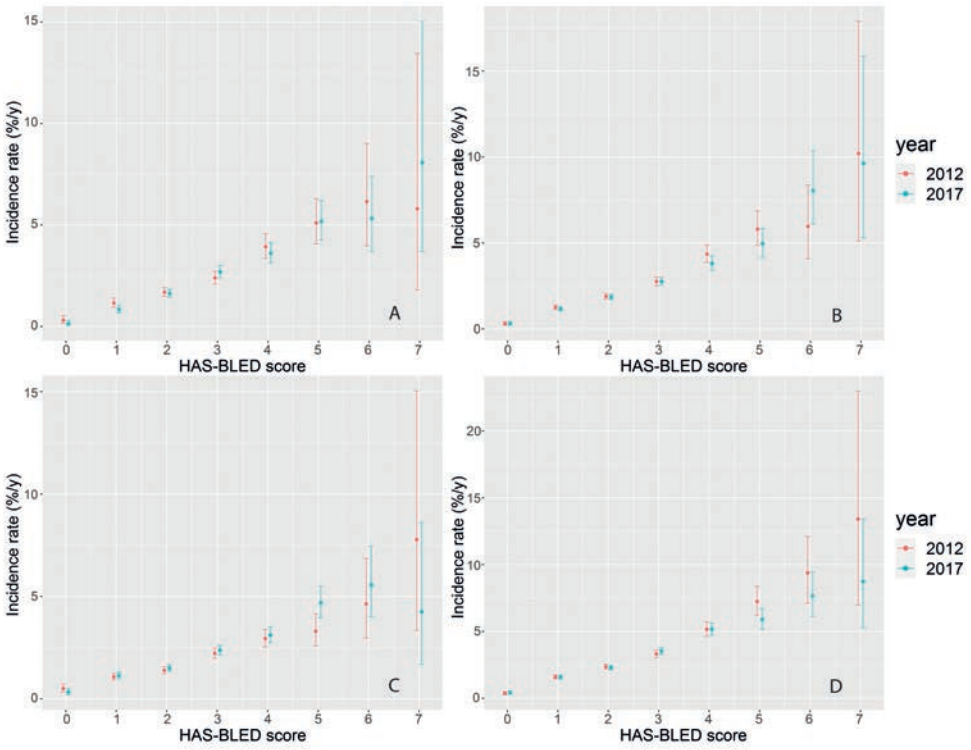

Figure 2. Bleeding rate per HAS-BLED score for each country. A (top left panel): Stockholm; B: Denmark; C: Scotland; D: Norway

The uptake of NOACs in clinical practice represents a great improvement in stroke prevention in AF occurring between 2012 and 2017. Through the availability of another, more convenient, treatment option, more patients were treated with an oral anticoagulant in 2017. We were not able to exactly pinpoint how much this has contributed to the reduced stroke rate, but adjusting for age, sex, or the CHA_2DS_2-VASc score did not indicate that the improvements were due to a change of those characteristics. There are, however, some other factors that also may have contributed to the reduced stroke rates, especially since the stroke rates were already declining in most countries before 2012. One explanation might be an overall healthier AF population in 2017, for example with lower blood-pressure levels and healthier lifestyles [20]. In addition, the AF patient population increased with 27% and it could be that these were healthier patients now diagnosed with AF, for example through additional screening [21]. Another factor may have been the introduction of the CHA_2DS_2-VASc score in 2010 [18], after which identification of AF patients with an indication for oral anticoagulant treatment has become more clear, and abandoning aspirin as a stroke-prevention therapy in the guidelines from 2012 onwards [22]. In addition, both adherence and persistence to anticoagulation therapy have increased in later years, which likely also improves the safety and effectiveness of the treatment [23, 24].

There are some limitations to our study. First, although the databases were similar in content, there will always be differences in databases and healthcare systems in countries that make cross-country comparisons complicated. However, since the analyses were comparing two periods in the same database, the results for each country will not be impacted by inter-country variability. Second, we were only able to show patterns of drug utilization and outcome rates, but we could not draw any causal conclusion what factors were driving the observed changes. Third, we required each patient to have claimed a treatment only at least once in six months to be on that treatment. This is a very simplified presentation of the actual treatment of a patient over time, for example through stopping, switching, or combining therapies. However, since we are not comparing outcomes occurring with different treatment strategies, we believe this is of less importance and our approach is sufficient to present changes in treatment practices over time. Fourth, some patients were already using a NOAC in 2012, however, this was only a very small number of patients.

There are strengths to our study as well. First, we used data from four large well-validated databases [12–17] and included all patients diagnosed with AF in our cohorts with only very limited exclusion criteria. Through this, we were able to present the full picture of how stroke prevention has changed on a population level during the introduction of NOACs on the market. Second, this study provides a framework how to holistically assess the effect of an introduction of a new drug to the market, both on how this affects prevalence of the disease, treatment and how this affects clinical outcomes.

In conclusion, from 2012 to 2017, stroke prevention treatment in patients with AF improved. More patients were receiving oral anticoagulants, especially more NOACs, and less patients were receiving aspirin. This was accompanied by a reduction in stroke rates without a corresponding increase in bleeding rates, which were unchanged.

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Appendix table 1. Description of databases.

	Origin	Data available from	Sample / full population	Sample size
Stockholm Healthcare Database	Stockholm County	July 2010	Full population	2.3 million
Danish National Registries	Denmark	1995	Full population	5.6 million
Norwegian National Registries	Norway	2004	Full population	5.3 million
Scotland	NHS Scotland	January 2009 (until 12.2017)	Full population	5.3 million

	Pharmacy data coding	Dispensing / Prescribed	Diagnostic data	Primary and/or secondary care
Stockholm Healthcare Database	ATC code	Dispensed medication	ICD	Primary and secondary (inpatient and outpatient)
Danish National Registries	ATC code	Dispensed medication	ICD	Secondary (inpatient and outpatient)
Norway	ATC code	Dispensed medication	ICD10	Secondary (inpatient and outpatient)
Scotland	BNF code (manually added ATC code)	Dispensed medication	ICD10	Secondary care (inpatient and outpatient)

	Typical prescription length	Medication Reimbursement
Stockholm Healthcare Database	90 days	Fully reimbursed, after yearly co-payment
Danish National Registries	90-120 days	Increasing reimbursement with additional purchases. Maximum yearly self-payment of ~500€.
Norway	90 days	Initially ~62% reimbursement then fully reimbursed when yearly patient co-payment limit reached (~210 Euro in 2018 for all expenses on drugs, physician visits)
Scotland	30-90 days (depending on whether the GP wants to check in with the patient more frequently for any reason)	There is no co-payment, all services – including prescription drugs – are free of charge (patients have to pay for OTC drugs if they don't have a prescription though).

Appendix table 2. ICD-10 and ATC-codes

Outcome	ICD-10 code beginning with
Ischemic stroke	I63
Stroke/TIA	I63, I64, G450, G451, G452, G453, G458, G459
Major bleed	K25 – K28 (subcode 0, 2, 4, 6 only), K625, K922, I60, I61, I62, S064, S065, S066, D500, D62, J942, I312, H431, H356
Gastrointestinal bleed	K25 – K28 (subcode 0, 2, 4, 6 only), K625, K922
Intracranial bleed	I60, I61, I62, S064, S065, S066
Comorbidity	ICD-10 code beginning with
Anemia	D50, D51, D52, D53, D54, D55, D56, D57, D58, D59, D60, D61, D62, D63, D64
Prior Bleed	I60, I61, I62, S064, S065, S066, I850, I983, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K922, D62, S063C, K920, I312, J942, K661, N02, R04, R31, R58
Diabetes	E10, E11, E12, E13, E14, G590, G632, H280, H360, N083, O240, O241, O242, O243; ATC codes: A10A, A10B
Heart Failure	I43, I50, I110, I130, I132, I255, I420, I425, I426, I427, I428, I429
Hypertension	I10, I11, I12, I13, I14, I15, I16; ATC codes: C03A, C08C, C08D, C09A-D
stroke/TIA/embolism	I63, I64, I679, I693, I694, I698, I679, I69, G451, G452, G453, G458, G459, I74
Liver disease	K70, K71, K72, K73, K74, K75, K76, K77
Renal disease	N183, N184, N185, N189, E102, E112, E122, E132, E142, I12, N03, N083, N085, N118, N14, N150, N16, N19, N26, P960, Q601, Q602, Z992
Exclusion Criteria	ICD-10
Mitral Stenosis or Mechanical	'Z952', 'I050', 'I052', 'I342'
Heart Valve	Procedure codes for mechanical heart valve differ per country
Medication	**ATC code beginning with**
Apixaban	B01AF02
Dabigatran	B01AE07
Edoxaban	B01AF01
Rivaroxaban	B01AF03
Vitamin K antagonist	B01AA
Antiplatelets	B01AC
NSAIDS	M01A
Corticosteroids	H02AB
Diuretics	C03A, C03B, C03C, C03D, C03E
Beta blocker	C07A, C07B, C07C, C07D, C07E, C07F
Ca channel blocker	C08C, C08D, C08E, C08G
RAAS inhibitor	C09A, C09B, C09C, C09D, C09X
Statin	C10AA
Oral antidiabetics	A10B
Insulin	A10A
PPIs	A02BC
Antidepressants	N06A

Appendix table 3. Full baseline characteristics per country and per year.

	Stockholm		Denmark		Scotland		Norway	
	2012	**2017**	**2012**	**2017**	**2012**	**2017**	**2012**	**2017**
n patients	40898	49933	87179	114346	63597	76016	88685	116484
Age (mean)	74.54 (12.68)	75.18 (12.04)	72.95 (12.83)	73.93 (12.20)	74.50 (12.24)	75.35 (11.95)	74.35 (13.30)	73.97 (13.36)
Sex (% female)	17888 (43.7%)	21003 (42.1%)	37898 (43.5%)	48547 (42.5%)	29377 (46.2%)	34619 (45.5%)	37263 (42.0%)	47818 (41.1%)
CHADS-VASc (mean)	3.64 (2.01)	3.62 (1.92)	3.13 (1.84)	3.11 (1.77)	3.38 (1.82)	3.36 (1.76)	3.31 (1.88)	3.21 (1.84)
HAS-BLED (mean)	2.21 (1.30)	2.31 (1.30)	1.93 (1.26)	1.93 (1.23)	2.13 (1.27)	2.23 (1.30)	1.95 (1.25)	2.01 (1.31)
Age category								
< 65	7697 (18.8%)	8108 (16.2%)	19331 (22.2%)	21561 (18.9%)	11956 (18.8%)	12478 (16.4%)	17669 (19.9%)	22836 (19.6%)
65 - 74	10891 (26.6%)	14185 (28.4%)	25226 (28.9%)	34344 (30.0%)	15802 (24.8%)	19021 (25.0%)	22320 (25.2%)	32547 (27.9%)
75 - 84	12585 (30.8%)	16104 (32.3%)	25987 (29.8%)	36321 (31.8%)	22503 (35.4%)	27194 (35.8%)	27155 (30.6%)	34891 (30.0%)
≥ 85	9725 (23.8%)	11536 (23.1%)	16635 (19.1%)	22120 (19.3%)	13336 (21.0%)	17323 (22.8%)	21541 (24.3%)	26210 (22.5%)
CHADs-VASc score								
0	2536 (6.2%)	2805 (5.6%)	6430 (7.4%)	7421 (6.5%)	3794 (6.0%)	4120 (5.4%)	6273 (7.1%)	8065 (6.9%)
1	3934 (9.6%)	4373 (8.8%)	11297 (13.0%)	14343 (12.5%)	6280 (9.9%)	7318 (9.6%)	10097 (11.4%)	14147 (12.1%)
2-4	20687 (50.6%)	26686 (53.4%)	49739 (57.1%)	68208 (59.7%)	36601 (57.6%)	45363 (59.7%)	48849 (55.1%)	66268 (56.9%)
≥ 5	13741 (33.6%)	16069 (32.2%)	19713 (22.6%)	24374 (21.3%)	16922 (26.6%)	19215 (25.3%)	23466 (26.5%)	28004 (24.0%)
HAS-BLED score								
0	3553 (8.7%)	3674 (7.4%)	10002 (11.5%)	11450 (10.0%)	5175 (8.1%)	5466 (7.2%)	9399 (10.6%)	12310 (10.6%)
1-2	21944 (53.7%)	26084 (52.2%)	51363 (58.9%)	70172 (61.4%)	35864 (56.4%)	41394 (54.5%)	52939 (59.7%)	67262 (57.7%)
≥ 3	15401 (37.7%)	20175 (40.4%)	25814 (29.6%)	32724 (28.6%)	22558 (35.5%)	29156 (38.4%)	26347 (29.7%)	36912 (31.7%)
Comorbidities								
Hypertension	25191 (61.6%)	33426 (66.9%)	36880 (42.3%)	48864 (42.7%)	28125 (44.2%)	32365 (42.6%)	38851 (43.8%)	50283 (43.2%)
Anaemia	6139 (15.0%)	7122 (14.3%)	7169 (8.2%)	9391 (8.2%)	6923 (10.9%)	8082 (10.6%)	8090 (9.1%)	12997 (11.2%)
Liver disease	532 (1.3%)	732 (1.5%)	1066 (1.2%)	1697 (1.5%)	1197 (1.9%)	1846 (2.4%)	972 (1.1%)	1535 (1.3%)
Renal disease	2435 (6.0%)	4690 (9.4%)	4289 (4.9%)	7043 (6.2%)	7505 (11.8%)	11492 (15.1%)	7211 (8.1%)	11451 (9.8%)
Alcoholism	1496 (3.7%)	1765 (3.5%)	2585 (3.0%)	3377 (3.0%)	3410 (5.4%)	3822 (5.0%)	1676 (1.9%)	2457 (2.1%)

Appendix table 3. (continued)

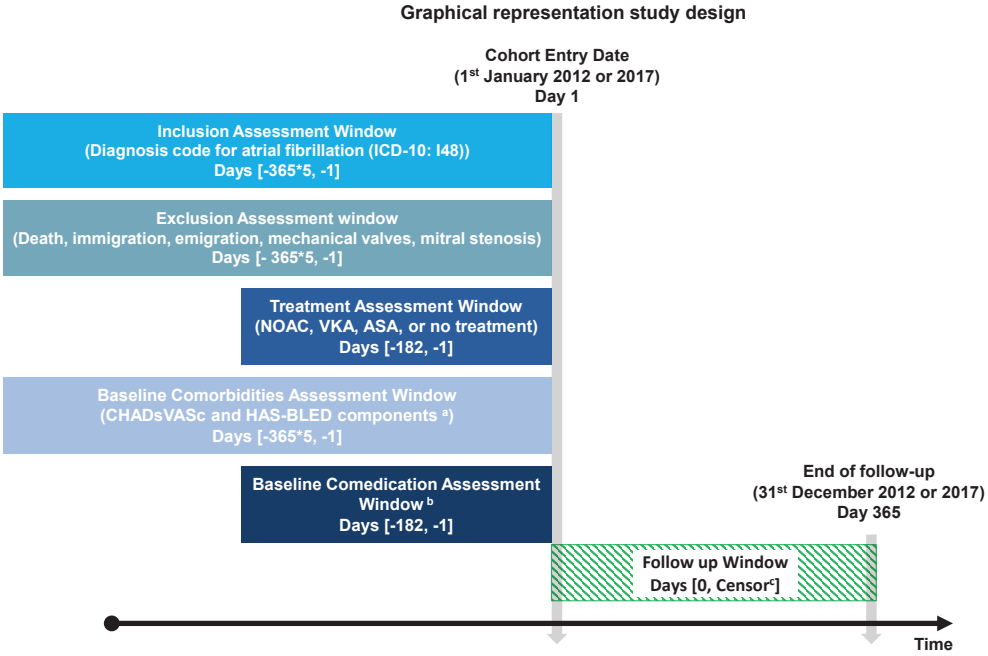
	Stockholm		Denmark		Scotland		Norway	
	2012	2017	2012	2017	2012	2017	2012	2017
Prior bleed	6920 (16.9%)	9357 (18.7%)	12858 (14.7%)	17381 (15.2%)	7983 (12.6%)	9946 (13.1%)	12599 (14.2%)	21778 (18.7%)
Stroke/TIA/embolism	9346 (22.9%)	10447 (20.9%)	16334 (18.7%)	20775 (18.2%)	10815 (17.0%)	12776 (16.8%)	15821 (17.8%)	19858 (17.0%)
Heart failure	13234 (32.4%)	15144 (30.3%)	17344 (19.9%)	21298 (18.6%)	13861 (21.8%)	14469 (19.0%)	21335 (24.1%)	25989 (22.3%)
Vascular disease	11003 (26.9%)	11281 (22.6%)	25600 (29.4%)	28507 (24.9%)	24523 (38.6%)	26358 (34.7%)	31791 (35.8%)	38384 (33.0%)
Diabetes	7447 (18.2%)	9653 (19.3%)	12065 (13.8%)	16078 (14.1%)	10037 (15.8%)	13625 (17.9%)	13094 (14.8%)	17090 (14.7%)
Comedication								
P2Y12 inhibitor	780 (1.9%)	816 (1.6%)	4842 (5.6%)	5604 (4.9%)	5095 (8.0%)	7422 (9.8%)	2651 (3.0%)	3172 (2.7%)
NSAID	2875 (7.0%)	2408 (4.8%)	13088 (15.0%)	9604 (8.4%)	8489 (13.3%)	11774 (15.5%)	9491 (10.7%)	9974 (8.6%)
Corticosteroid	2844 (7.0%)	4055 (8.1%)	5887 (6.8%)	7610 (6.7%)	8453 (13.3%)	12359 (16.3%)	8157 (9.2%)	11054 (9.5%)
Diuretic	13914 (34.0%)	15686 (31.4%)	40734 (46.7%)	46332 (40.5%)	30928 (48.6%)	33527 (44.1%)	27790 (31.3%)	30401 (26.1%)
Beta blocker	26650 (65.2%)	34261 (68.6%)	50620 (58.1%)	68960 (60.3%)	34378 (54.1%)	45356 (59.7%)	54564 (61.5%)	71505 (61.4%)
Ca channel blocker	6470 (15.8%)	11335 (22.7%)	22931 (26.3%)	26629 (23.3%)	15455 (24.3%)	17280 (22.7%)	19570 (22.1%)	24110 (20.7%)
RAAS inhibitor	16366 (40.0%)	21790 (43.6%)	40121 (46.0%)	51386 (44.9%)	30460 (47.9%)	33580 (44.2%)	40295 (45.4%)	52686 (45.2%)
Statin	8954 (21.9%)	16399 (32.8%)	35185 (40.4%)	45373 (39.7%)	34770 (54.7%)	39991 (52.6%)	36632 (41.3%)	48452 (41.6%)
Oral diabetic drug	2958 (7.2%)	4335 (8.7%)	10090 (11.6%)	14639 (12.8%)	7478 (11.8%)	9833 (12.9%)	8492 (9.6%)	11032 (9.5%)
Insulin	2270 (5.6%)	2921 (5.8%)	4000 (4.6%)	5435 (4.8%)	2321 (3.6%)	3118 (4.1%)	3428 (3.9%)	4492 (3.9%)
Antidepressant	3766 (9.2%)	6312 (12.6%)	14166 (16.2%)	15863 (13.9%)	12639 (19.9%)	16702 (22.0%)	9327 (10.5%)	11245 (9.7%)
PPI	7775 (19.0%)	10428 (20.9%)	20275 (23.3%)	29479 (25.8%)	27164 (42.7%)	34362 (45.2%)	15477 (17.5%)	28245 (24.2%)

Appendix table 4. Treatment per age category, year, and database. VKA: vitamin K antagonist; NOAC: non vitamin K antagonist oral anticoagulant

		Stockholm		Denmark		Scotland		Norway	
		2012	2017	2012	2017	2012	2017	2012	2017
Age <65	VKA	31,2%	15,8%	31,8%	19,9%	33,8%	20,6%	30,5%	8,2%
	NOAC	0,4%	24,4%	2,4%	26,4%	0,1%	23,6%	0,7%	26,0%
	Aspirin	22,2%	6,4%	21,6%	6,5%	33,1%	15,1%	27,4%	14,1%
	No treatment	46,3%	53,4%	44,2%	47,2%	33,0%	40,7%	41,4%	51,7%
Age 65 - 74	VKA	55,6%	36,4%	52,6%	33,8%	48,1%	36,8%	53,5%	20,6%
	NOAC	0,5%	38,5%	4,4%	45,0%	0,1%	28,2%	1,3%	49,9%
	Aspirin	22,9%	5,4%	23,8%	6,2%	35,4%	15,7%	28,5%	13,9%
	No treatment	21,0%	19,8%	19,2%	15,0%	16,3%	19,3%	16,7%	15,5%
Age 75 - 84	VKA	59,0%	45,2%	57,4%	38,9%	48,7%	40,4%	61,5%	30,0%
	NOAC	0,5%	33,8%	3,9%	43,8%	0,1%	26,8%	0,9%	47,3%
	Aspirin	23,7%	6,3%	23,7%	6,0%	35,6%	14,3%	22,3%	10,9%
	No treatment	16,8%	14,7%	15,0%	11,3%	15,6%	18,4%	15,3%	11,8%
Age ≥ 85	VKA	36,5%	41,0%	37,8%	31,9%	30,3%	28,2%	46,0%	29,2%
	NOAC	0,1%	26,4%	2,9%	43,0%	0,0%	23,8%	0,5%	36,8%
	Aspirin	45,3%	14,6%	39,3%	8,8%	47,8%	19,1%	24,7%	10,4%
	No treatment	18,1%	18,0%	19,9%	16,3%	21,9%	29,0%	28,8%	23,5%

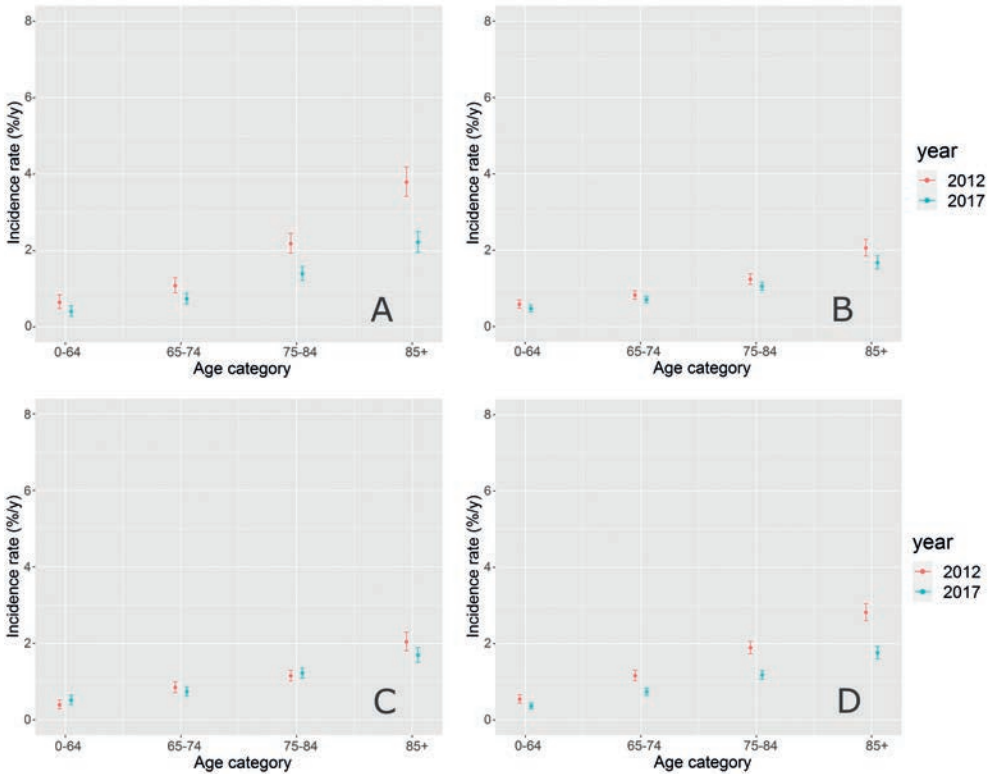
Appendix table 5. Number of patients and patient characteristics after the sensitivity analysis of only having access to data from 2008 onwards as in Norway.

		Main	Sensitivity
Stockholm	n patients	40898	38805
	mean age	74,54	74,7
	% female	43,7%	43,6%
	CHA_2Ds_2-VASc score	3,64	3,68
	HAS-BLED score	2,21	2,23
	stroke rate	2,11	2,15
	bleeding rate	2,16	2,20
Denmark	n patients	87179	79634
	mean age	73,9	73,0
	% female	42,5%	43,4%
	CHA_2Ds_2-VASc score	3,11	3,16
	HAS-BLED score	1,93	1,95
	stroke rate	1,21	1,23
	bleeding rate	2,15	2,22
Scotland	n patients	63597	57645
	mean age	74,5	74,6
	% female	46,2%	46,4%
	CHA_2Ds_2-VASc score	3,38	3,42
	HAS-BLED score	2,13	2,16
	stroke rate	1,21	1,25
	bleeding rate	1,81	1,88

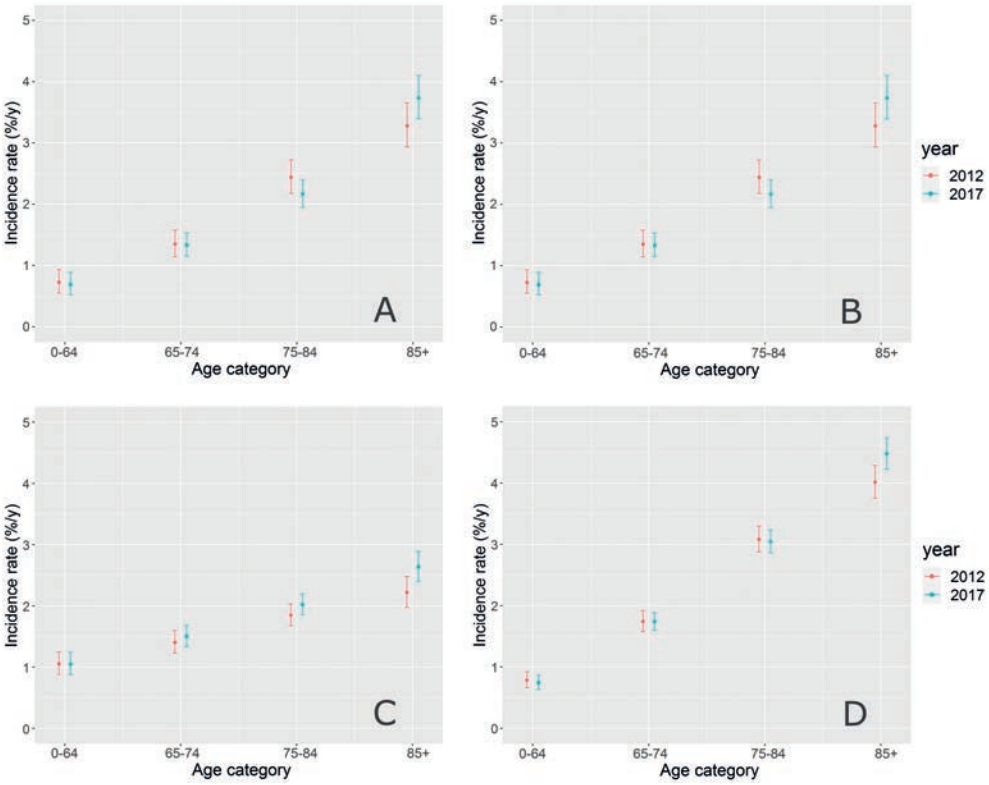


a. Comorbidities: heart failure, hypertension, stoke/TIA/embolism, vascular disease, diabetes, renal disease, liver disease, prior bleeding, and alcoholism.
b. Comedication: NSAIDs, P2Y12-inhibitors, corticosteroids, diuretics, beta-blockers, ca-channel blockers, RAAS-inhibitors, statins, oral diabetic drugs, insulin, PPIs, and antidepressants
c. Earliest of: emigration, death, outcome of interest, end of follow-up (i.e., 31 December 2012 or 2017)

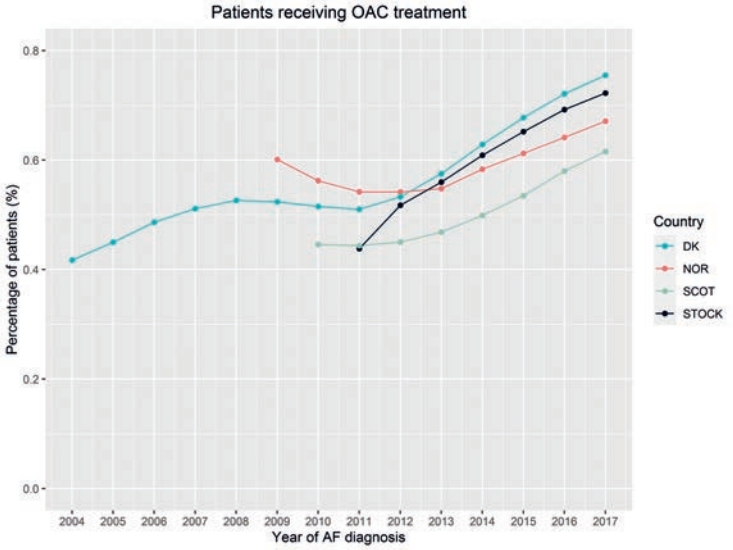
Appendix figure 1. Graphical presentation of the study design and the creation of the two cohorts.



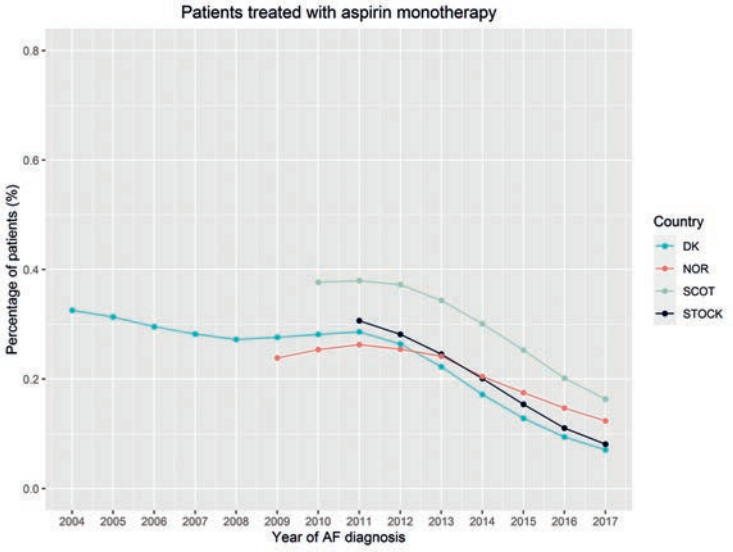
Appendix figure 2. Stroke rates per age group for each country. A (top left panel): Stockholm; B: Denmark; C: Scotland; D: Norway



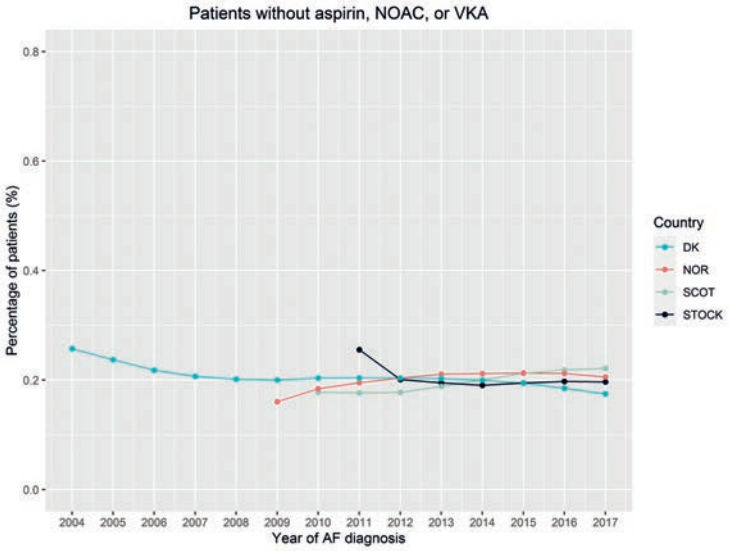
Appendix figure 3. Bleeding rates per age group for each country. A (top left panel): Stockholm; B: Denmark; C: Scotland; D: Norway



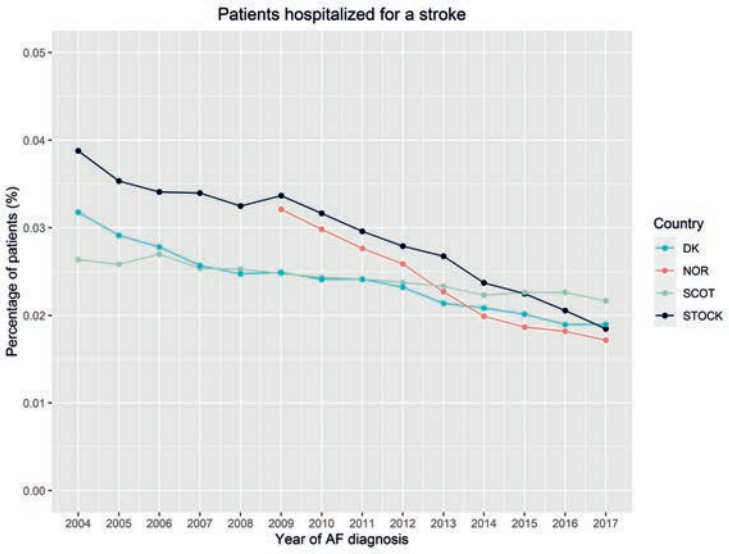
Appendix figure 4. Proportion of AF patients receiving oral anticoagulant treatment over time.



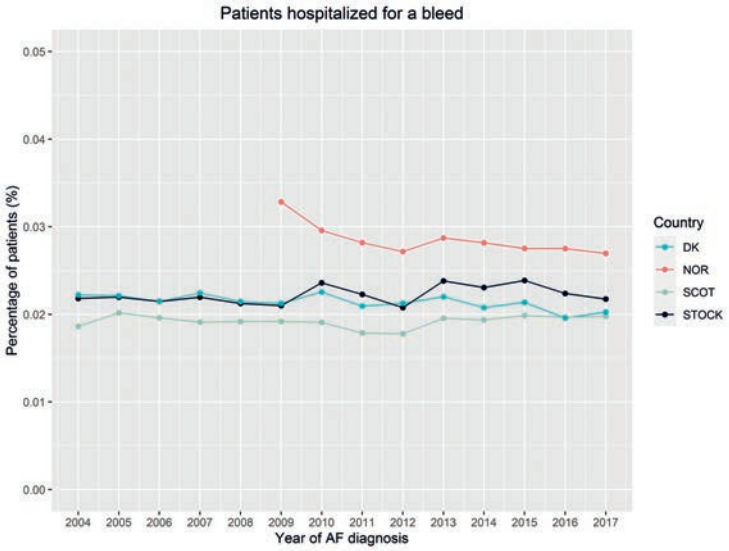
Appendix figure 5. Proportion of AF patients receiving aspirin monotherapy over time.



Appendix figure 6. Proportion of AF patients untreated over time.



Appendix figure 7. Proportion of AF patients suffering from a stroke over time.



Appendix figure 8. Proportion of AF patients suffering from a bleed over time.

2.5

LONG-TERM PERSISTENCE AND ADHERENCE WITH NON-VITAMIN K ORAL ANTICOAGULANTS IN PATIENTS WITH ATRIAL FIBRILLATION AND THEIR ASSOCIATIONS WITH STROKE RISK

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ABSTRACT

Background

Studies on adherence and persistence with non-vitamin K oral anticoagulant (NOAC) treatment have relied on data from the early years of NOAC availability. We aimed to study long-term adherence and persistence with NOACs and their association with stroke risk.

Methods and results

From the Stockholm Healthcare database, we included 21 028 atrial fibrillation (AF) patients claiming a first NOAC prescription from July 2011 until October 2018, with more than 1000 patients having more than 5 years of follow-up (median: 2.0, IQR: 1.0 – 3.2). Persistence rates, defined as continuing to claim NOAC prescriptions within a 90-day gap, decreased to 70% at the end of follow-up. However, 85% of the patients were treated at the end of the study due to reinitiations. Adherence, calculated as medication possession rate (MPR) in three and six-month intervals among persistent users, remained stable at 90%, with 75% of patients having an MPR >95% throughout the study period. Using a case-control design, we calculated associations of persistence and adherence with stroke risk, adjusting for potential confounders. The outcome was a composite of ischemic or unspecified stroke and TIA. Non-persistence and poor adherence were both associated with increased stroke risk (non-persistence adjusted odds ratio (aOR): 2.05; 95% confidence interval (CI): 1.49–2.82, one percent reduction MPR aOR: 1.03; CI: 1.01–1.05). There was no association between non-persistence or poor adherence and the falsification endpoints; fractions and respiratory infections, indicating no 'healthy-adherer' effect.

Conclusion

Persistence rates decreased slowly over time, but persistent patients had high adherence rates. Both non-persistence and poor adherence were associated with an increased stroke risk.

INTRODUCTION

Non-vitamin K oral anticoagulants (NOACs) are the preferred oral anticoagulants (OACs) for stroke prevention in patients with atrial fibrillation (AF) according to current guidelines [1, 2]. Besides their efficacy and safety compared to vitamin K antagonists (VKAs) as shown in both randomized clinical trials [3] and in observational studies [4–6], the NOACs do not require regular monitoring of prothrombin time through International Normalized Ratio (INR). However, measuring the INR is a useful tool to monitor the intensity of treatment and may improve the adherence and persistence with VKA therapy. As a consequence of the lack of monitoring, guidelines stress the importance of actively promoting adherence and persistence to NOAC treatment [1, 2]. Contrary to the VKAs, the NOACs have short half-lives and the protection against ischemic stroke wanes rather rapidly, making adherence and persistence to NOAC treatment even more important [7].

Several studies have assessed the adherence and persistence to NOAC treatment in patients with AF [8–10]. However, these studies were conducted in the period shortly after marketing approval of NOACs. The most recent article included in a systematic review from 2019, was a study from China with data until 2017 and a maximum of 36 months of follow-up, but the vast majority of studies included in this systematic review only had data until 2014 and shorter follow-up [10]. Studies on adherence and persistence with longer follow-up are missing, as well as recent studies on medication behaviour when NOACs have become the mainstay in stroke prevention in AF patients. Studies that have assessed associations of poor adherence and non-persistence with clinical outcomes have also relied on data from the early years of NOAC availability [11, 12]. In these early years the initiation and follow-up of NOAC treatment was most likely concentrated to doctors with special interest in AF whereas this treatment has now shifted towards primary care. In addition, previous work has shown that the pattern of antithrombic treatment in AF has changed since the introduction of the NOACs when aspirin treatment was common and OACs markedly underused [13]. The aim of the present study was to describe the long-term adherence and persistence to NOAC treatment in AF patients, and to assess associations between poor adherence and persistence to NOAC treatment and stroke risk.

METHODS

Database

We used the Stockholm healthcare database for this population based study [14]. It contains demographic and diagnostic data, and pharmacy claims of all prescription drugs for all 2.3 million inhabitants in the Stockholm region. Diagnostic data (ICD-10 codes) cover both inpatient care, specialist ambulatory care, and primary care. The pharmacy claims data are from the Swedish prescribed drug registry, containing data on all pharmaceutical claims for prescription drugs in Sweden [15].

Patient selection

From the Stockholm healthcare database, we created a cohort of all patients initiated on NOAC treatment with a known history of AF (ICD-10: I48) who, after a wash-out period of one year, claimed a first prescription for a NOAC from July 2011 until October 2018. We excluded patients

with a warfarin prescription or a diagnosis code for deep venous thromboembolism or a procedure code for knee/hip replacement surgery in the year before the cohort inclusion date, the latter to remove those with indications for short-term NOAC treatment (see appendix Table 1 for ICD-10 and procedure codes). Patients in the cohort were followed until they claimed a warfarin prescription, died, moved out of the region, or the end of the study period being October 2018.

2.5 Long term persistence and adherence

We partitioned the follow-up time into three-month periods during the first year of follow-up, and six-month periods in the years thereafter. For each interval, we assessed persistence and adherence in the cohort. We used shorter periods in the first year, as we expected that changes in persistence and adherence would occur more frequently during the first year of treatment.

We considered patients to be persistent if they claimed a new NOAC prescription within 91 days after the calculated end of supply from a prior prescription. If patients had the same NOAC available from a previous prescription before claiming a new prescription, the additional days theoretically covered were added to their new prescription [16]. The maximum number of spill over days was set at 91 days. Patients could switch between NOACs and still be considered persistent. If the patient failed to claim a new prescription within the given gap, we defined the date of non-persistence at the calculated end of supply from the last prescription. For the first day of each interval, we calculated the proportion of persistent users by dividing the number of persistent users by the number of patients in the cohort. In addition, we assessed the proportion of patients who had a bleeding event in the 180 days prior to non-persistence, as this might be a reason for discontinuation (see appendix table 1 for ICD codes).

As patients may restart their treatment after being considered non-persistent, we performed an additional analysis in which we defined the proportion of patients having a NOAC available at the start of each interval [17]. With that, it is possible to capture patients restarting treatment after non-persistence, and to calculate the actual proportion of patients receiving treatment at a certain point in time.

We only measured adherence in persistent users, to avoid mixing non-adherence and non-persistence. Adherence was measured using the medication possession rate (MPR) [16]. For each interval we divided the number of days a NOAC was available by the number of days in the interval. Similarly, as for persistence, we took stockpiling from previous prescriptions into account. We further categorized the MPRs as >95%, 95–91%, 90–81%, 80–71%, 70–61%, and <61%.

In addition, to analyse whether persistence and adherence changed over time, we measured persistence and perfect adherence (>95% MPR) during the first year of treatment. For this, we selected patients who were not censored during their first year of treatment.

Case control selection

To assess the associations of non-persistence and poor adherence with stroke risk, we performed a nested case-control study (see appendix Figures 1a and 1b for a visual presentation of the study design) [18].

Case selection

As adherence in a patient might not be stable over time, we chose a case-control study which gave us the possibility to measure adherence in a fixed time-period prior to the event. To assess non-persistence, we included all patients in the cohort suffering an outcome. To assess poor adherence, we only included persistent users suffering an outcome among those who were in the cohort for at least one year. The latter was in order to be able to adequately measure adherence.

Our stroke outcome definition was a composite endpoint of ischemic stroke, unspecified stroke, and transient ischemic attack (TIA). The outcomes had to be registered in secondary inpatient care, require acute care, and be registered as a primary or secondary diagnosis. Validation studies have shown a positive predictive value of 98.6% for these diagnoses in the Swedish database [19].

Control selection

Controls were extracted from the same cohort using risk-set sampling. For analysis of non-persistence, this meant that all AF patients in the initial cohort could be selected as controls, as long as they had not experienced the outcome. For the analysis of poor adherence, patients were only eligible to become controls if they were still persistent users of a NOAC and if they were in the cohort for a minimum of one year.

For each case, a maximum of 5 controls were matched by gender, 5-year age category, year of cohort inclusion, and days since NOAC initiation. With risk-set sampling, patients could be selected as controls even if they experienced the outcome at a later stage. In addition, patients could be selected multiple times as controls. With that procedure, the resulting odds ratios (OR) are equal to an incidence rate ratio that would be generated in a cohort study in the same study population [20].

Covariates

For comedication, we included drugs that might be associated with stroke risk. We searched for the following claims during six months prior to the cohort inclusion date: aspirin, clopidogrel, other antiplatelets, NSAIDs, corticosteroids, diuretics, beta-blockers, calcium channel blockers, RAAS inhibitors, statins, oral antidiabetics, insulin, and antidepressants. For comorbidities, we searched for components of the CHA_2DS_2-VASc score, the HAS-BLED score, and other complicating comorbidities during five years prior to the cohort inclusion date: heart failure, hypertension, prior stroke/TIA/embolism, vascular disease, diabetes; renal disease, liver disease, prior bleed, anaemia, alcoholism; COPD, cancer, and rheumatoid arthritis (see appendix table 1 for ICD-10 and ATC codes).

Statistical analysis

We used descriptive statistics to present persistence and adherence rates in the different intervals. To assess if adherence and persistence changed over time, we used logistic regression to calculate the odds ratios (OR) for persistence and perfect adherence (MPR >95%) during the first year of treatment. Both models included a continuous variable for the year of cohort inclusion, to test if there was a significant trend over time for the proportion of patients being

persistent and adherent in the first year of treatment. All models were adjusted for age, sex, and the aforementioned covariates.

For the case control study, we used conditional logistic regression to assess the associations of non-persistence and poor adherence with stroke risk. For persistence, we first included a binary variable for non-persistence in the model. In another model, we included a categorical variable for the time of non-persistence, starting at the calculated day of the end of the last prescription, categorized as less than 31 days, 31 – 90 days, 91 – 365 days, and over 365 days, with persistent users as the reference category. For adherence, we first included a continuous variable for the MPR in the model. In another model, we included a variable for the aforementioned MPR categories, with >95% MPR as the reference category. Potential confounders were sex and time on treatment, which are adjusted for in the study design. The models were adjusted for age (as a continuous variable) and the aforementioned covariates.

We performed a formal dose-response analysis to whether the risk of stroke increased with longer non-persistence and lower MPR categories. We restricted our analysis to nonpersistent and non-perfect adherent users (MPR ≤ 95%) only and estimated the OR for each category increase of adherence and non-persistence. We used logistic regression with the MPR categories or days of non-persistence as continuous variables. The models were adjusted for age, sex, and all aforementioned covariates.

Sensitivity analyses

Since patients with a CHA_2DS_2-VASc score of 0 or 1 may have an indication for short term NOAC treatment when they undergo cardioversion, we created new figures for persistence and adherence rates where we removed all patients with a CHA_2DS_2-VASc score below 2.

To disentangle the potential 'healthy adherer' effect, we used falsification endpoints. A falsification endpoint is an endpoint that is associated with potential unmeasured confounders, such as frailty, but is not associated with the exposure, in this case nonadherence and poor persistence [21]. We tested the associations of non-persistence and poor adherence with the risk for bone fractures (ICD-10: S0 – S9 (sub code 2 only) and with the risk for respiratory infections (ICD-10: J0 – J1).

In addition, we altered our definition of non-persistence by changing the 91-day gap to 182 days. We performed another analysis where we measured adherence only in the 182 days prior to inclusion, so that cases that occurred after six months of treatment could also be included, instead of only after one year of treatment. With that, we were able to capture more events, at the cost of less accurate adherence measurements.

We performed an exploratory analysis where we assessed persistence with each different NOAC. This is only an exploratory analysis as in Stockholm the vast majority of patients is treated with apixaban, which makes persistence with other NOACs difficult to interpret.

RESULTS

In total, we included 21 028 AF patients who were newly initiated with a NOAC, of whom 15 810 (75.2%) started with apixaban. Their mean age was 73.6 (S.D. 11.0) years and 44.3% were female.

The median follow-up time was 2.0 years (IQR: 1.0 – 3.2) with a maximum of 7.4 years and more than 1000 patients had more than five years of follow-up (see appendix figure 2). During follow-up, 905 patients switched to VKA treatment and were censored. Hypertension was the most common comorbidity (65.1%) and beta-blockers were the most commonly used drugs at baseline (52.4%) (Table 1). The stroke risk in the population was comparable to that found in other large registries [22].

Table 1. Baseline characteristics of all patients included in the cohort. TIA: Transient ischemic attack, COPD: chronic obstructive pulmonary disease, NSAID: non-steroidal anti-inflammatory drug, RAAS: renin angiotensin aldosterone antagonist.

Characteristic	Number of patients, %
Age at index date (mean, sd)	73.61 (10.96)
0 - 64	3745 (17.8%)
65 - 74	7299 (34.7%)
75 - 84	6474 (30.8%)
85 +	3510 (16.7%)
Female	9315 (44.3%)
Type of NOAC	
Dabigatran	3172 (15.1%)
Rivaroxaban	2009 (9.6%)
Apixaban	15810 (75.2%)
Edoxaban	37 (0.2%)
Year of inclusion	
2011	84 (0.4%)
2012	588 (2.8%)
2013	1586 (7.5%)
2014	2289 (10.9%)
2015	3853 (18.3%)
2016	4456 (21.2%)
2017	5100 (24.3%)
2018 (up to October)	3072 (14.6%)
CHA2DS2-VASc (mean, sd)	3.29 (1.92
0	1054 (5.0%)
1	2619 (12.5%)
2	4126 (19.6%)
3	4563 (21.7%)
4	3772 (17.9%)
5	2036 (9.7%)
6	1234 (5.9%)
7	1079 (5.1%)
8	473 (2.2%)
9	72 (0.3%)
Hypertension	13699 (65.1%)
Anaemia	2343 (11.1%)
Abnormal liver function	363 (1.7%)

Table 1. (continued)

Characteristic	Number of patients, %
Renal disease	1329 (6.3%)
Alcoholism	776 (3.7%)
Prior bleed	2034 (9.7%)
Previous stroke/TIA/embolism	4191 (19.9%)
Myocardial infarction	1155 (5.5%)
Heart failure	3420 (16.3%)
Vascular disease	4370 (20.8%)
COPD	3305 (15.7%)
Rheumatoid arthritis	983 (4.7%)
Diabetes	3535 (16.8%)
Cancer	2508 (11.9%)
Aspirin	8137 (38.7%)
Clopidogrel	862 (4.1%)
Other antiplatelets	417 (2.0%)
NSAID	2244 (10.7%)
Corticosteroid	1666 (7.9%)
Diuretic	4341 (20.6%)
Beta blocker	11029 (52.4%)
Ca channel blocker	5503 (26.2%)
RAAS inhibitor	8036 (38.2%)
Statin	5965 (28.4%)
Oral antidiabetic drug	1858 (8.8%)
Insulin	956 (4.5%)
Antidepressant	2353 (11.2%)

Persistence and adherence

Persistence rates declined the most in the first year of treatment, to approximately 85%, and subsequently decreased steadily to approximately 70% at the end of the study. When including patients restarting treatment, we found that the proportion of patients receiving treatment declined to approximately 85% after 1 year and remained stable at that rate, while the proportion of fully persistent users kept declining (Figure 1). There were no large differences in persistence with different NOACs, but the persistence with apixaban and rivaroxaban was better than that for dabigatran. However, numbers for rivaroxaban and dabigatran treated patients were low (Appendix figure 4). Among the 3 270 patients who became non-persistent, 212 patients experienced a bleeding event in the 180 days prior to this date (6.5%).

Among the patients who were persistent, the MPR remained stable at around 90%. Approximately 75% of them had an MPR >95% throughout the study (Figure 2). Figure 3 shows that the proportion of patients with perfect adherence (MPR >95%) and with persistent use in the first year increased with each year. Results from the logistic regression show that there was a significant trend towards increasing persistence and adherence over the years, after adjusting for baseline characteristics.

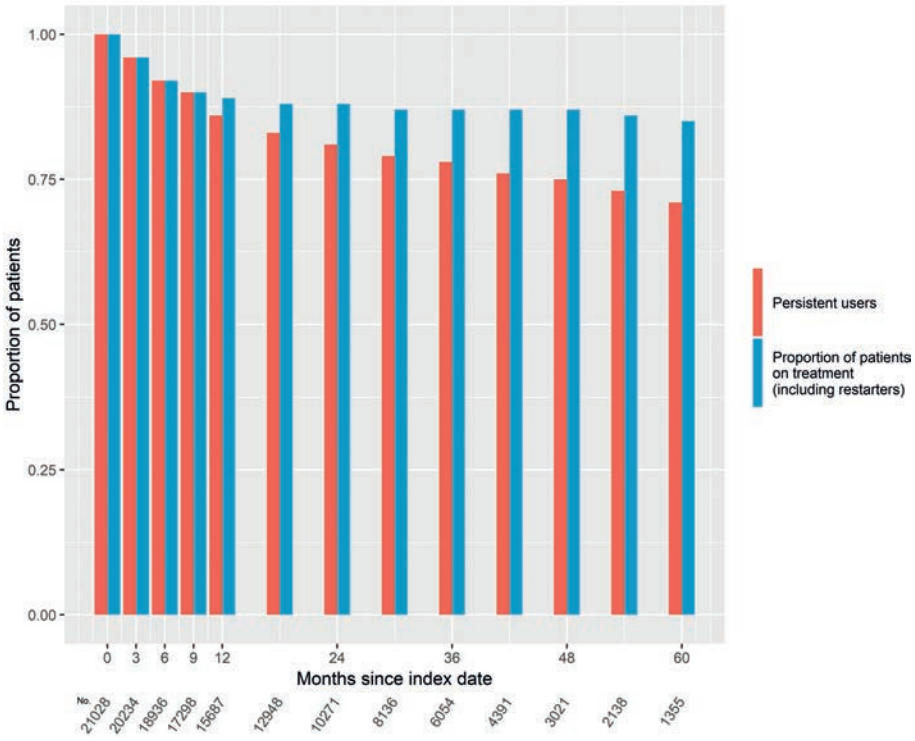

Figure 1. Number of persistent users and proportion of patients on treatment at each interval during follow-up. The numbers below represent the number of patients that are in the cohort at the beginning of each interval.

The aOR for being persistent increased by 1.11 (95% CI: 1.07 – 1.14) for each additional year, and for being perfectly adherent this aOR was 1.04 (95% CI: 1.02 – 1.07).

Associations with stroke risk

During follow-up, 454 patients suffered a stroke or a TIA and 452 of them were included as cases for the analysis of non-persistence. Two cases could not be matched to a control. The 452 cases were matched to 2252 controls. In four cases fewer than five controls could be matched. Of the 454 patients suffering a stroke or TIA, 139 were persistent users and were on treatment for at least a year and were thus eligible as cases for the analysis of poor adherence. The 139 patients included as cases were matched to 690 controls in the adherence analysis. In two cases fewer than five controls could be matched. Baseline characteristics of the case-control sets, along with the MPRs and non-persistence rates, are presented in Table 2. Non-persistence was associated with an increased stroke risk (aOR: 2.05; CI: 1.49 – 2.82). The increased risk for stroke/TIA appeared not to occur directly after becoming non-persistent (Figure 4), and there was no association between time since non-persistence and stroke risk (aOR: 0.89; CI: 0.63 – 1.60).

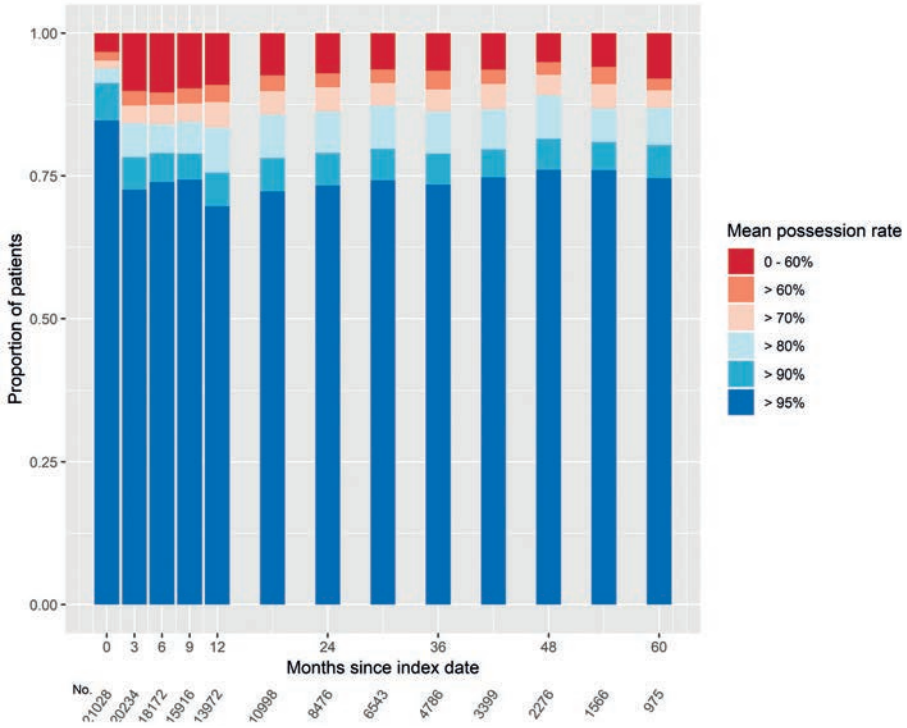

Figure 2. Proportion of patients in each category of the mean possession rate for each interval during follow-up. MPR. mean possession rate.

Decreased adherence was associated with an increased stroke risk (Figure 4). When analysing adherence as a continuous variable we found that a 1 percent decrease in the MPR was associated with a 3 percent increase of stroke risk (aOR: 1.03; CI: 1.01 – 1.05). The logistic regression with categorical MPRs showed that for each reduction in MPR category, the odds for a stroke was 1.43 times higher (aOR: 1.43; CI: 1.11 – 1.86).

Sensitivity analyses

When excluding patients with a CHA_2DS_2-VASc score below 2, which could have an indication for short-term NOAC treatment, the persistence and adherence rates were similar to those in the main analysis (Appendix figures 3a and 3b).

For the falsification endpoints there were no significant associations between poor persistence and fractures (aOR: 1.05; CI: 0.78 – 1.42) or respiratory infections (aOR: 1.20; CI: 0.93 – 1.56), or between reduced MPR and fractures (aOR: 0.99; CI: 0.98 – 1.01) or respiratory infections (aOR: 1.00; CI: 0.98 – 1.01).

Changing the definition of non-persistence from 91 days to 182 days without coverage yielded similar results. The aOR for the association of non-persistence with stroke risk was 1.76

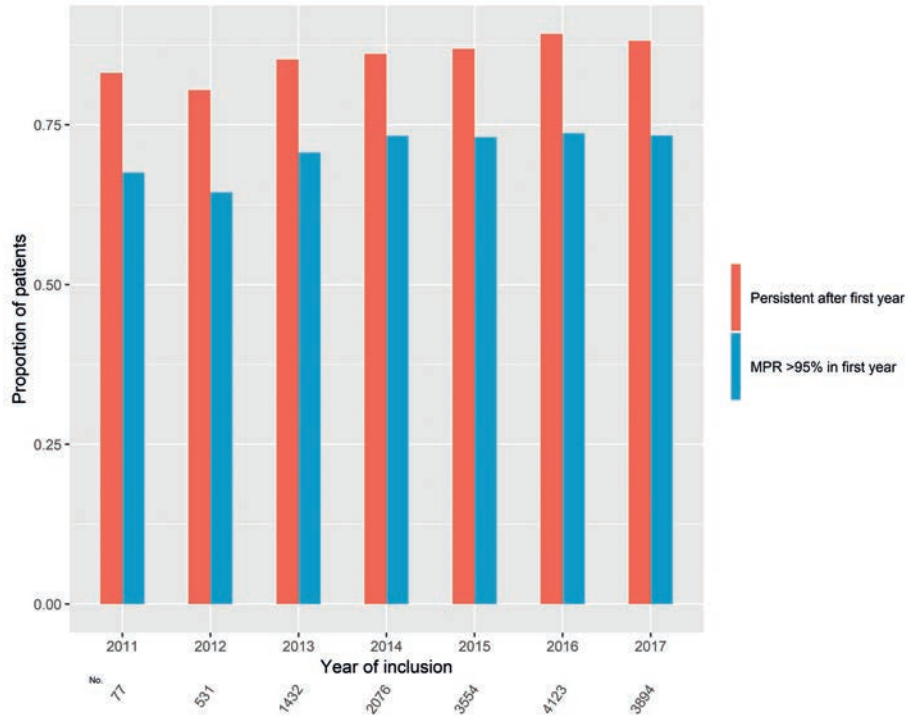

Figure 3. Proportion of patients that are persistent after one year and proportion of patients that have perfect adherence (MPR >95%) in their first year of treatment, stratified per inclusion year.

(CI: 1.27 – 2.43), and for the association with a one percent decrease in MPR the aOR was 1.03 (CI: 1.01 – 1.05).

For the analysis in which we measured adherence in the 182 days prior to the event instead of one year, we included 219 events instead of 139. This yielded a similarly increased stroke risk; if the MPR decreased by 1 percent the aOR was 1.02 (CI: 1.01 – 1.03).

There were no large differences in persistence with different NOACs, but the persistence with apixaban and rivaroxaban was better than that for dabigatran. However, numbers for rivaroxaban and dabigatran treated patients were low (see appendix figure 4).

DISCUSSION

In the current population-based cohort study with up to 7.4 years of follow-up and more than 1000 patients having over five years of follow-up, we found that persistence rates declined steadily throughout follow-up, from 85% after the first year to 70% at the end of the study, while adherence rates remained stable. However, many non-persistent patients reinitiated therapy and the proportion of patients actually receiving NOAC treatment remained stable around 85% during the entire follow-up. Persistence and adherence during the first year of treatment increased

Table 2. Baseline characteristics and measures of persistence and adherence of cases and controls, for both the persistence and the adherence associations. TIA: Transient ischemic attack, COPD: chronic obstructive pulmonary disease, NSAID: non-steroidal anti-inflammatory drug, RAAS: renin angiotensin aldosterone antagonist.

	Persistence		Adherence	
	Cases	**Controls**	**Cases**	**Controls**
Number of patients	452	2252	139	690
Non persistence	78 (17.3%)	222 (9.9%)	*NA*	*NA*
MPR (sd)	*NA*	*NA*	90.46 (12.30)	93.57 (9.67)
Age at index date (mean, sd)	76.73 (9.93)	76.66 (9.97)	76.76 (8.46)	76.49 (8.68)
Female	209 (46.2%)	1042 (46.3%)	60 (43.2%)	297 (43.0%)
Hypertension	327 (72.3%)	1494 (66.3%)	100 (71.9%)	447 (64.8%)
Anaemia	55 (12.2%)	268 (11.9%)	20 (14.4%)	68 (9.9%)
Abnormal liver function	7 (1.5%)	30 (1.3%)	3 (2.2%)	15 (2.2%)
Renal disease	29 (6.4%)	123 (5.5%)	11 (7.9%)	41 (5.9%)
Alcoholism	25 (5.5%)	66 (2.9%)	8 (5.8%)	13 (1.9%)
Prior bleed	55 (12.2%)	210 (9.3%)	17 (12.2%)	71 (10.3%)
Stroke/TIA/embolism	114 (25.2%)	498 (22.1%)	29 (20.9%)	141 (20.4%)
Myocardial infarction	39 (8.6%)	128 (5.7%)	11 (7.9%)	42 (6.1%)
Heart failure	54 (11.9%)	356 (15.8%)	14 (10.1%)	130 (18.8%)
Vascular disease	75 (16.6%)	476 (21.1%)	21 (15.1%)	157 (22.8%)
COPD	65 (14.4%)	337 (15.0%)	24 (17.3%)	108 (15.7%)
Rheumatoid arthritis	19 (4.2%)	117 (5.2%)	4 (2.9%)	33 (4.8%)
Diabetes	75 (16.6%)	335 (14.9%)	24 (17.3%)	94 (13.6%)
Cancer	68 (15.0%)	284 (12.6%)	24 (17.3%)	82 (11.9%)
Aspirin	235 (52.0%)	1046 (46.4%)	90 (64.7%)	346 (50.1%)
Clopidogrel	17 (3.8%)	100 (4.4%)	5 (3.6%)	33 (4.8%)
Other antiplatelets	6 (1.3%)	44 (2.0%)	3 (2.2%)	19 (2.8%)
NSAID	41 (9.1%)	199 (8.8%)	12 (8.6%)	74 (10.7%)
Corticosteroid	28 (6.2%)	165 (7.3%)	6 (4.3%)	58 (8.4%)
Diuretic	113 (25.0%)	511 (22.7%)	41 (29.5%)	162 (23.5%)
Beta blocker	250 (55.3%)	1254 (55.7%)	85 (61.2%)	398 (57.7%)
Ca channel blocker	114 (25.2%)	582 (25.8%)	40 (28.8%)	181 (26.2%)
RAAS inhibitor	195 (43.1%)	867 (38.5%)	66 (47.5%)	259 (37.5%)
Statin	108 (23.9%)	656 (29.1%)	43 (30.9%)	221 (32.0%)
Oral antidiabetic drug	33 (7.3%)	163 (7.2%)	10 (7.2%)	52 (7.5%)
Insulin	20 (4.4%)	84 (3.7%)	9 (6.5%)	27 (3.9%)
Antidepressant	51 (11.3%)	244 (10.8%)	17 (12.2%)	78 (11.3%)

significantly over time. Importantly, both non-persistence and poor adherence were associated with an increased stroke risk.

Both persistence and adherence are required for a drug to have a clinical effect, especially for NOACs, given their short half-lives [7]. There was no correlation between the time since non-persistence and an increasing stroke risk. This finding is as expected if there is no rebound

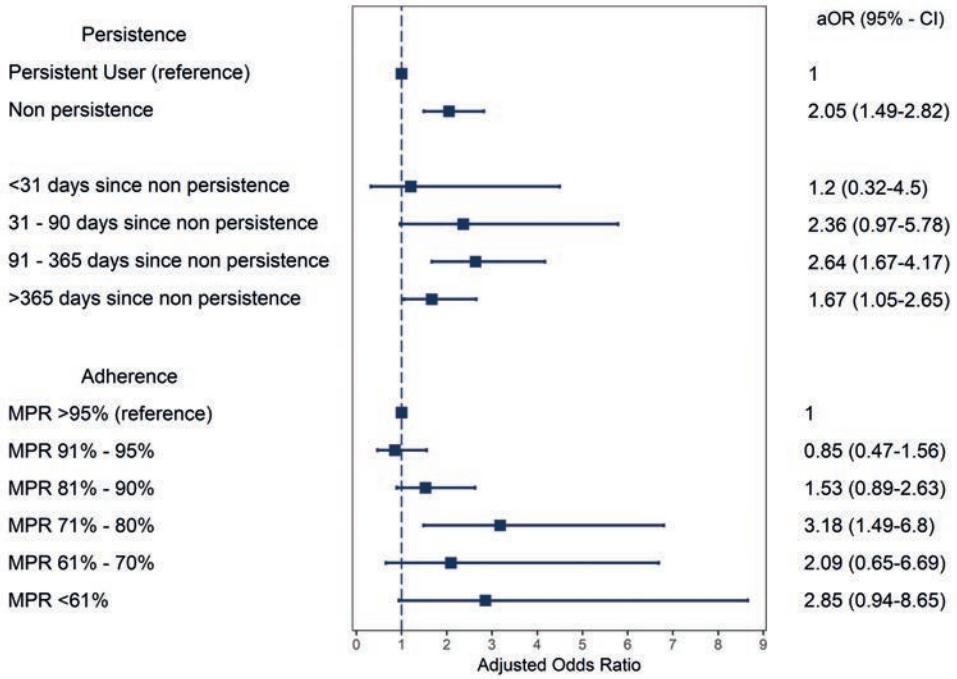

Figure 4. Adjusted odds ratios for the association of non-persistence or poor adherence and the risk for stroke. aOR: adjusted odds ratio, MPR: mean possession rate

procoagulant effect upon discontinuation. Patients rapidly lose their protection against stroke when they stop taking the NOAC, but this risk should not change after a longer period of being unprotected. However, the increased risk was not visible in the first 31 days of non-persistence. Some patients may still have had the drug available due to poor adherence, and this might partly explain the lack of an increased stroke risk immediately after being defined as non-persistent.

For adherence, there was a linear correlation between the degree of non-adherence and the risk for stroke, stressing the importance of improving adherence in patients [23]. Figure 3 shows that the risk of suffering a stroke is clearly increased when the MPR is below 80%. An additional analysis showed no further increase in the stroke risk when the MPR was further reduced below 80%. We found that the protective effect of the NOACs was intact at an MPR above 90%. This is in line with a recent Korean study with data up to 2016, also showing a protective effect above 90% [24]. These two studies in different settings emphasize that clinicians and patients should strive for an MPR >90%. Future studies on anticoagulant adherence should abandon the frequently used MPR >80% as a binary cut-off for adherence or non-adherence [10], as the protective effect of NOAC treatment is maintained at an MPR >90%.

The proportion of persistent patients declined steadily after an initially larger drop, while adherence rates remained stable. Importantly, when incorporating reinitiators, we found that approximately 85% of the patients were on NOAC treatment throughout the study period. Previous

studies have reported persistence rates after two years ranging from 80% to below 30%, thus persistence rates were high in the current study [10]. Interestingly, both persistence and adherence rates in the first year of follow-up of each patient increased year by year from 2011 to 2018. This indicates that a shift of NOAC treatment away from specialist care did not lead to worsened persistence or adherence.

Our results are in line with previous studies showing an increased stroke risk with lower adherence rates [11, 12, 24, 25]. However, these studies did not take non-persistence into account, and their results appear to be a combined effect of patients having stopped the treatment and patients being non-adherent while treated. Our approach to only measure adherence in patients who were considered to be persistent users reflects the effect of poor adherence on stroke risk more precisely. Compared to previously published adherence rates from a systematic review [8], the adherence rates in our study are amongst the highest. Again, this can be explained by only measuring adherence in patients who were still persistent users. In addition, we found that adherence and persistence rates increased over time. Therefore, having more recent data can also partially explain higher adherence in our study.

We did not have access to explanations for non-persistence since patients in our cohort could not be identified and contacted to collect additional information, but bleeding might be a reason for discontinuation of NOAC therapy, as well as dyspepsia during dabigatran treatment. A study from Denmark examined events preceding NOAC discontinuation and reported that 7.6% of the patients experienced a bleed prior to discontinuation, which is in line with the 6.5% we found [26].

Our study has several strengths. First, we distinguish between adherence and persistence, and only measured adherence in patients who were actually still on treatment. With that approach, we describe clinical practice more precisely, since there is a clear difference between stopping the treatment and not taking the treatment as intended. In addition, we did not split adherent and non-adherent patients at a clinically meaningless MPR of 80% but treated adherence as a continuous variable. Our results show that an MPR of ≥90% would be a more reasonable cut-off if adherence is treated as a binary variable. Second, we are the first to present adherence and persistence with a long follow-up time and including more contemporary data which reflect the current panorama of treatment and treating doctors. As NOACs usually are to be used life-long by AF patients, persistence and adherence beyond the first couple years of treatment are important. Third, the VAL database is a complete population database, including diagnoses from both specialist care and primary care, and data on all claimed prescriptions. This results in a full picture of all patient's healthcare consumption in a complete healthcare setting. Previous work from the region has shown that 12% of AF patients would not be captured if only secondary care data were used, indicating the importance of having data from all levels of care [13, 14]. In addition, the VAL database contains pharmacy claims data which provide dependable indices of persistence [23]. Relying on prescription data involves uncertainty as to whether the patient had claimed the prescription, and would also require that all potential prescribers were accessed in the database [27]. Fourth, we used falsification endpoints and other sensitivity analyses, indicating that our results are not likely explained by a 'healthy-adherer' effect, and that our results are not sensitive to the definitions chosen for non-persistence. Finally,

we used advanced methods to measure adherence, taking stockpiling from previous prescriptions into account.

Our study also has some limitations. First, with pharmacy claims data we cannot assure whether and exactly how patients actually took the treatment. In addition, it is impossible from pharmacy claims data to distinguish between patients who take drug holidays and patients who regularly forget to take their medication, which can ultimately affect the risk for ischemic events. However, it is very likely that non-persistent patients were not taking any drug as they no longer claimed prescriptions and, similarly, it is very likely that patients with poor adherence were skipping doses. Second, when relying on observational data, one can never rule out residual confounding. However, observational data are needed to evaluate treatments in ordinary healthcare, and we found no associations between adherence or persistence and falsification endpoints, i.e., no signs of residual confounding. Third, for the association of non-adherence with stroke risk, we only included cases who had at least one year of follow-up to be able to adequately measure adherence in the primary analysis. Therefore, stroke cases occurring in the first year of treatment were excluded, which could introduce selection bias. However, we also excluded controls with less than one year of follow-up and in the sensitivity analysis including cases and controls that had at least 182 days of follow-up, we found similar associations.

In conclusion, we found that both persistence and adherence rates were high in the Stockholm region compared to previously published data, even with longer follow-up. Both persistence and adherence increased in more recent years with the NOACs having been longer on the market. This gradual improvement rather than deterioration of drug-taking behaviour is important, as there are clear associations between persistence or the level of adherence and stroke risk. Interventions aimed at further improving persistence and adherence should be encouraged, as the protective effect of NOACs disappeared with non-persistence and at low adherences rates.

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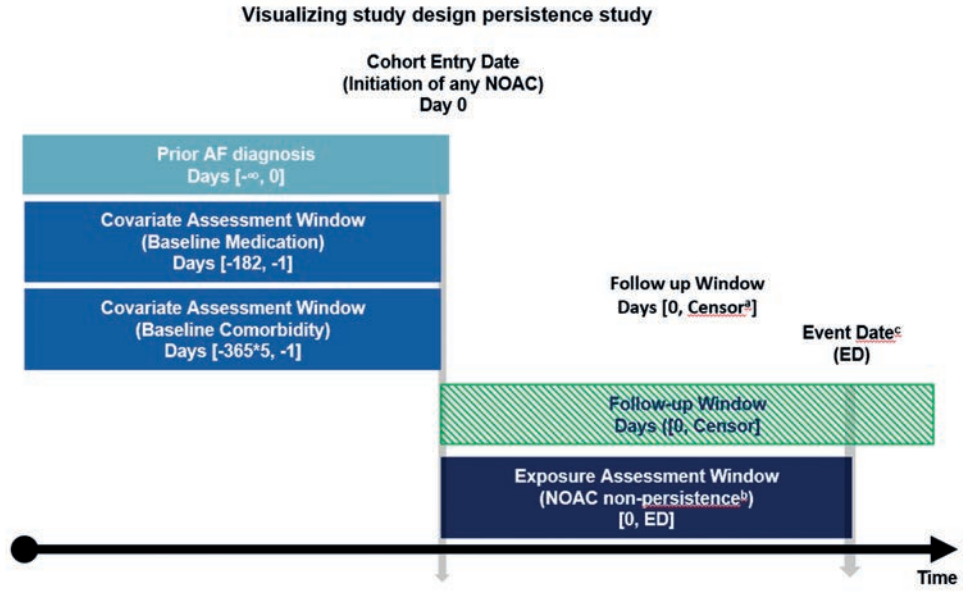
APPENDICES

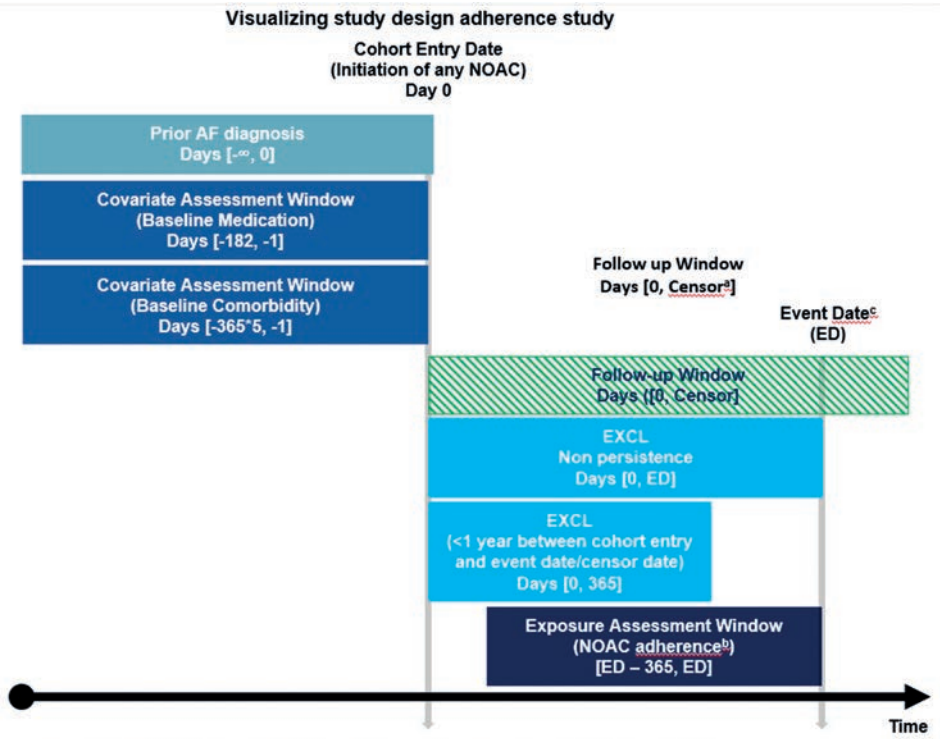
Appendix table 1. ICD-10 codes and ATC codes used for outcomes, comorbidities and comedication.

Outcome definition	ICD-code beginning with
Stroke or TIA	I63, I64, G450, G451, G452, G453, G458, G459
Baseline comorbidities	ICD-code beginning with
Hypertension	I10-I16
Anaemia	D50-59, D60-64
Abnormal liver function	B15-19, C22, D684C, I928B, K70-77, DQ618A, Z944
Renal disease	E102, E112, E132, E142, I120, M300, M313, M319, M321B, N02-08, N11, N12, N14, N18, N19, N26, N158-160, N162-164, N168, Q612, Q613, Q615, Q619
Alcoholism	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90, Y91, Y91, Z502, Z714
Prior bleed	I60, I61, I62, S064, S065, S066, I850, I983, K25-28 (subcodes 0-2 and 4-6 only), K625, K922, D62
Previous stroke, TIA, or embolism	I63, I64, I679, I693, I694, I698, I67, I69, Z866, Z876, G453, G458, G459, I74
Myocardial infarction	I21, I22, I252
Heart failure	I43, I50, I099, I110, I130, I132, I255, I420, I425-429, P290
Vascular disease	I70, I71, I731, I738, I739, I711, I790, I792, K551, K558, K559, Z958, Z959, G45, G46, I60-69, H340
COPD	J40-47, J60-67, I278, I279, J684, J701, J703
Rheumatoid arthritis	M05, M06, M32-34, M315, M351, M353, M360
Diabetes	E100-147
Cancer	C00-09, C10-14, C30-39, C40-41, C43, C45-C49, C50-58, C60-69, C70-88, C90-97
DVT or knee/hip replacement (exclusion criteria)	I26, I80, I81, I82, NGB, NGC, NFB, NFG (procedure codes)
Medication	**ATC code beginning with**
Warfarin	B01AA03
NOAC	B01AF02, B01AE07, B01AF03, B01AF01
Aspirin	B01AC06
Clopidogrel	B01AC04
NSAID	M01A
Other antiplatelet	B01AC22, B01AC24, B01AC07
Corticosteroids	H02AA01, H02AA02, H02AA03, H02AB
Diuretic	C03A, C03B, C03C, C03D, C03E
Beta blocker	C07A, C07B, C07C, C07D, C07E, C07F
Ca channel blocker	C08C, C08D, C08E, C08G
RAAS inhibitor	C09A, C09B, C09C, C09D, C09X
Statin	C10AA
Oral antidiabetic drug	A10B
Insulin	A10A
Antidepressant	N06A



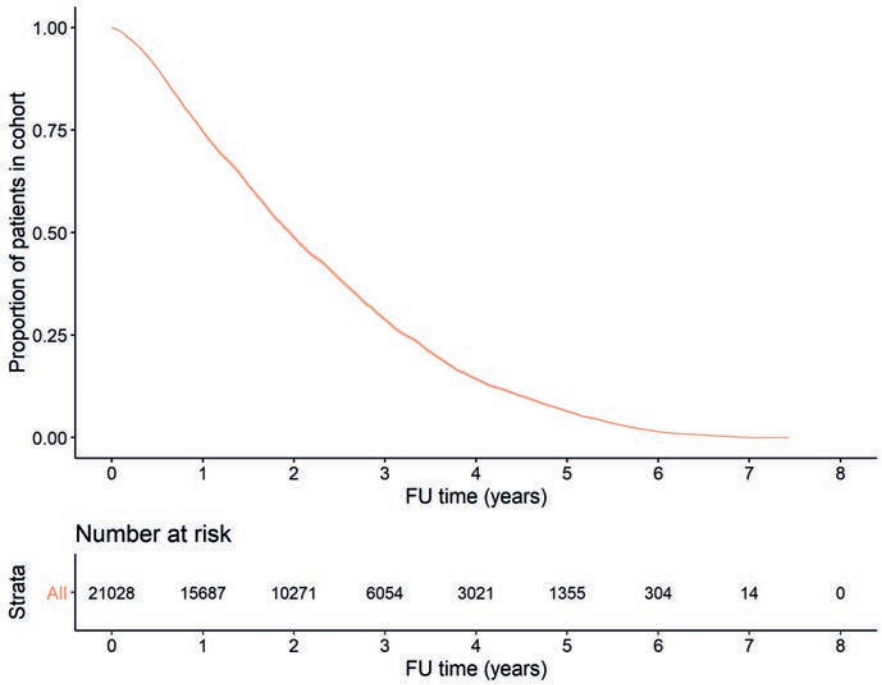
a. Censored at minimum of stroke, death, warfarin prescription or end of the study period.
b. NOAC non-persistence is defined as no NOAC claimed at 90 days after calculated end of last NOAC prescription
c. Controls risk-set matched on year of cohort entry, duration of follow up (from cohort entry), age and sex

Appendix figure 1a. Visual representation of the case-control design for the association of non-persistence with stroke risk. NOAC: non-vitamin K oral anticoagulant, AF : atrial fibrillation, ED : event date

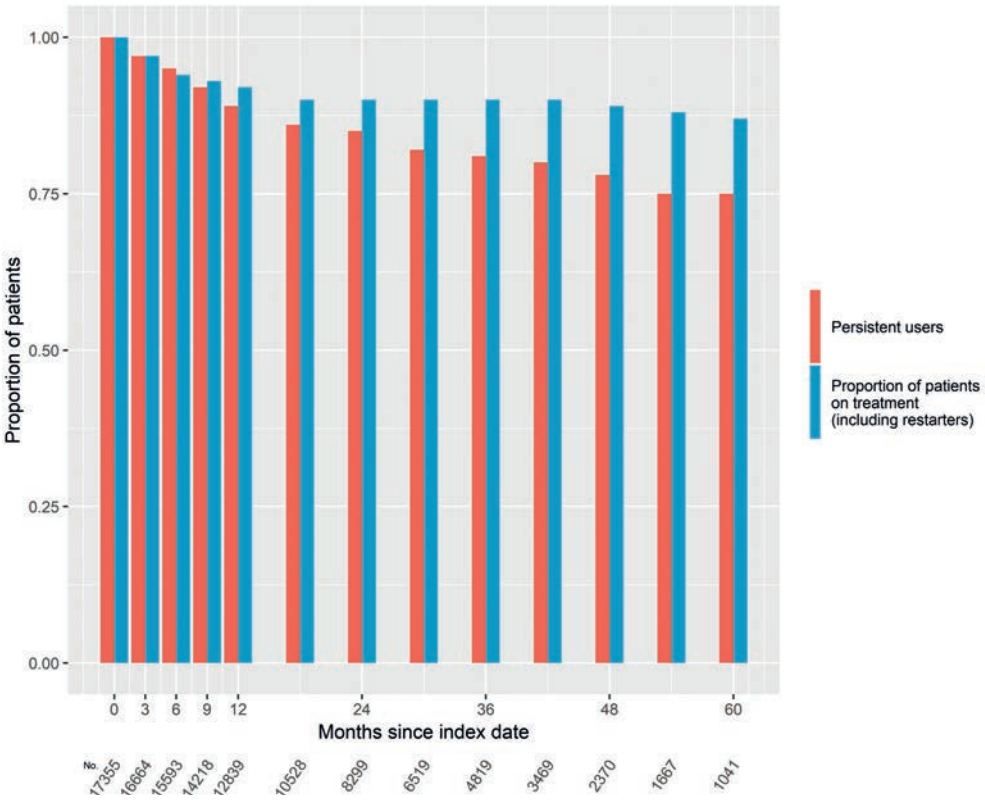


a. Censored at minimum of stroke, death, emigration, or a warfarin prescription.
b. NOAC adherence is measured as the mean possession rate, split into categories (>95%, 90 – 95%, 80 – 90%, 70 – 80%, 60 – 70%, and <60%).
c. Controls risk-set matched on year of cohort entry, duration of follow up (from cohort entry), age and sex. Patients could only be a control if they were persistent users and if they were in the cohort for more than one year.

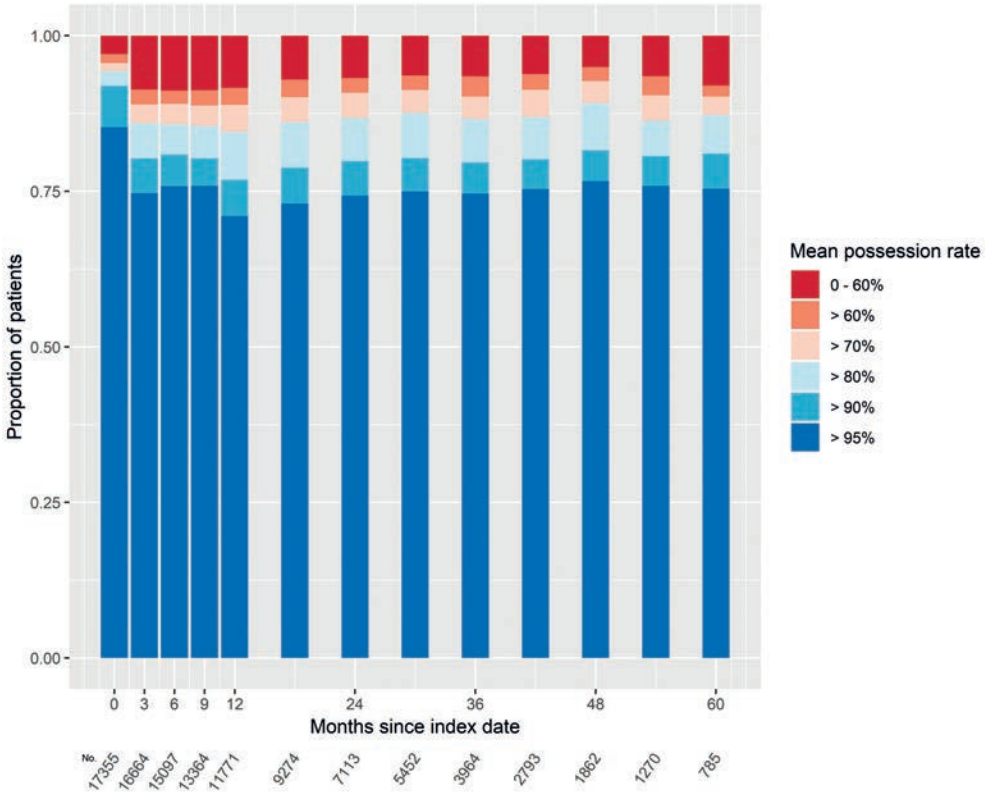
Appendix figure 1b. Graphical representation of the case-control design for the association of poor adherence with stroke risk. NOAC: non-vitamin K oral anticoagulant, AF : atrial fibrillation, ED : event date, EXCL : exclusion



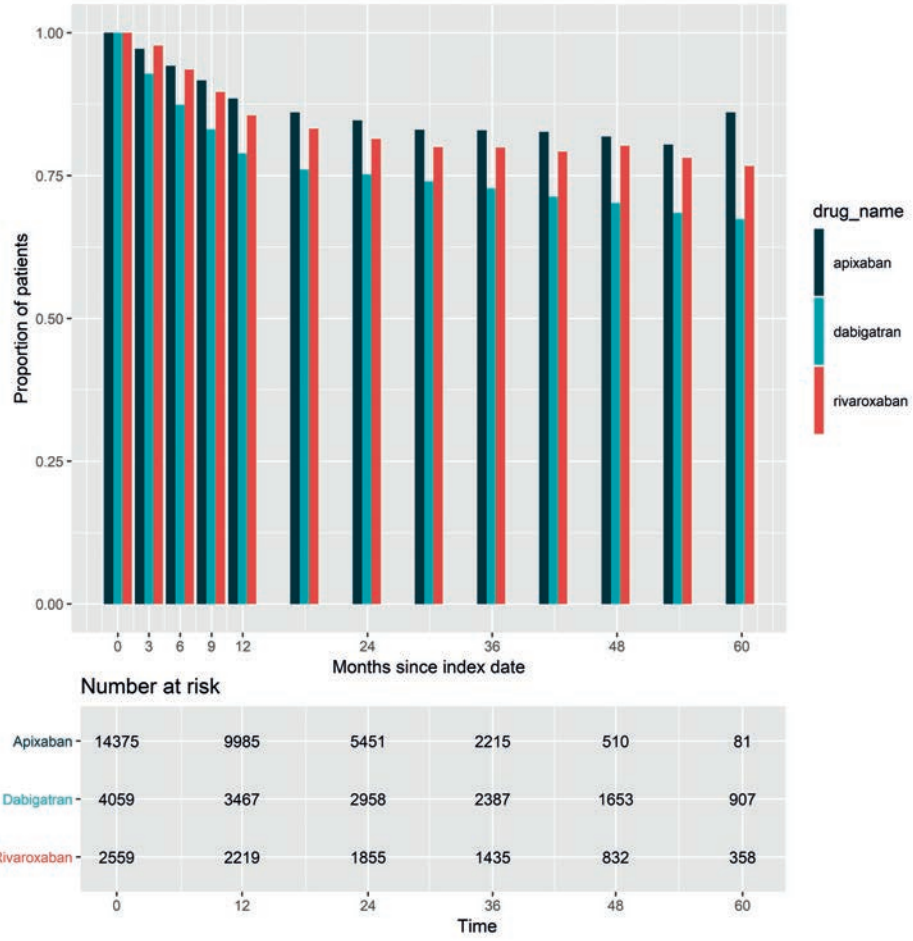
Appendix figure 2. Kaplan Meier curve for follow-up time of all patients in the cohort. FU: follow-up.



Appendix figure 3a. Number of persistent users and proportion of patients on treatment at each interval when excluding patients with a CHA_2DS_2-VASc score below 2. The numbers below represent the number of patients that are in the cohort at the beginning of each interval.



Appendix figure 3b. Proportion of patients in each category of the mean possession rate for each interval during follow-up when excluding patients with a CHA_2DS_2-VASc score below 2. MPR: mean possession rate.



Appendix figure 4. Number of persistent users and proportion of patients on treatment at each interval during follow-up stratified per NOAC. The numbers below represent the number of patients that are in the cohort at the beginning of each interval.

2.6

PERSISTENCE AND ADHERENCE TO NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANT TREATMENT IN PATIENTS WITH ATRIAL FIBRILLATION ACROSS FIVE WESTERN EUROPEAN COUNTRIES

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ABSTRACT

Aim

To assess persistence and adherence to non-vitamin K antagonist oral anticoagulant (NOAC) treatment in patients with atrial fibrillation (AF) in five Western European healthcare settings.

Methods

We conducted a multi-country observational cohort study, including 559 445 AF patients initiating NOAC therapy from Stockholm (Sweden), Denmark, Scotland, Norway, and Germany between 2011 and 2018. Patients were followed from their first prescription until they switched to a vitamin K antagonist, emigrated, died, or the end of follow-up. We measured persistence and adherence over time and defined adequate adherence as medication possession rate ≥90% among persistent patients only.

Results

Overall, persistence declined to 82% after one year and to 63% after five years. When including restarters of NOAC treatment, 85% of the patients were treated with NOACs after five years. The proportion of patients with adequate adherence remained above 80% throughout follow-up. Persistence and adherence were similar between countries and was higher in patients starting treatment in later years. Both first year persistence and adherence were lower with dabigatran (persistence: 77%, adherence: 65%) compared to apixaban (86% and 75%) and rivaroxaban (83% and 75%) and were statistically lower after adjusting for patient characteristics. Adherence and persistence with dabigatran remained lower throughout follow-up.

Conclusion

Persistence and adherence were high among NOAC users in five Western European healthcare settings and increased in later years. Dabigatran use was associated with slightly lower persistence and adherence compared to apixaban and rivaroxaban.

INTRODUCTION

To prevent stroke in patients with non-valvular atrial fibrillation (AF), non-vitamin K antagonist oral anticoagulants (NOACs) are recommended as first line antithrombotic treatment [1]. Randomised clinical trials have shown comparable efficacy and safety profiles of NOACs compared to vitamin K antagonists (VKAs) [2], but, among other advantages, NOACs do not require regular monitoring of their anticoagulative effect. The lack of regular monitoring, as is required with VKAs, has led to concerns about lower persistence and adherence with NOACs than with VKAs [1]. Thus, guidelines stress the importance of active promotion of adherence and persistence in patients on NOAC treatment by discussing these issues with patients.

Several single-centre studies have assessed the persistence and adherence to NOAC treatment [3]. Persistence refers to whether a patient continues treatment after initiation, while adherence refers to whether a patient takes the treatment as prescribed [4]. Currently reported results on persistence and adherence to NOAC treatment vary considerably; a recent systematic review, based on 23 publications, reports persistence after 12 months ranging from 45% to 88%, and adherence in the first 6 months ranging from 48% to 92% [3]. Furthermore, there is an ongoing debate whether once or twice daily dosing of NOACs is preferable in terms of adherence [5]. A lower number of doses per day is zgenerally associated with increased adherence, but, on the other hand, once daily dosing of NOACs may be less forgiving in patients with low adherence, given their relatively short half-lives [5] .

Comparisons of results from different studies on adherence and persistence are challenged by variations in essential definitions, e.g. for treatment discontinuation. Furthermore, studies vary in how they measure adherence and handle stockpiling. As such, large-scale studies applying a consistent methodology to estimate adherence and persistence across different healthcare settings, thereby generating comparable and generalizable data, are warranted. In addition, most persistence and adherence studies were conducted shortly after the NOACs were introduced to the market, and studies showing how persistence and adherence have evolved over time are scarce.

Being able to adequately describe adherence and persistence with different NOACs is important for both clinicians and policy makers in order to show where efforts are warranted to improve treatment, especially since large-scale studies comparing the different NOACs are lacking. Adequate adherence and persistence with NOACs for stroke prevention is essential, as shown by two recent publications in which adherence above 90% gave optimal stroke prevention, while both non-persistence and lower adherence were associated with two-fold increases in the risk of stroke [6, 7]. This makes the comparison of persistence and adherence between NOACs an essential aspect of the overall relative comparative effectiveness in this drug class.

Therefore, the aim of the current study was to assess persistence and adherence with NOAC treatment, overall and by specific drug, in patients with AF using large healthcare databases from five Western European healthcare settings.

METHODS

Setting

We analysed data from five Western European healthcare settings: Denmark, Norway, Scotland, Germany and the Stockholm Region in Sweden. All data sources are described in detail elsewhere and an overview is provided in Appendix Table 1. In short, each data source contains data on dispensed prescriptions and secondary care diagnoses, except for Germany where there is no distinction between primary and secondary care, but only between inpatient and outpatient care, which are both captured in the data source (see Appendix Table 1). Data from Stockholm also include diagnoses from primary care. The data from Stockholm, Denmark, Norway, and Scotland cover unselected populations from an entire region/country, while the data from Germany cover unselected populations from four statutory health insurances in Germany (~20% of the German population overall).

Patient selection

Patients were included in the cohort when they claimed their first prescription of a NOAC, after a washout period of one year, between April 2011 (European Medicine's Agency approval date for dabigatran) and the end of data availability (2018 for Stockholm, Denmark, and Norway; 2017 for Scotland and Germany). The first prescription claim date was considered the index date (see Appendix Figure 1). We only included patients with a recorded diagnosis of AF prior to or on the date of their first NOAC claim. Patients assumed to use their NOAC for other reasons than AF were excluded. Specifically, we excluded patients with a diagnosis of deep venous thromboembolism or pulmonary embolism or a procedure code for knee/hip replacement surgery in the 30 days before and after the index date, or for whom a prescription was linked to these procedures (for Norway only). We followed patients until they claimed a VKA prescription, died, moved out of the country/region, reached the end of data availability, or reached the maximum follow-up time of five years.

We measured the baseline medication use in the six months prior to index date, and comorbidities in the five years prior to index date. For baseline medication, we searched for prescriptions of VKA, low-dose aspirin, P2Y12-inhibitors, NSAIDs, corticosteroids, diuretics, beta-blockers, calcium channel blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors, statins, oral antidiabetics, insulin, and antidepressants. For comorbidities, we searched for components of the CHA_2DS_2-VASc and modified HAS-BLED scores (without labile INR): heart failure, hypertension, prior stroke/TIA/embolism, vascular disease, diabetes; renal disease, liver disease, prior bleed, anaemia, and alcohol abuse.

Follow-up time was partitioned into six-month intervals, and persistence and adherence were calculated for each interval in patients for which data was available in the specific interval. In the first year of treatment, we partitioned the follow-up time into three-month intervals, as changes in persistence and adherence are common during the first year of treatment.

Persistence

We considered patients to be persistent (i.e., continuing the treatment) when they claimed a NOAC prescription within 91 days after the end of the estimated duration of a prior prescription (see

Appendix Figure 1). We calculated the duration of a prescription by dividing the quantity dispensed by the recommended dose for each NOAC (once daily for rivaroxaban and edoxaban, twice daily for dabigatran and apixaban). In addition, if patients had tablets/capsules of the same NOAC available from prior prescriptions (i.e., stockpiling), we added those to the supply of a following prescription, with a maximum of 61 days added to a prescription [8]. If a patient claimed a different NOAC during follow-up than the NOAC the patient started with, we considered the patient to be on continued NOAC treatment with the initially started NOAC (intention to treat analysis). If a patient switched, potential stockpiling from prior prescriptions was disregarded, and we assumed the patient started with the new prescription on the first day of claiming it. If a patient failed to reclaim a NOAC prescription within the given limits, we considered the patient to be non-persistent. The date of non-persistence was set at the calculated end of the last prescription plus a permissible gap of 91 days. We calculated the proportion of patients in the cohort that was persistent on the first day of each follow-up interval.

Besides persistence, we also measured the proportion of patients in the cohort on treatment on the first day of each follow-up interval to obtain treatment coverage [9]. Using this approach, we also captured patients who restarted NOAC treatment after having stopped the treatment for a while, as discontinuation did not lead to censoring.

Adherence

During the time a patient was persistent with the treatment, we calculated the adherence. Adherence was only measured in persistent patients as it cannot meaningfully be calculated in non-persistent patients. We used the medication possession rate (MPR) to quantify adherence [8]. The MPR was calculated by dividing the number of days in which a patient had the drug available by the number of days in each interval. Again, we took stockpiling from previous prescriptions into account. For each time-point during follow-up, we assessed the proportion of persistent patients with an MPR ≥ 90%. We chose the MPR cut-off of 90%, as adherence below 90% has been found to be associated with reduced stroke protection [6, 7].

Persistence and adherence over time and across NOACs

For each calendar-year of inclusion into the study, we measured the proportion of patients persistent after one year and the proportion of patients with an MPR ≥ 90% during their first year of treatment, to analyse if and how persistence and adherence changed over time. We excluded patients with a follow-up of less than one year for this analysis. We used the same approach to describe first-year persistence and adherence with the different NOACs. As edoxaban was only recently introduced to the market and had few users, we discarded edoxaban from this analysis.

Statistical analysis

We used a common data model to analyse data from the databases available in the different centres (specifications from the common data model are available from the authors at request). All databases included comparable data, coded in a similar manner. Therefore, the common data model only required information on renaming variables. The same R-script for the generation of

the analytical datasets and conduct of the statistical analyses was used in all databases, to ensure identical analyses in the different centres. The R-script was sent to all centres, and therefore all individual data stayed locally, and only the final results (descriptive characteristics, point estimates) left the centre.

We used descriptive statistics to describe the cohorts and persistence and adherence over time. To analyse whether first year persistence and adequate first year adherence (i.e., MPR ≥ 90%) differed between the NOACs, we used logistic regression. The dependent variable in the model was either persistence after one year or adequate adherence (i.e., MPR ≥ 90%) during the first year. We included the different NOACs as an independent categorical variable in the model with apixaban as the reference NOAC, and adjusted for age, sex, the aforementioned covariates on baseline medication and comorbidity, and year of inclusion. Using the same model, we also evaluated whether adherence and persistence changed over time. We excluded patients initiated on edoxaban from these analyses due to small sample size.

All statistical analyses were performed with the statistical software R. We used the 'AdhereR' package to create treatment episodes.

Sensitivity analyses

There might be a lag in the recording of AF diagnoses, especially for databases with only secondary care data [10]. Therefore, we performed a sensitivity analysis in which we also included patients with an AF diagnosis in the 91 days after their first NOAC prescription, instead of only patients with an AF diagnosis prior to or on the date of the first NOAC prescription.

The Stockholm Healthcare database had access to both primary and secondary care data and this might result in a patient population different from the other data sources due to the additional data availability. To assess if this affected the results, we performed a sensitivity analysis in which we only included data from secondary care in Stockholm and compared this to the main analysis from Stockholm with both primary and secondary care data.

RESULTS

In total, we included 555 943 patients claiming a first NOAC. The largest cohort (n = 290 043) was from the German database and the smallest (n = 34 837) was from the Stockholm database (Table 1 and Supplementary Table 2). The median follow-up was more than one year (data not shown), there were fewer female than male patients, and the mean age was approximately 75 years in all countries. In Stockholm, Scotland, and Norway, apixaban was prescribed to more than 50% of the new NOAC users. The proportion of patients initiated with dabigatran varied markedly, from 4% in Scotland to 29% in Denmark. In Germany, most patients were initiated on rivaroxaban (51% of all first prescriptions), while in Denmark, there was no clearly preferred NOAC. Edoxaban comprised a small proportion of all prescriptions across all countries (≤ 5%). During follow-up, 8.0% of the patients switched to warfarin and were censored from further analysis. Switchers to warfarin decreased from 21.9% of all patients initiated on a NOAC in 2011 to 1.4% in 2018.

The stroke risk according to CHA_2DS_2-VASc was similar in all countries. The mean CHA_2DS_2-VASc score ranged from 2.9 in Denmark to 3.7 in Germany, and more than 50% of the patients had

a CHA_2DS_2-VASc score between 2 and 4 in all countries. The bleeding risk according to modified HAS-BLED scores ranged from 1.9 in Denmark to 2.4 in Germany, and more than 50% of the patients had HAS-BLED scores of 1-2 in all countries (Table 1). Approximately 30% claimed a VKA and 30% claimed aspirin in the 6 months prior to index date in all countries except for Germany, where only 20% had claimed a VKA and 12% aspirin.

Persistence declined steadily to 82% after one year and 63% after five years, in patients for whom data was available (Figure 1A). Among patients who were persistent, more than 75% had an MPR ≥ 90% which remained stable from one year of follow-up onwards (Figure 1B). The rate declined sharply and moved back up in the beginning of follow-up, as non-persistence and non-adherence can overlap during that period. The proportion of patients treated with a NOAC, i.e., all patients classified as on therapy at the beginning of a given time period and thus including restarts, dropped to 85% after one year and remained stable at that level (Figure 1C).

Table 1. Summary of baseline characteristics of patients included per database. Full baseline characteristics with all comorbidities and comedication can be found in Appendix table 1. SD, standard deviation; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist

	Stockholm	Denmark	Scotland	Norway	Germany
Number of patients	34 837	97 077	35 934	98 052	290 043
Female (%)	15725 (45.1%)	43804 (45.1%)	17015 (47.4%)	41057 (41.9%)	139121 (48.0%)
Age					
Years, mean (SD)	74.64 (11.00)	74.75 (11.07)	75.15 (10.94)	74.74 (10.82)	74.44 (10.68)
0-64	5492 (15.8%)	15717 (16.2%)	5586 (15.5%)	15172 (15.5%)	47257 (16.3%)
65 - 74	11242 (32.3%)	30259 (31.2%)	9677 (26.9%)	31574 (32.2%)	80166 (27.6%)
75 - 84	11267 (32.3%)	31439 (32.4%)	13478 (37.5%)	31883 (32.5%)	115180 (39.7%)
≥ 85	6836 (19.6%)	19662 (20.3%)	7193 (20.0%)	19423 (19.8%)	47440 (16.4%)
Baseline treatment					
VKA	10188 (29.2%)	27011 (27.8%)	12819 (35.7%)	26304 (26.8%)	59185 (20.4%)
Aspirin	9528 (27.4%)	28241 (29.1%)	11071 (30.8%)	35840 (36.6%)	33401 (11.5%)
NOAC of inclusion					
Apixaban	23547 (67.6%)	33447 (34.5%)	20932 (58.3%)	51754 (52.8%)	88275 (30.4%)
Dabigatran	6301 (18.1%)	28025 (28.9%)	1449 (4.0%)	20387 (20.8%)	38860 (13.4%)
Edoxaban	98 (0.3%)	1746 (1.8%)	78 (0.2%)	752 (0.8%)	14552 (5.0%)
Rivaroxaban	4891 (14.0%)	33859 (34.9%)	13475 (37.5%)	25159 (25.7%)	148356 (51.1%)
CHA_2DS_2-VASc					
mean (SD)	3.10 (1.80)	2.94 (1.67)	3.20 (1.74)	2.96 (1.66)	3.70 (1.93)
0	2041 (5.9%)	5726 (5.9%)	1937 (5.4%)	5644 (5.8%)	11855 (4.1%)
1	4713 (13.5%)	13272 (13.7%)	4030 (11.2%)	12986 (13.2%)	26267 (9.1%)
2 - 4	20513 (58.9%)	61130 (62.8%)	21769 (60.6%)	62156 (63.4%)	152306 (52.5%)
≥ 5	7570 (21.7%)	16949 (17.5%)	8193 (22.8%)	17266 (17.6%)	99615 (34.3%)
HAS-BLED					
mean (SD)	1.96 (1.13)	1.90 (1.11)	2.06 (1.14)	1.95 (1.10)	2.37 (1.31)
0	2659 (7.6%)	7655 (7.9%)	2290 (6.4%)	6947 (7.1%)	16636 (5.7%)
1 - 2	21738 (62.4%)	63133 (65.0%)	22015 (61.3%)	63233 (64.5)	146916 (50.7%)
≥ 3	10440 (30.0%)	26288 (27.1%)	11624 (32.3%)	27872 (28.4%)	126491 (43.6%)

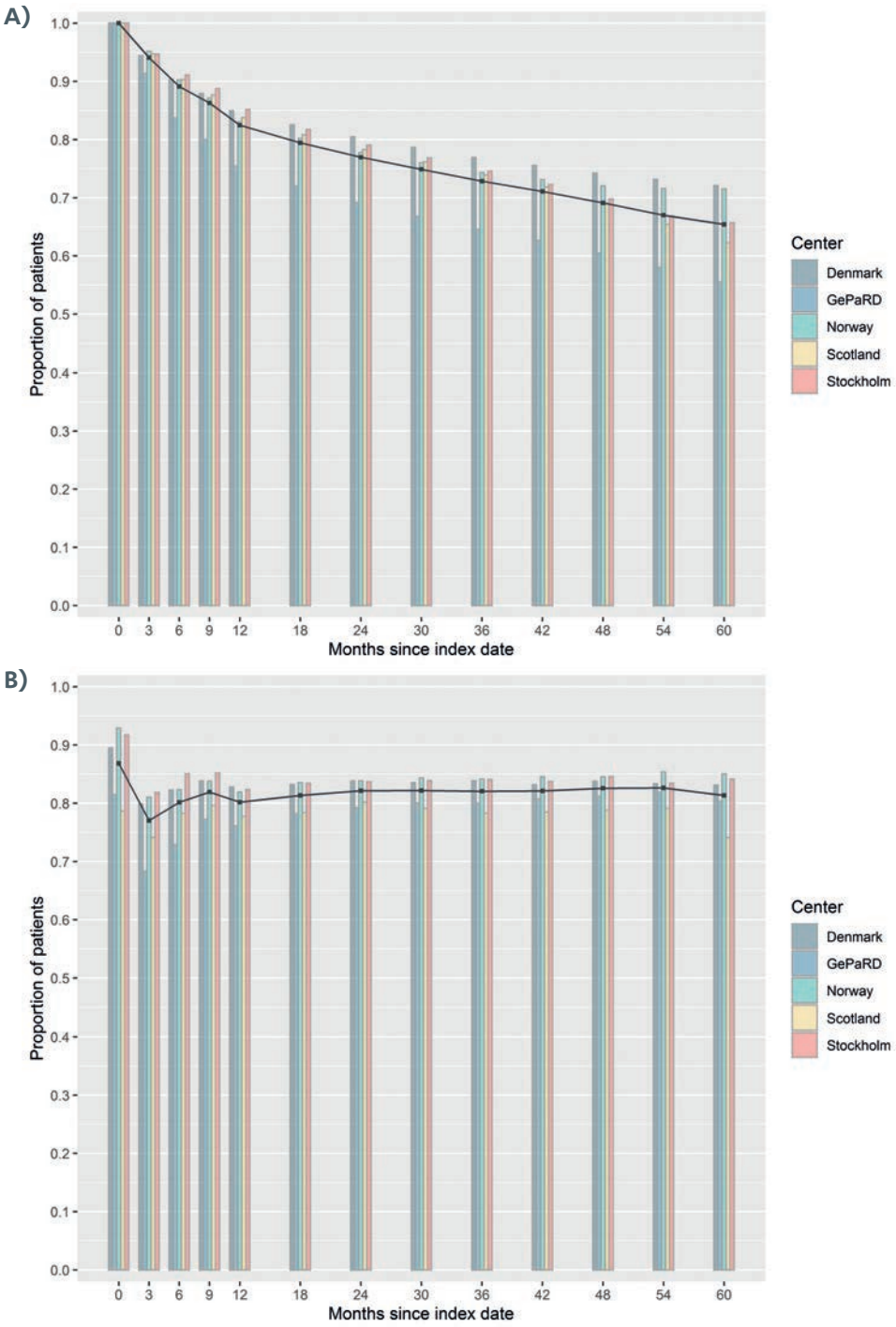

Figure 1A-C. Proportion of patients during follow-up overall and per country. The line is the average value in the five countries. The values on the x-axis represent the start of an interval. A: Persistence over time, B: Adequate adherence over time (i.e., MPR ≥ 90%), C: Patients on treatment over time including restarters.

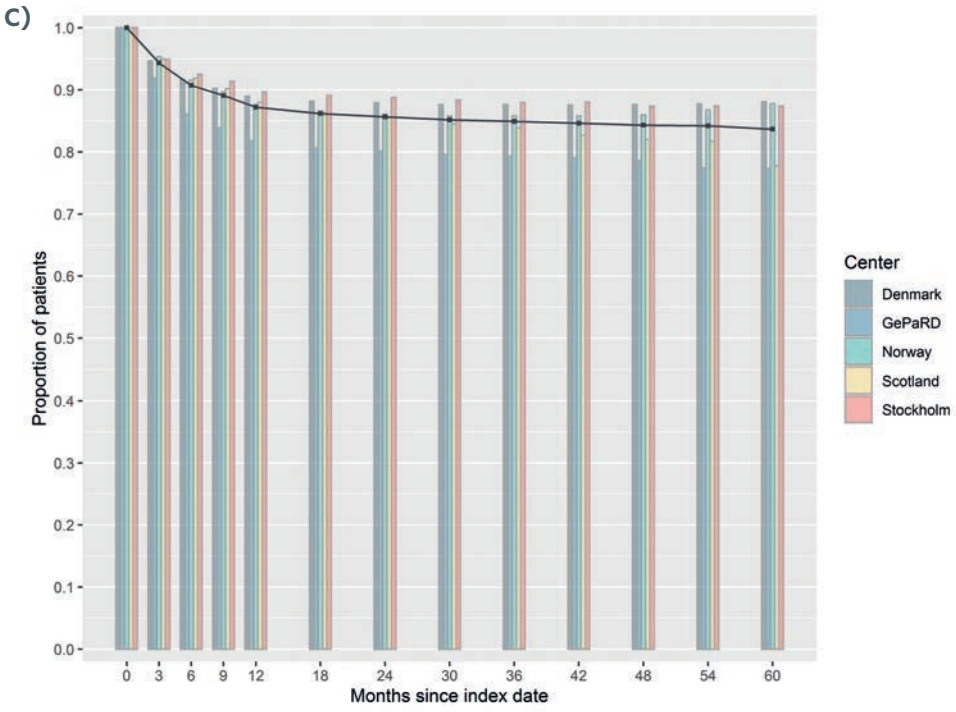

Figure 1A-C. (continued)

The proportion of patients that was persistent after one year of treatment increased in later calendar years (Figure 2A). Among patients initiating in 2011, 76% were on treatment after one year and this steadily increased to 84% of patients initiating in 2016 (and 87% in 2017, without data from Germany and Scotland). Results from logistic regression showed this gradual increase was statistically significant and independent of changes in baseline characteristics; there were significant increases in one-year persistence per calendar year in four of the five countries (Table 2). Only in Stockholm, where the proportion was already 87% in 2011, was there no further increase. The proportion of patients with adequate adherence (MPR ≥ 90%) during the first year of treatment increased from 62% in 2011 to 75% in 2016 (and 80% in 2017, without data from Germany and Scotland, Figure 2B). Again, the increase was statistically significant in all regions except Stockholm, where the rate was 81% in 2011 already.

The mean first-year persistence was 79% for dabigatran, 84% for rivaroxaban, and 86% for apixaban, and persistence continued to be highest with apixaban and lowest with dabigatran throughout follow-up (Figure 3A). After adjusting for covariates, apixaban was associated with a significantly higher one-year persistence than both rivaroxaban and dabigatran in all countries except Norway where there was no difference between apixaban and rivaroxaban (Table 2). The mean first-year adherence (MPR ≥ 90%) was 65% with dabigatran, 75% with apixaban, and 76% with rivaroxaban, and was highest for rivaroxaban and lowest for dabigatran throughout follow-up (Figure 3B). Apixaban and rivaroxaban use was associated with higher first-year adherence

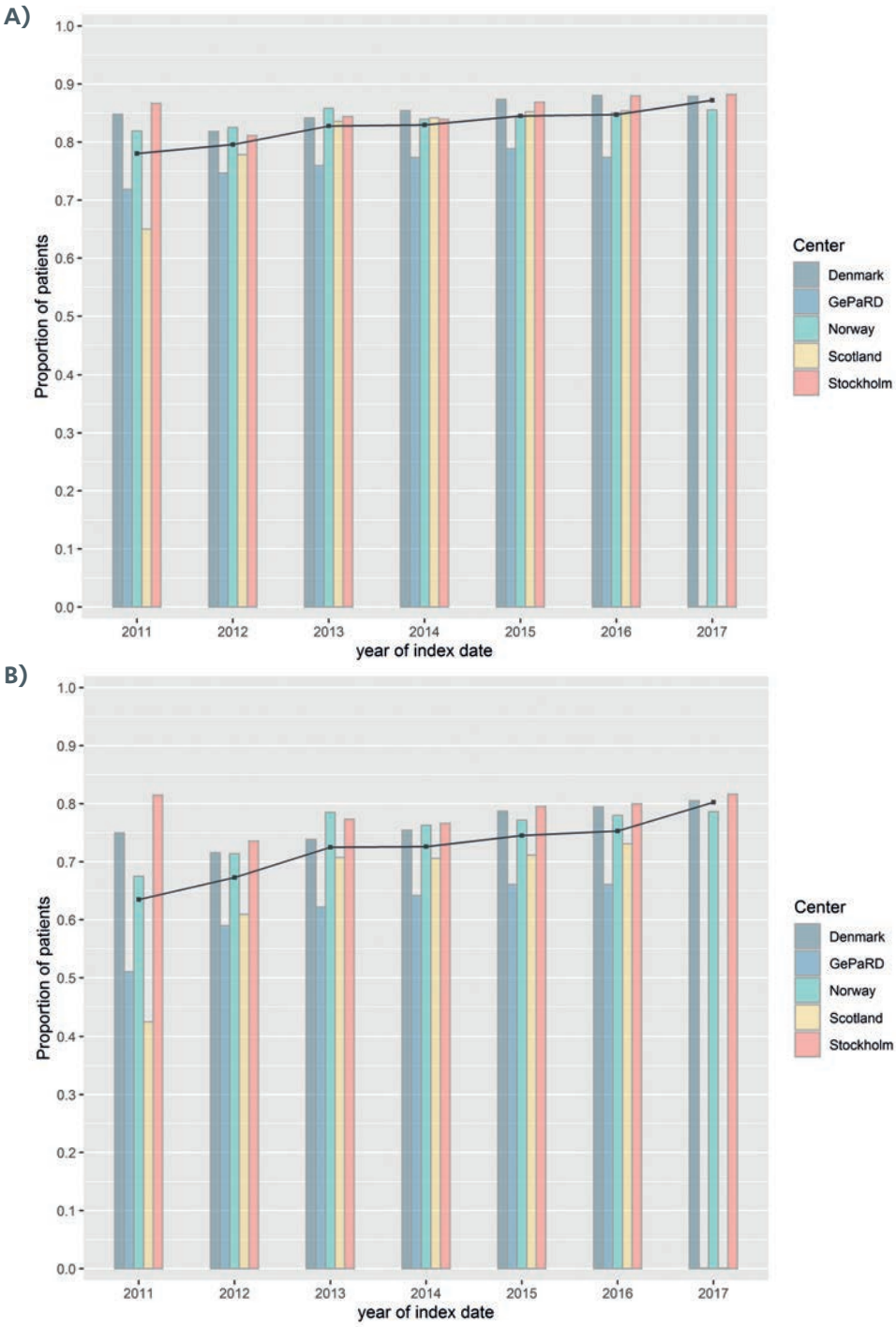

Figure 2A-B. Proportion of patients with at least one year of follow-up who were (A) persistent after one year of follow-up, or (B) had a medication possession rate ≥ 90% in their first year of follow-up, per calendar year per country. The line is the average proportion in the five countries.

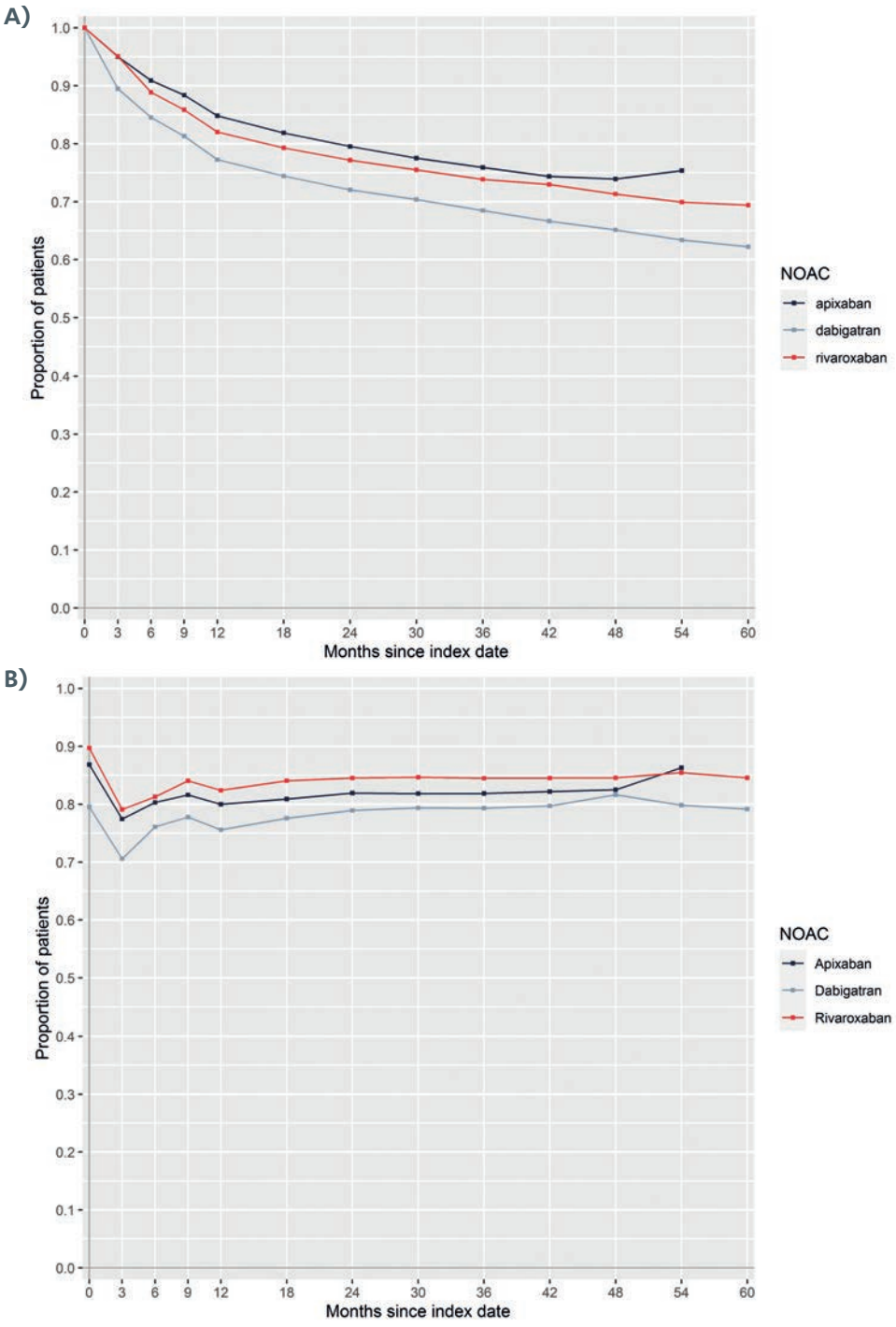

Figure 3A-B. (A) Proportion of persistent patients and (B) proportion of patients with a medication possession rate ≥ 90%, during follow-up per NOAC. Patients initiated on edoxaban were excluded given the limited sample size.

Table 2. Proportion of patients that were persistent or adequately adherent in their first year of treatment, and results from the logistic regression. The first three columns represent the crude proportion of patients that were persistent or adherent in their first year of treatment, per country. The last three columns show the odds ratios and 95% confidence intervals of being persistent or adherent comparing dabigatran to apixaban, comparing rivaroxaban to apixaban, and per increasing calendar year of index date. The logistic regression model was adjusted for age, sex, baseline comedication and comorbidities and year of inclusion. We removed edoxaban from this analysis, given the limited sample size.

	Persistent after 1 year						
	Apix	**Dabi**	**Riva**	**Dabi:apix**	**Riva:apix**	**Dabi:riva**	**Year increase**
Stockholm	0,89	0,80	0,85	0,56 (0,50-0,63)	0,66 (0,59-0,74)	1,24 (1,11-1,37)	1,01 (0,97-1,04)
Denmark	0,89	0,83	0,87	0,72 (0,67-0,77)	0,88 (0,83-0,94)	1,43 (1,36-1,52)	1,07 (1,05-1,09)
Scotland	0,87	0,75	0,83	0,44 (0,37-0,52)	0,71 (0,65-0,77)	1,75 (1,52-2,01)	1,04 (1,01-1,08)
Norway	0,85	0,82	0,86	0,80 (0,75-0,85)	1,00 (0,95-1,06)	1,53 (1,45-1,61)	1,04 (1,02-1,05)
Germany	0,80	0,76	0,76	0,89 (0,86-0,93)	0,91 (0,89-0,94)	1,38 (1,34-1,42)	1,09 (1,08-1,10)
Overall	0,86	0,79	0,84	*N/A*	*N/A*	*N/A*	*N/A*
	MPR > 90% in first year						
	Apix	**Dabi**	**Riva**	**Dabi:apix**	**Riva:apix**	**Dabi:riva**	**Year increase**
Stockholm	0,82	0,73	0,79	0,68 (0,62-0,75)	0,84 (0,77-0,93)	1,17 (1,04-1,32)	1,02 (0,99-1,04)
Denmark	0,79	0,72	0,80	0,78 (0,74-0,83)	1,12 (1,06-1,18)	1,23 (1,15-1,32)	1,06 (1,04-1,07)
Scotland	0,72	0,57	0,72	0,60 (0,52-0,69)	1,04 (0,97-1,11)	1,62 (1,38-1,90)	1,08 (1,05-1,11)
Norway	0,78	0,73	0,81	0,79 (0,75-0,84)	1,21 (1,15-1,27)	1,25 (1,18-1,33)	1,05 (1,03-1,07)
Germany	0,64	0,57	0,65	0,87 (0,84-0,90)	1,20 (1,17-1,23)	1,02 (0,99-1,06)	1,12 (1,11-1,13)
Overall	0,75	0,66	0,76	*N/A*	*N/A*	*N/A*	*N/A*

compared to dabigatran in all countries except Germany where there was no difference between rivaroxaban and dabigatran. Rivaroxaban use was associated with higher first-year adherence compared to apixaban in Denmark, Norway, and Germany, while in Stockholm rivaroxaban use was associated with lower adherence than apixaban, and in Scotland this association was neutral (Table 2). The lower adherence and persistence with dabigatran remained after stratifying on year of inclusion (Appendix Figures 2 and 3).

Including patients with an AF diagnosis registered during the first 91 days after NOAC initiation led to a higher number of patients included; the increase was largest in Denmark with 11% more patients, and smallest in Norway with only 1% more patients. Baseline characteristics and persistence were similar when using this extended patient selection (Supplementary Table 3). Restricting the Stockholm data to only secondary care yielded 4 349 fewer patients (-12%) but had no impact on baseline characteristics or estimates of persistence.

DISCUSSION

In this large cross-national population-based cohort study of 559 445 European AF patients on NOAC treatment, we found that both persistence and adherence were high. When taking restarters

of treatment into account, more than 80% of patients remained on treatment throughout five years of follow-up. Both persistence and adherence during the first year of treatment increased in later years, independently of changing baseline covariates. Early discontinuation of NOAC therapy was more common among dabigatran and rivaroxaban users compared to apixaban users. In persistent patients, 80% of them had an MPR ≥ 90% during follow-up. When comparing adherence with the different NOACs, dabigatran had the lowest MPR in all countries and rivaroxaban performed slightly better than apixaban, although this was not visible in all five countries.

Comparing the different NOACs after adjustment for baseline characteristics, we found both lower persistence and adherence with dabigatran compared to the other two NOACs. In general, a low number of doses per day is usually associated with better adherence, and the adherence was substantially better for rivaroxaban (once daily) compared to dabigatran (twice daily) in agreement with this notion. However, adherence rates with apixaban (twice daily) and rivaroxaban differed little. This is in line with randomized trial data, showing that persistence with apixaban and rivaroxaban was comparable to warfarin after approximately two years, but the rates were statistically lower when comparing dabigatran to warfarin (79% vs 83%) [11–13]. Some factors that could explain the lower persistence with dabigatran are, first, dyspepsia, a known side effect of dabigatran and a cause for treatment discontinuation [14]. Second, dabigatran was the first approved NOAC for use during cardioversion and ablation [15], which can be an indication for short term use. Finally, dabigatran cannot be repackaged to other dispensing systems, which are known to improve adherence [16].

Persistence and adherence were both high. At the end of follow-up, approximately 63% of the patients were persistent with the initial treatment without a treatment break, but many patients resumed NOAC treatment after a break and more than 80% were actually NOAC treated during the follow-up. In persistent patients, 20% of them had inadequate adherence with an MPR < 90%. Previous work has shown that both non-persistence and inadequate adherence are associated with two-fold increases in the risk for stroke [7]. Therefore, additional efforts are needed to optimize these important aspects of treatment, especially in patients initiated on dabigatran [17].

Our study has several strengths. First, this is, to our knowledge, the first multi-country persistence and adherence study using a common protocol, a common data model, and centrally developed programming scripts. This makes it possible to obtain valid comparisons between countries as the comparability is not influenced by study design, analytical choices or variation in programming. This is especially important in persistence and adherence studies, as there are numerous ways to measure these parameters, which can influence study results considerably [4, 8]. Second, we used data from five Western European healthcare systems and found consistent results, making our results generalizable to other countries with similar healthcare systems. Third, we examined adherence and persistence separately, as they are two different phenomena. Without distinction between them, adherence will be underestimated among patients who stopped treatment and they will inadvertently have extremely low adherence. In addition, we used advanced methods to measure persistence and adherence, taking stockpiling from previous prescriptions into account.

Our study has some limitations. First, our study relied on pharmacy claims data, assuming that patients claiming their prescriptions are truly taking the treatment, which may not always be

the case. However, if patients do not redeem new prescriptions, it is very likely that they have indeed stopped treatment. The same goes for adherence; if a patient claims too little of the medication within a given timespan, it is very unlikely the patient is taking the drug as prescribed. In addition, there may be some differences amongst countries in prescription regulations and reimbursement systems, as well as coding practices. Second, the prevalence of diseases may partly have been over- or underestimated. Especially in Germany, where algorithms with a high sensitivity, but a low specificity were used to assess comorbidities, which could explain the higher overall comorbidity prevalence in Germany. Third, we did not have data on reasons for discontinuation. In some instances, a severe bleed can be a reason for treatment discontinuation [1, 18]. Prior work from Denmark and Stockholm has shown that 7.6% and 6.5% of the patients stopping treatment suffered a severe bleed [7, 19]. Fourth, we censored patients when they claimed a VKA prescription, therefore we have no data on whether patients actually continued treatment with an oral anticoagulant after a switch.

In conclusion, in more than half a million AF patients initiated on NOAC therapy from five Western European healthcare settings, both adherence and persistence were high and increasing in later years, which is important given the increased risk for stroke associated with non-persistence and poor adherence. Dabigatran users had lower persistence and adherence compared to apixaban and rivaroxaban users, after taking baseline characteristics into account. This finding indicates a need for additional monitoring and efforts to remain on treatment in patients initiated on dabigatran.

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APPENDICES

Appendix table 1. Description of databases.

	Origin	Data available from	Sample / full population	Sample size
Stockholm Healthcare Database	Stockholm County	July 2010	Full population	2.3 million
Danish National Registries	Denmark	1995	Full population	5.6 million
Norwegian National Registries	Norway	2004	Full population	5.3 million
Scotland	NHS Scotland	January 2009 (until 12.2017)	Full population	5.3 million
Germany	Germany	2004	20%	~25 million[1]

	Pharmacy data coding	Dispensing / Prescribed	Diagnostic data	Primary and/or secondary care
Stockholm Healthcare Database	ATC code	Dispensed medication	ICD	Primary and secondary (inpatient and outpatient)
Danish National Registries	ATC code	Dispensed medication	ICD	Secondary (inpatient and outpatient)
Norway	ATC code	Dispensed medication	ICD10	Secondary (inpatient and outpatient)
Scotland	BNF code (manually added ATC code)	Dispensed medication	ICD10	Secondary care (inpatient and outpatient)
Germany	ATC code	Dispensed medication	ICD 10 GM	Inpatient and outpatient[2]

Appendix table 1. (continued)

	Typical prescription length	Medication Reimbursement
Stockholm Healthcare Database	90 days	Fully reimbursed, after yearly co-payment
Danish National Registries	90-120 days	Increasing reimbursement with additional purchases. Maximum yearly self-payment of ~500€.
Norway	90 days	Initially ~62% reimbursement then fully reimbursed when yearly patient co-payment limit reached (~210 Euro in 2018 for all expenses on drugs, physician visits)
Scotland	30-90 days (depending on whether the GP wants to check in with the patient more frequently for any reason)	There is no co-payment, all services – including prescription drugs – are free of charge (patients have to pay for OTC drugs if they don't have a prescription though).
Germany	90 -100 days	There is a co-payment for each medicine, max 10€, depends on price of the drug. Patients can be exempt from co-payment if a limit of 2% of the gross income is reached, or 1% in case of chronically ill patients.

[1] It includes information on approximately 25 million persons who have been insured with one of the participating providers since 2004 or later. The sample size of 25 million people in GePaRD overall does not correspond to the 20% of the general population. Per data year, there is information on approximately 20% of the general population (i.e. about 17-20 million people based on a current population if ~ 83 million in Germany) and all geographical regions of Germany are represented.

[2] Distinction in primary and secondary care is not applicable to Germany. There is a free choice of providers. When using German claims data, one typically distinguishes between inpatient and outpatient setting. It is possible to determine the medical specialty of the physicians in the outpatient setting. There is no exact date of diagnoses in the ambulant setting. Therefore, the date is determined indirectly. In the outpatient setting, physicians are expected to code the disease(s) for which they treat their patients, and thus the indications for drugs, once per quarter. Outpatient diagnosis codes are thus available on a quarterly basis, while an exact date is available for inpatient visits. If there was only one outpatient visit per quarter, the diagnosis can be assigned to this visit. If the date was not available, the date was set to the beginning of the quarter.

Appendix table 2. Full baseline characteristics of patients included per database.

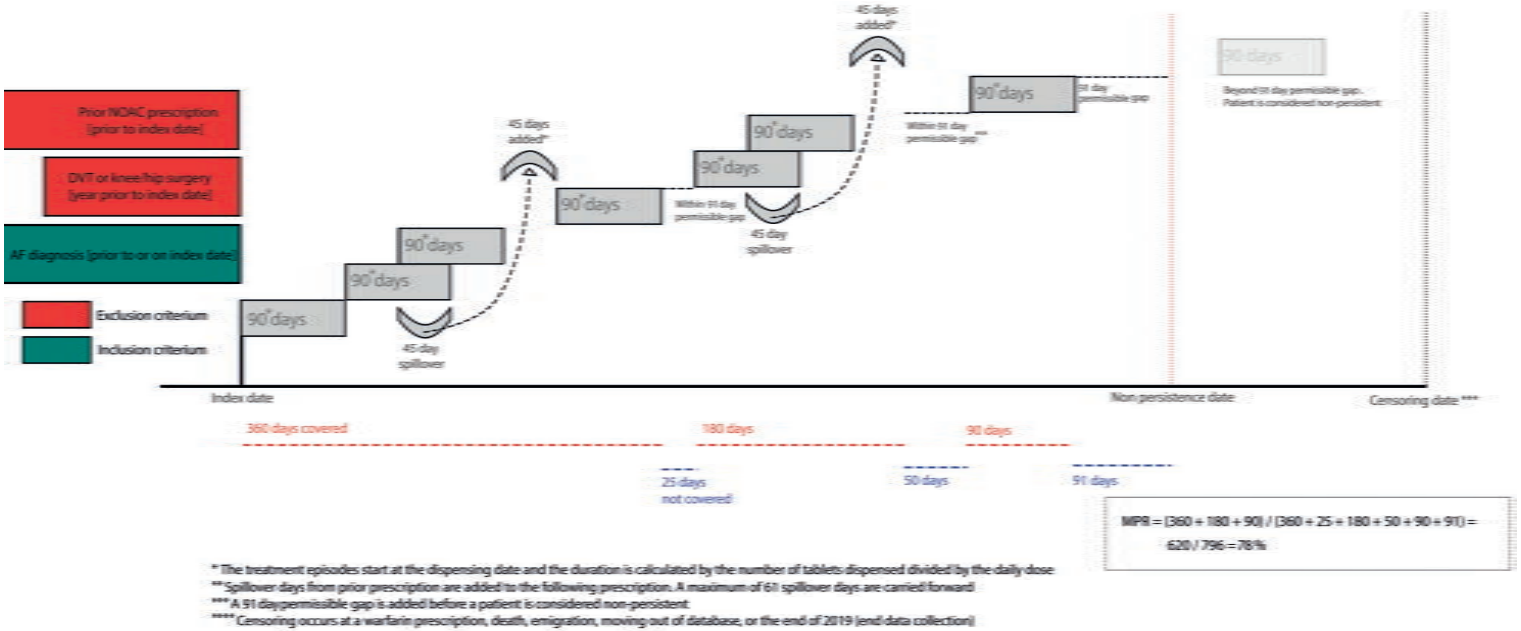
	Stockholm	Denmark	Scotland	Norway	Germany
Number of patients	34 837	97 077	35 934	98 052	290 043
Female (%)	15725 (45.1%)	43804 (45.1%)	17015 (47.4%)	41057 (41.9%)	139121 (48.0%)
Age					
mean (SD)	74.64 (11.00)	74.75 (11.07)	75.15 (10.94)	74.74 (10.82)	74.44 (10.68)
0-64	5492 (15.8%)	15717 (16.2%)	5586 (15.5%)	15172 (15.5%)	47257 (16.3%)
65 - 74	11242 (32.3%)	30259 (31.2%)	9677 (26.9%)	31574 (32.2%)	80166 (27.6%)
75 - 84	11267 (32.3%)	31439 (32.4%)	13478 (37.5%)	31883 (32.5%)	115180 (39.7%)
≥ 85	6836 (19.6%)	19662 (20.3%)	7193 (20.0%)	19423 (19.8%)	47440 (16.4%)
NOAC of inclusion					
Apixaban	23547 (67.6%)	33447 (34.5%)	20932 (58.3%)	51754 (52.8%)	88275 (30.4%)
Dabigatran	6301 (18.1%)	28025 (28.9%)	1449 (4.0%)	20387 (20.8%)	38860 (13.4%)
Edoxaban	98 (0.3%)	1746 (1.8%)	78 (0.2%)	752 (0.8%)	14552 (5.0%)
Rivaroxaban	4891 (14.0%)	33859 (34.9%)	13475 (37.5%)	25159 (25.7%)	148356 (51.1%)
CHA_2DS_2-VASc					
mean (SD)	3.10 (1.80)	2.94 (1.67)	3.20 (1.74)	2.96 (1.66)	3.70 (1.93)
0	2041 (5.9%)	5726 (5.9%)	1937 (5.4%)	5644 (5.8%)	11855 (4.1%)
1	4713 (13.5%)	13272 (13.7%)	4030 (11.2%)	12986 (13.2%)	26267 (9.1%)
2 - 4	20513 (58.9%)	61130 (62.8%)	21769 (60.6%)	62156 (63.4%)	152306 (52.5%)
≥ 5	7570 (21.7%)	16949 (17.5%)	8193 (22.8%)	17266 (17.6%)	99615 (34.3%)
HAS-BLED					
mean (SD)	1.96 (1.13)	1.90 (1.11)	2.06 (1.14)	1.95 (1.10)	2.37 (1.31)
0	2659 (7.6%)	7655 (7.9%)	2290 (6.4%)	6947 (7.1%)	16636 (5.7%)
1 - 2	21738 (62.4%)	63133 (65.0%)	22015 (61.3%)	63233 (64.5)	146916 (50.7%)
≥ 3	10440 (30.0%)	26288 (27.1%)	11624 (32.3%)	27872 (28.4%)	126491 (43.6%)
Hypertension	16015 (46.0%)	32330 (33.3%)	12163 (33.8%)	33212 (33.9%)	196620 (67.8%)
Anaemia	2306 (6.6%)	5382 (5.5%)	2300 (6.4%)	6364 (6.5%)	39031 (13.5%)
Liver disease	256 (0.7%)	777 (0.8%)	535 (1.5%)	815 (0.8%)	10947 (3.8%)
Renal disease	1591 (4.6%)	3350 (3.5%)	4104 (11.4%)	6224 (6.3%)	47970 (16.5%)
Alcoholism	842 (2.4%)	1878 (1.9%)	1146 (3.2%)	1342 (1.4%)	5824 (2.0%)
Major bleed	3505 (10.1%)	9043 (9.3%)	2494 (6.9%)	10367 (10.6%)	41990 (14.5%)
Stroke/TIA/embolism	5416 (15.5%)	16214 (16.7%)	6359 (17.7%)	13569 (13.8%)	48526 (16.7%)
Heart failure	7207 (20.7%)	14954 (15.4%)	6299 (17.5%)	16823 (17.2%)	87484 (30.2%)
Vascular disease	5763 (16.5%)	18616 (19.2%)	10194 (28.4%)	24567 (25.1%)	90139 (31.1%)
Diabetes	5006 (14.4%)	11086 (11.4%)	5659 (15.7%)	13152 (13.4%)	57316 (19.8%)
Vitamin K antagonist	10188 (29.2%)	27011 (27.8%)	12819 (35.7%)	26304 (26.8%)	59185 (20.4%)
Aspirin	9528 (27.4%)	28241 (29.1%)	11071 (30.8%)	35840 (36.6%)	33401 (11.5%)
P2Y12	1269 (3.6%)	9009 (9.3%)	4345 (12.1%)	3754 (3.8%)	14248 (4.9%)
NSAID	3001 (8.6%)	12141 (12.5%)	6126 (17.0%)	12311 (12.6%)	63218 (21.8%)
Oral corticosteroid	3026 (8.7%)	8424 (8.7%)	6339 (17.6%)	10281 (10.5%)	27631 (9.5%)
Diuretic	9286 (26.7%)	37521 (38.7%)	15927 (44.3%)	22489 (22.9%)	104207 (35.9%)
Beta blocker	20910 (60.0%)	44666 (46.0%)	19871 (55.3%)	51313 (52.3%)	179356 (61.8%)
Ca channel blocker	8928 (25.6%)	25306 (26.1%)	10042 (27.9%)	22952 (23.4%)	71175 (24.5%)
RAAS inhibitor	14891 (42.7%)	43680 (45.0%)	16995 (47.3%)	46890 (47.8%)	176506 (60.9%)

Appendix table 2. (continued)

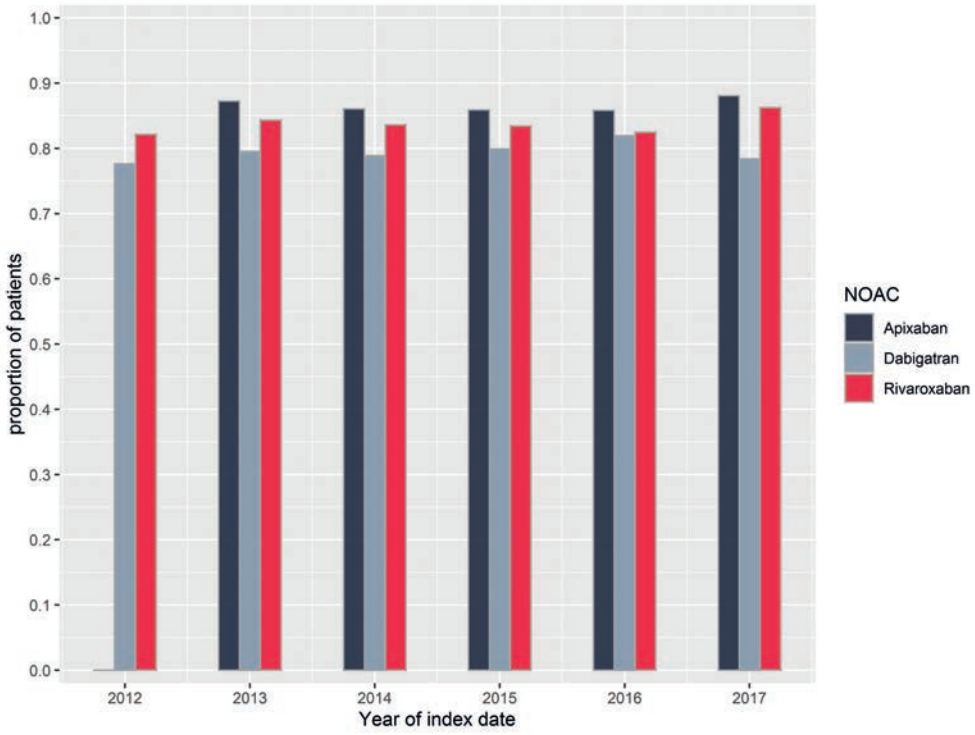
	Stockholm	Denmark	Scotland	Norway	Germany
Statin	10968 (31.5%)	36854 (38.0%)	18965 (52.8%)	40516 (41.3%)	86363 (29.8%)
Oral antidiabetic drug	3261 (9.4%)	11986 (12.3%)	4778 (13.3%)	9954 (10.2%)	38040 (13.1%)
Insulin	1920 (5.5%)	13246 (13.6%)	1403 (3.9%)	3500 (3.6%)	20272 (7.0%)
Antidepressant	4460 (12.8%)	13246 (13.6%)	7236 (20.1%)	9292 (9.5%)	34832 (12.0%)
Year of inclusion					
2011	169 (0.5%)	3448 (3.6%)	53 (0.1%)	655 (0.7%)	937 (0.3%)
2012	1126 (3.2%)	8018 (8.3%)	827 (2.3%)	2603 (2.7%)	30715 (10.6%)
2013	2617 (7.5%)	11069 (11.4%)	2257 (6.3%)	16072 (16.4%)	49516 (17.1%)
2014	3749 (10.8%)	12364 (12.7%)	5009 (13.9%)	13567 (13.8%)	51645 (17.8%)
2015	5763 (16.5%)	13289 (13.7%)	7959 (22.1%)	14943 (15.2%)	58799 (20.3%)
2016	6864 (19.7%)	15055 (15.5%)	9457 (26.3%)	16635 (17.0%)	65693 (22.6%)
2017	8220 (23.6%)	17878 (18.4%)	10372 (28.9%)	17350 (17.7%)	32738 (11.3%)
2018	6329 (18.2%)	15956 (16.4%)	NA	16227 (16.5%)	NA

Appendix table 3. Summary baseline characteristics and persistence rates of the main analysis and the sensitivity analysis which includes patients with an AF diagnosis in the 91 days after NOAC initiation in the different countries. The final part of the table shows the sensitivity analysis where Stockholm data was restricted to only secondary care.

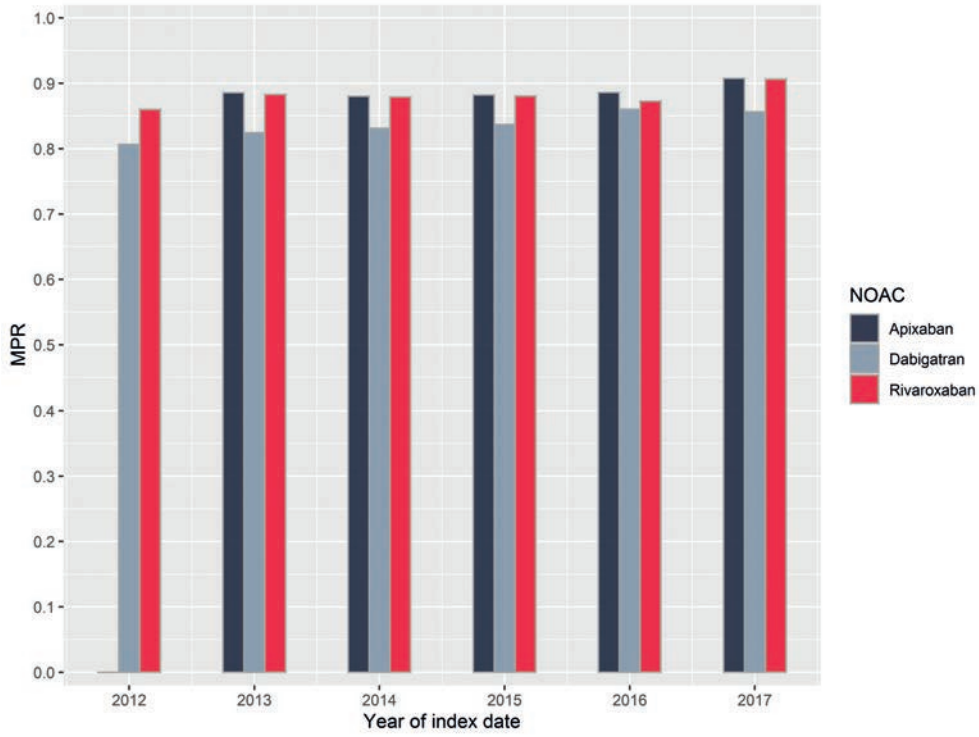
		Main	Sensitivity
Stockholm	n	34 837	36 540
	Mean age (sd)	74.64 (11.00)	74.59 (11.00)
	Female (%)	15725 (45.1%)	16467 (45.1%)
	Mean CHA2D2s-VASc-score (sd)	3.10 (1.80)	3.04 (1.80)
	Mean HAS-BLED score (sd)	1.96 (1.13)	1.91 (1.14)
	% persistent after year	0,85	0,85
Denmark	n	97 077	108 035
	Mean age (sd)	74.75 (11.07)	74.60 (10.98)
	Female (%)	43804 (45.1%)	47924 (44.4%)
	Mean CHA2D2s-VASc-score (sd)	2.94 (1.67)	2.81 (1.66)
	Mean HAS-BLED score (sd)	1.90 (1.11)	1.79 (1.11)
	% persistent after year	0,85	0,85
Scotland	n	35 934	38 150
	Mean age (sd)	75.15 (10.94)	74.92 (11.11)
	Female (%)	17015 (47.4%)	17905 (46.9%)
	Mean CHA2D2s-VASc-score (sd)	3.20 (1.74)	3.11 (1.75)
	Mean HAS-BLED score (sd)	2.06 (1.14)	1.98 (1.16)
	% persistent after year	0,84	0,83
Norway	n	98 052	99 055
	Mean age (sd)	74.74 (10.82)	74.68 (10.84)
	Female (%)	41057 (41.9%)	41344 (41.7%)
	Mean CHA2D2s-VASc-score (sd)	2.96 (1.66)	2.94 (1.66)
	Mean HAS-BLED score (sd)	1.95 (1.10)	1.93 (1.11)
	% persistent after year	0,83	0,83
Germany	n	290 043	303 963
	Mean age (sd)	74.44 (10.68)	74.44 (10.64)
	Female (%)	139121 (48.0%)	145462 (47.9%)
	Mean CHA2D2s-VASc-score (sd)	3.70 (1.93)	3.61 (1.94)
	Mean HAS-BLED score (sd)	2.37 (1.31)	2.30 (1.32)
	% persistent after year	0,75	0,75
Stockholm Secondary Only	n	34 837	30 488
	Mean age (sd)	74.64 (11.00)	74.59 (11.21)
	Female (%)	15725 (45.1%)	13783 (45.2%)
	Mean CHA2D2s-VASc-score (sd)	3.10 (1.80)	3.21 (1.83)
	Mean HAS-BLED score (sd)	1.96 (1.13)	2.02 (1.14)
	% persistent after year	0,85	0,85



Appendix figure 1. Theoretical study design and definitions of non-persistence and adherence. The index date was the date of a first NOAC prescription. The red bars indicate exclusion criteria, namely having claimed a NOAC prescription prior to index date and having a diagnosis code for deep venous thromboembolism or knee/hip replacement surgery in the 30 days surrounding the index date. Patients were only included when they had a diagnosis code for AF prior to or on the index date. Each grey bar indicates a claimed prescription with a certain length and shows how stockpiling is taken into account and how a patient is censored after 91 days without medication. The red and blue dotted lines show that the medication possession rate is calculated by dividing the days covered with the days of follow-up.



Appendix figure 2. Proportion of patients persistent with treatment after one year per NOAC, stratified on year of inclusion. Patients initiated on edoxaban were excluded given the limited sample size.



Appendix figure 3. Mean MPR in the first year of treatment per NOAC, stratified on year of inclusion. Patients initiated on edoxaban were excluded given the limited sample size.

3

SAFETY AND EFFECTIVENESS OF NOAC THERAPY IN CLINICAL PRACTICE

3.1

ORAL ANTICOAGULANT OR NO TREATMENT IN PATIENTS WITH ATRIAL FIBRILLATION AT MODERATE STROKE RISK: A MULTI-CENTRE OBSERVATIONAL STUDY

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ABSTRACT

Background

There is currently no consensus on whether atrial fibrillation (AF) patients at moderate risk for stroke (1 non-sex-related CHA_2DS_2-VASc point) should be treated with an oral anticoagulant.

Methods and results

We conducted a multi-country cohort study in Sweden, Denmark, Norway, and Scotland. In total, 59 076 patients diagnosed with AF at moderate stroke-risk were included. We assessed the risk of stroke or major bleed during non-vitamin K antagonist oral anticoagulant (NOAC), vitamin K antagonist (VKA), or no treatment using inverse probability of treatment weighted (IPTW) Cox regression. We calculated the net clinical benefit based on strokes and intracranial haemorrhages (ICH). The risk for stroke was 0.58 per 100 person-years and the risk for bleed 0.76 per 100 person-years. Comparing NOAC to no treatment, the risk for stroke was lower (hazard ratio (HR): 0.72 (95% confidence interval (CI) 0.56- 0.94)), and the risk for ICH was not increased during NOAC treatment (HR: 0.84; CI: 0.54-1.30). Comparing VKA to no treatment, the risk for stroke tended to be lower (HR: 0.81; CI: 0.59-1.09), and the risk for ICH tended to be higher during VKA treatment (HR: 1.41; CI: 0.88-2.14). Comparing NOAC to VKA treatment, the risk for stroke was similar (HR: 0.92; CI: 0.70-1.22), but the risk for ICH was lower during NOAC treatment (HR: 0.63; CI: 0.42-0.94).

Conclusion

In this observational study including only moderate-risk AF patients, NOAC treatment was associated with a lower ICH risk without an increased stroke risk, although the absolute risk for events was small.

INTRODUCTION

Patients with atrial fibrillation (AF) have a five-fold increased risk for stroke. However, risk varies considerably between patients and can be estimated using the CHA_2DS_2-VASc score [1,2]. The CHA_2DS_2-VASc score is based on five characteristics adding one point: age (65-74), sex, chronic heart-failure, hypertension, vascular disease, and diabetes, and two characteristics adding two points: age ≥ 75 and a prior stroke/transient ischemic attack (TIA)/embolism. If this score, and thus the stroke risk, exceeds a certain level, the benefit of treatment with an oral anticoagulant in terms of stroke prevention is considered to outweigh the risks of bleeding associated with treatment. Current guidelines recommend treatment with an oral anticoagulant if a patient has a CHA_2Ds_2-VASc score of two or higher for males, or three or higher for females [3,4]. For patients at moderate risk, i.e., having a CHA_2DS_2-VASc score of 1 for males, and 2 for females, guidelines state that treatment with an oral anticoagulant *should be individualized based on net clinical benefit and consideration of patient values and preferences* [3].

Some observational studies have shown a positive net clinical benefit of treatment with vitamin K antagonists (VKA) compared to no treatment or antiplatelet treatment in such moderate-risk patients [5,6]. On the other hand, there have also been studies showing no clinical benefit [7], leading to a class IIa recommendation that treatment for patients at moderate risk can be considered [8]. However, all studies investigating the effects of anticoagulation therapy compared to no therapy among moderate-risk patients were conducted prior to the availability of non-vitamin K antagonist oral anticoagulants (NOACs). Given that NOAC treatment has a superior safety and efficacy profile compared to VKA treatment as documented in randomized clinical trials [9], as well as in observational studies [10], it might be that the net clinical benefit is more positive with NOAC treatment in these moderate-risk patients, especially given the generally lower risk for intracranial haemorrhage (ICH) with NOAC compared to VKA treatment.

Even though trials only included a limited number of patients at moderate risk [11–14], the meta-analysis of randomized trials by Ruff *et al.* [9] indicated that the point estimate in patients with a $CHADS_2$ score of 0 or 1 was more in favour of NOAC treatment compared to VKA for both the safety and efficacy outcomes. Because there is currently only limited randomized trial data available from these subgroups comparing NOAC to VKA treatment, and no data at all comparing NOAC to no treatment, observational research is required to provide relevant information for decision making in this setting. Therefore, the aim of the current study was to compare the safety and effectiveness of NOAC, VKA, or no treatment in patients with AF at moderate stroke risk.

METHODS

Setting

We developed a common protocol and used a common data model to analyse and pool results from four Western European databases, namely Denmark, Norway, Scotland, and the Stockholm region in Sweden. Detailed information on the databases can be found elsewhere and a summary overview is given in Appendix Table 1[15–20]. All databases contain diagnoses from secondary care, both inpatient

and outpatient. The Stockholm database also contains diagnoses from primary care. In addition, all databases contain data on medications dispensed at pharmacies.

Patient selection

We selected all patients with a diagnosis of AF from the first of January 2011 until 31st of October 2018, the end of data availability. After the date of the first AF diagnosis, we added a 14-day run-in period and considered day 15 as the cohort entry date. This 14-day period was added to avoid including outcomes that are possibly related to the diagnosis of AF, i.e., experiencing a stroke which led to diagnostic workup revealing underlying AF.

As in the clinical trials, we excluded patients if they suffered from a major bleeding in the six months prior to the cohort entry date, especially since these patients might have a clear indication to withhold anticoagulant treatment. In addition, we excluded patients if they had a diagnosis or procedure code for mechanical valves and/or mitral stenosis in the five years prior to the cohort entry date or immigrated in the five years prior to the cohort entry date (see Figure 1, procedure codes were not available in Norway).

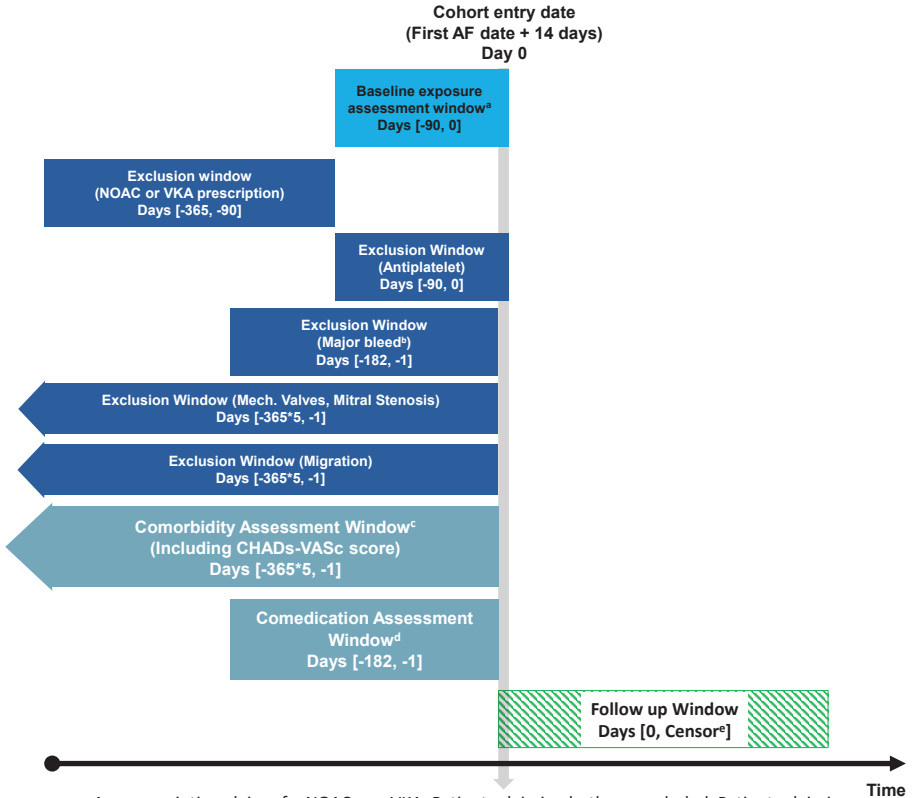
We only included patients at moderate stroke risk and thus included male patients with a CHA_2DS_2-VASc score of 1 and female patients with a CHA_2Ds_2-VASc score of 2. We determined age and sex at the cohort entry date and searched for a registration of any of the diagnoses in the five years prior to the cohort entry date, to include only patients with one non-sex related single-point stroke risk factor.

As hypertension and diabetes are often solely treated in primary care, and three databases (Norway, Denmark, Scotland) do not contain diagnostic data from primary care, we are likely to underestimate the proportion of patients diagnosed with hypertension and diabetes. Therefore, in those databases, we not only searched for diagnoses in secondary care, but also asserted whether patients had claimed two different antihypertensive drugs in the five years prior to the index date to identify hypertension or an antidiabetic drug to identify diabetes. We tested several approaches in the Stockholm database, in which we had access to both primary and secondary care data, finding that this approach led to the best positive predictive value and sensitivity (see Appendix eMethods).

Antithrombotic treatment

We considered three levels of treatment status, namely no treatment, NOAC treatment, and VKA treatment. A patient's baseline treatment status was defined in the 90 days prior to the cohort entry date. If a patient did not claim a NOAC or VKA in this period, the patient was considered untreated at baseline.

We excluded all patients claiming both a VKA and a NOAC prescription in the 90 days prior to cohort entry date, or patients claiming a prescription for antiplatelet treatment in the 90 days prior to the index date. In addition, we excluded patients that claimed either a VKA or a NOAC between a year prior to cohort entry date and 90 days prior to cohort entry date, to only include new users of VKAs and NOACs.



a. Any prescription claim of a NOAC or a VKA. Patients claiming both are excluded. Patients claiming none are considered untreated. After the cohort entry date, untreated patients could switch to treated once.
b. The same definition and ICD-10 codes for a major bleed were used as for defining the outcome.
c. Baseline comorbidities are: alcoholism, anaemia, cancer, COPD, dementia, diabetes, heart failure, hypertension, renal disease, stroke/TIA/embolism, and vascular disease
d. Baseline comedications are: aspirin, antidepressants, beta blockers, calcium channel blockers, corticosteroids, diuretics, insulin, NSAIDs, oral diabetic drugs, P2Y12-inhibitors, proton pump inhibitors, RAAS inhibitors, and statins.
e. Censoring at an earliest of: outcome of interest, death, emigration, end of study period, or CHADs-VASc score increase.

Figure 1. Graphical representation of patient inclusion; starting on top and going down the boxes mean the following. Patients enter cohort at 14 days after their AF diagnosis. Baseline exposure window is 90 days prior to cohort entry date. Patients are excluded if they have claimed a NOAC or VKA in the 365 to 90 days prior to cohort entry. Patients are excluded if they have claimed an antiplatelet prescription in the 90 days prior to cohort entry. Patients are excluded if they suffered from a major bleed in the 182 days prior to cohort entry. Patients are excluded if they have a diagnosis or procedure code for mechanical valves or mitral stenosis in the five years prior to cohort entry. Patients are excluded if they immigrated in the five yours prior to cohort entry. Baseline comorbidities were assessed in the five years prior to cohort entry. Baseline comedication was assessed in the 182 days prior to cohort entry. Patients were followed from cohort entry until censored.

Study design

We used a modified intention-to-treat (ITT) analysis as our main analysis (see Appendix for the rationale for this study design). This modified ITT design is different from the traditional ITT

design, as patients can switch once from untreated status to treated status after cohort entry. The person time prior to the switch is then considered as untreated status, to avoid immortal time bias. After a patient has claimed his/her first treatment, the patient remained on that treatment status throughout the study period. Thus, a patient with no claim of a NOAC or a VKA in the 90 days prior to the cohort entry-date, was considered untreated at baseline, but, after claiming a prescription, would switch to NOAC or VKA treatment status and remained on this status until the end of follow-up, disregarding potential stopping or switching after this point. If a patient did not claim any NOAC or VKA during follow-up, the patient would have the untreated status until the end of the study.

Outcome definition

We analysed both a composite effectiveness and safety outcome (see ICD-10 codes in Appendix Table 2). The composite effectiveness outcome included ischemic or unspecified stroke. The primary safety outcome was any major bleed. The secondary safety outcomes were gastrointestinal bleeds (GIB) and intracranial haemorrhages (ICH) considered separately. Finally, we included a net clinical benefit outcome, which was a composite of stroke, major bleed, or death, as was done in the clinical trials of NOACs. All outcomes were included only if they were registered in a secondary care inpatient setting, to only include severe outcomes and reduce misclassification.

Net clinical benefit

We used two approaches to calculate the net clinical benefit comparing the three different treatment arms. First, we used the composite net clinical benefit endpoint as described above. Second, we used the method described by Singer *et al.* [21], using the following formula:

$$Net\ Clinical\ Benefit = (Ischemic\ Rate_{off\ treatment} - Ischemic\ Rate_{on\ treatment}) - weight * (ICHRate_{on\ treatment} - ICHRate_{off\ treatment})$$

We used the crude rates from the untreated group and multiplied them by the HR from the Cox regression to obtain the rates on treatment. We varied the weight given to an ICH with 1.0, 1.5, and 2.0 and considered 1.5 as the main analysis as has been done earlier [21].

Follow-up time

Patients were followed from the cohort entry date until censoring at the first occurrence of either; the outcome of interest, death, emigration, end of the 2.5 years follow-up, a claim of an antiplatelet prescription, or an increase in the CHA_2DS_2-VASc score. A patient's CHA_2DS_2-VASc score could increase by passing the age threshold or being newly diagnosed with another component from the risk score.

Covariates

We defined the use of baseline medication as claiming a prescription in the six months prior to the cohort entry date. Baseline medications of interest were prescriptions for antidepressants, antiplatelet agents, beta blockers, calcium channel blockers, corticosteroids, diuretics, insulin, NSAIDs, oral diabetic drugs, proton pump inhibitors, RAAS inhibitors, and statins (see Appendix Table 2 for ATC codes).

We defined baseline comorbidities as having a registered diagnosis code in the five year prior to the cohort entry date. Baseline comorbidities of interest, besides the components of the CHA_2DS_2-VASc score, were diagnoses of a prior bleed, abnormal liver function, alcohol misuse, anaemia, cancer, COPD, dementia, and renal disease (see Appendix Table 2 for ICD-10 codes).

Statistical analysis

We used descriptive statistics to present patient characteristics of the three treatment arms. To contrast the risks for stroke and major bleeds, we used an inverse probability of treatment weighted (IPTW) Cox regression with a robust variance estimator. The probability of treatment was calculated with logistic regression, having age, sex, the year of cohort entry, and the aforementioned baseline medication and comorbidities as independent variables. We calculated the standardized mean differences (SMD) to check whether IPTW yielded comparable cohorts, considering an SMD below 0.1 as indicating satisfactory covariate balance [22].

Subgroup analyses

We performed several subgroup analyses. First, we stratified by sex. Second, we stratified by age 65 and over or under 65. Third, we stratified by low and moderate bleeding risk as defined by a HAS-BLED score of 0-1 or more than 1.

Meta-analysis

All analyses were performed using the same analytical R script on a local analytical dataset that was transferred into a common data model. This procedure allowed data to stay locally and only results were shared, while ensuring an identical analysis in all databases. The results from the different databases were combined using a meta-analysis and we used Cochran's Q statistic to test whether a fixed or random effects meta-analysis was required. We used fixed-effects meta-regression to calculate p-values for subgroup analyses.

Additional analysis

We performed several additional analyses to test the robustness of our findings. First, we used an on-treatment approach. In this approach, patients could switch between treatment statuses during follow-up. A patient would switch between NOAC and VKA status after claiming a different prescription, and a treated patient could switch to untreated, if they did not claim a new prescription within 180 days after a prior prescription. Second, we used a classical ITT analysis to compare NOAC to VKA treatment. For this analysis, stopping and switching of treatment status were disregarded,

and follow-up started at the first claim of a NOAC or VKA, instead of being anchored to an AF diagnosis. Patients were included if they had an AF diagnosis prior to claiming their treatment, or within 90 days after; all other analyses were performed as in the main analysis. Third, as primary care data was only available in the Stockholm database, we performed an analysis where we only included data from secondary care in Stockholm. Some diagnoses from the CHA_2DS_2-VASc score might only be captured in primary care, and hence the patient selection can be affected by this. Fourth, we used a shorter follow-up of a maximum of one year. Fifth, we used a falsification endpoint, which was a composite of acute upper respiratory infection and osteoarthritis, recorded in inpatient secondary care (see Appendix Table 2 for ICD-10 codes). These outcomes are not causally linked with any of the treatments but are associated with unmeasured potential confounders, such as frailty. By analysing the falsification endpoint with the same approach as the main analysis, bias from unmeasured confounders may be detected [21].

RESULTS

We included 59 076 patients newly diagnosed with AF at moderate stroke risk: 7352 from Stockholm, 21 272 from Denmark, 19 789 from Norway, and 10 663 from Scotland. In total, 21 926 (37%) of the patients were treated with a NOAC, 11 201 (19%) with a VKA, and 31 385 (53%) were untreated at one time throughout follow-up (Table 1, untreated patients switching to VKA or NOAC were included in both cohorts). Of the patients treated with a NOAC, 47% were treated with apixaban, 29% with rivaroxaban, 23% with dabigatran, and only 1% with edoxaban. In Denmark, only 39% of the patients were untreated at baseline, while this was 66% in Scotland. In all countries but Scotland, more patients were receiving a NOAC compared to VKA, in Denmark and Norway more than twice as often (Table 2).

There were no large differences in baseline characteristics between the three treatment groups. The mean age was 65.2 years in NOAC treated patients, 64.2 years in VKA treated patients, and 63.5 years in untreated patients. The mean HAS-BLED score was 1.22, 1.25, and 1.38, respectively. There were more patients with a history of vascular disease in the untreated group, while heart failure was more common amongst VKA users. Of the untreated patients, only 38% received a beta-blocker at baseline, compared to 65% in NOAC treated patients, and 63% in VKA treated patients. In addition, untreated patients more often had aspirin or P2Y12 inhibitor therapy 180 days before baseline. After weighting, all SMDs were below 0.01 in all databases, for all comparisons, for all covariates (data not shown).

In total, 423 patients suffered from a stroke during follow-up and 566 suffered from a major bleed, of which 146 were an ICH and 250 a GIB (Table 3) The overall incidence rate (IR) for stroke was 0.58 events per 100 person years (%/py), 0.76 %/py for bleeds, 0.20%/py for ICH, and 0.34%/py for GIB. The highest crude IR for stroke was in the untreated group at 0.70 %/py. The highest IR for bleeds was in the VKA treated group at 0.83%/py, partly driven by the highest rate in ICH as well: 0.25%/py.

The results from the meta-analyses of all databases showed that NOAC treatment was associated with a reduced risk for stroke compared to no treatment (hazard ratio $(HR)_{stroke}$: 0.72; 95% confidence

Table 1. Characteristics of the patients included in the cohort. Patients switching from untreated status to treated status were included twice in this Table. Values percentage the number of patients and the percentage between brackets, unless stated otherwise. COPD: chronic obstructive pneumatic disease. NSAID: non-steroidal anti-inflammatory drug. PPI: proton pump inhibitor. RAAS: renin angiotensin aldosterone system.

	NOAC	VKA	No treatment
Number of patients	21925 (34%)	11201 (17%)	31385 (49%)
Age (mean)	65,3	64,2	63,5
Sex	8380 (38%)	4053 (36%)	11829 (38%)
HAS-BLED (mean)	1,23	1,25	1,38
NOAC			
Apixaban	10284 (47%)	0 (%)	0 (%)
Dabigatran	4975 (23%)	0 (%)	0 (%)
Edoxaban	220 (1%)	0 (%)	0 (%)
Rivaroxaban	6446 (29%)	0 (%)	0 (%)
Hypertension	4969 (23%)	2687 (24%)	7325 (23%)
Heart failure	1542 (7%)	1180 (11%)	1601 (5%)
Vascular disease	762 (3%)	563 (5%)	3571 (11%)
Diabetes	557 (3%)	251 (2%)	1113 (4%)
Abnormal liver function	219 (1%)	115 (1%)	911 (3%)
Alcoholism	551 (3%)	342 (3%)	2101 (7%)
Anaemia	436 (2%)	268 (2%)	1732 (6%)
Prior bleed	1119 (5%)	520 (5%)	2056 (7%)
Cancer	2393 (11%)	1073 (10%)	5741 (18%)
COPD	1259 (6%)	710 (6%)	2958 (9%)
Dementia	75 (%)	25 (%)	233 (1%)
Renal disease	181 (1%)	252 (2%)	806 (3%)
Aspirin	3271 (15%)	2401 (21%)	8297 (26%)
Antidepressant	1810 (8%)	987 (9%)	3717 (12%)
Beta blocker	14325 (65%)	7066 (63%)	11952 (38%)
Ca channel blocker	3381 (15%)	1884 (17%)	4024 (13%)
Corticosteroid	1687 (8%)	1049 (9%)	3873 (12%)
Diuretic	3769 (17%)	2493 (22%)	4278 (14%)
Insulin	145 (1%)	76 (1%)	365 (1%)
NSAID	3761 (17%)	1907 (17%)	5610 (18%)
Oral diabetes drug	736 (3%)	342 (3%)	898 (3%)
P2Y12 inhibitor	346 (2%)	226 (2%)	1336 (4%)
PPI	3964 (18%)	2042 (18%)	7608 (24%)
RAAS inhibitor	7291 (33%)	3656 (33%)	7436 (24%)
Statin	4726 (22%)	2588 (23%)	7274 (23%)

interval (CI): 0.55 – 0.94), but an increased risk for bleeds (HR_{bleed}: 1.26; CI: 1.00 – 1.58) (Table 4). This increased risk for bleeds was mainly driven by an increased GIB risk (HR_{GIB}: 1.48; CI: 1.05 – 2.08), and not by the ICH risk (HR_{ICH}: 0.84; CI: 0.54 – 1.30). This yielded a positive net clinical benefit for NOAC treatment, at each weight given to an ICH.

Table 2. Number of patients in the different treatment arms per database. Patients switching from untreated status to treated status were included twice in this Table.

	Stockholm	Denmark	Norway	Scotland
Untreated	4115 (51%)	8962 (39%)	9969 (48%)	8339 (66%)
VKA	1622 (20%)	4348 (19%)	2947 (14%)	2284 (18%)
NOAC	2389 (29%)	9592 (42%)	7927 (38%)	2017 (16%)
Apixaban	1613 (68%)	2989 (31%)	4413 (56%)	1269 (63%)
Dabigatran	477 (20%)	2857 (30%)	1570 (20%)	71 (4%)
Edoxaban	5 (%)	147 (2%)	63 (1%)	5 (%)
Rivaroxaban	294 (12%)	3599 (38%)	1881 (24%)	672 (33%)

Table 3. Number of events per treatment arm and the corresponding incidence rate, given in number of events per 100 person years. FU: follow-up; ICH: intracranial haemorrhage; GIB: gastrointestinal bleed.

	NOAC		VKA		Untreated	
	29801		17444		27230	
FU time (years)	n events	IR (%/y)	n events	IR (%/y)	n events	IR (%/y)
Stroke	155	0.52	87	0.50	190	0.70
Bleed	231	0.78	144	0.83	191	0.70
ICH	54	0.18	43	0.25	49	0.18
GIB	108	0.36	58	0.33	84	0.31
Stroke/bleed/death	857	2.88	528	3.03	2607	9.57

Comparing VKA treatment to no treatment showed tendencies towards a decreased stroke risk (HR_{stroke}: 0.81; 0.59 – 1.09) and an increased bleeding risk (HR_{bleed}: 1.44; 0.82 – 2.50). The risk for ICH tended to be increased on VKA treatment (HR_{ICH}: 1.37; 0.88 – 2.14), which yielded a neutral net clinical benefit at each weight given to an ICH.

Comparing NOAC to VKA treatment showed no statistically significant difference in either the stroke or the bleeding risk (HR_{stroke}: 0.92; CI 0.70 – 1.22); HR_{bleed}: 0.85; CI: 0.69 – 1.06). However, NOAC treatment was associated with a significantly reduced risk for ICH (HR_{ICH}: 0.63; CI: 0.42 – 0.94). The net clinical benefit calculation showed that there was a positive net clinical benefit for NOACs compared to VKA, at each weight given to an ICH. The composite endpoint of stroke, bleed, and death showed no significant differences (HR: 0.87; CI: 0.68 – 1.11).

Subgroup analyses

There were no significant differences between subgroups (Table 5). However, comparing NOACs to VKA, the hazard ratio for stroke was lower for female than for male patients (0.68 for female, 1.15 for male). In addition, when comparing VKA to no treatment for stroke, the protective effect was only visible in male patients (HR: 1.06 for female, 0.68 for male).

Table 4. Hazard ratios and 95% confidence intervals resulting from the meta-analysis comparing the different treatment arms and the different outcomes. The net clinical benefit is calculated based on the formula in the methods section. GIB: gastrointestinal bleed; ICH: intracranial haemorrhage.

	NOAC vs VKA		NOAC vs no treatment		VKA vs no treatment	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Stroke	0.94 (0.72-1.2)	0.92 (0.70-1.20)	0.63 (0.41-0.98)	0.72 (0.56-0.94)	0.76 (0.59-0.99)	0.81 (0.59-1.10)
Bleed	0.82 (0.67-1.0)	0.85 (0.69-1.10)	1.10 (0.88-1.30)	1.30 (1.00-1.60)	1.30 (0.90-1.90)	1.40 (0.83-2.50)
GIB	0.95 (0.69-1.3)	1.00 (0.72-1.40)	1.20 (0.88-1.60)	1.50 (1.10-2.10)	1.20 (0.64-2.30)	1.20 (0.62-2.30)
ICH	0.68 (0.45-1.0)	0.63 (0.42-0.94)	0.94 (0.64-1.40)	0.84 (0.54-1.30)	1.40 (0.94-2.10)	1.40 (0.88-2.10)
Stroke/bleed/death	0.85 (0.67-1.1)	0.87 (0.68-1.10)	0.32 (0.29-0.34)	0.45 (0.41-0.50)	0.38 (0.28-0.50)	0.50 (0.41-0.62)
Net Clinical Benefit						
ICH * 1	0.119	0.153	0.309	0.236	0.080	0.052
ICH * 1.5	0.162	0.207	0.315	0.254	0.044	0.019
ICH * 2	0.205	0.261	0.321	0.272	0.008	-0.014

Table 5. Hazard ratios from the meta-analyses of the stratified analyses. Has low: HAS-BLED score of 0 or 1; Has high: HAS-BLED score above 1.

		NOAC vs VKA	p for interaction	NOAC vs none	p for interaction	VKA vs none	p for interaction
Stroke	Female	0.68 (0.44-1.10)	0.071	0.65 (0.43-0.98)	0.591	1.10 (0.67-1.70)	0.140
	Male	1.20 (0.80-1.70)		0.57 (0.29-1.13)		0.68 (0.46-1.00)	
Bleed	Female	0.98 (0.67-1.40)	0.337	1.50 (1.10-2.20)	0.179	1.40 (0.89-2.10)	0.877
	Male	0.78 (0.60-1.00)		1.10 (0.84-1.50)		1.40 (1.10-1.90)	
Stroke	<65	1.20 (0.67-2.00)	0.404	0.58 (0.26-1.30)	0.984	0.81 (0.49-1.36)	0.979
	>65	0.88 (0.63-1.20)		0.73 (0.54-1.00)		0.81 (0.56-1.20)	
Bleed	<65	0.86 (0.58-1.30)	0.980	1.40 (0.95-2.10)	0.471	1.30 (0.82-1.90)	0.577
	>65	0.85 (0.66-1.10)		1.20 (0.90-1.60)		1.50 (1.10-2.00)	
Stroke	Has low	0.84 (0.60-1.20)	0.398	0.73 (0.53-1.00)	0.784	0.87 (0.60-1.30)	0.570
	Has high	1.10 (0.68-1.80)		0.50 (0.22-1.10)		0.73 (0.44-1.20)	
Bleed	Has low	0.77 (0.58-1.00)	0.270	1.30 (0.92-1.70)	0.815	1.60 (1.20-2.20)	0.172
	Has high	0.98 (0.70-1.40)		1.20 (0.85-1.60)		1.10 (0.54-2.10)	

Sensitivity analyses

In the on-treatment analysis, results were consistent with the main analyses (Appendix Table 3). Comparing NOACs to no treatment again showed a decreased risk for stroke, an increased risk for bleeding, but no increased risk for ICH. Comparing VKA to no treatment showed a reduced stroke risk, and an increased bleeding risk, although not statistically significant (HR_{bleed}: 1.54; CI: 0.95 – 2.48; HR_{ICH}: 1.42; CI: 0.91 – 2.23). In NOAC vs VKA treated patients, the risks for stroke and bleeding were not different, and during NOAC treatment there was statistically lower risk for ICH.

In the intention-to-treat analysis there was no statistically significant difference in stroke risk between users of NOACs and VKAs (HR_{stroke}: 0.85; CI: 0.64 – 1.14), but a lower risk for bleeding in NOAC treated patients compared to VKA treated patients (HR_{bleed}: 0.80; CI: 0.64 – 0.99), which was mainly driven by a lower risk for ICH (HR_{ICH}: 0.55; CI: 0.37 – 0.81).

None of the falsification endpoints was significantly associated with any of the treatment arms in any comparison. Censoring patients at one year of follow-up yielded similar results (Appendix Table 3).

DISCUSSION

In 59 076 patients newly diagnosed with AF at moderate stroke risk from Denmark, Norway, Scotland, and the Stockholm region in Sweden, we found that NOAC treatment was in general the most effective and safe choice, yielding a positive net clinical benefit compared to both VKA and to no treatment. Compared to no treatment, NOAC treatment was associated with a 28% decreased risk for stroke, but also a 26% increased risk for bleeding. This increased bleeding risk was not driven by ICH, but by a surplus of GIB in the NOAC treated group. When comparing VKA to no treatment, VKA treatment was associated with a lower risk for strokes, but an increased risk for bleeds, especially ICH, and therefore there was no net clinical benefit when comparing VKA to no treatment. Compared to VKA, NOAC treatment was associated with a 33% decreased risk for ICH, with similar rates for strokes and other bleeds. However, the absolute risk for events was low at 0.58%/py for strokes and 0.76%/py for bleeds.

Previous observational studies have also assessed the clinical benefit of VKA treatment compared to no treatment in patients with AF at moderate stroke-risk, with conflicting results [5–7]. After the introduction of NOACs, an observational study from Denmark compared the safety and effectiveness of the different NOACs and VKA. However, this study was relatively small, making it difficult to draw conclusions [23]. An observational study from the United States comparing rivaroxaban to VKA treatment showed both a lower risk for stroke (HR: 0.41 (0.17 – 0.98)) and a lower risk for ICH (HR: 0.33 (0.03 – 3.17)) in rivaroxaban treated patients [24].

Post-hoc analyses of RCTs comparing NOACs to VKA in moderate-risk patients show similar results; small differences in stroke reduction, but a substantially lower risk for ICH. In a post-hoc analysis of patients with a CHA_2DS_2-VASc score of 1 in the ARISTOTLE trial, the HR for ischemic stroke was 1.13 (0.68 – 1.90), and the HR for ICH was 0.45 (0.24 – 0.82) [25]. In the RE-LY trial, in patients with a $CHADS_2$-score of 0-1, dabigatran 150 mg performed better than warfarin for stroke prevention (HR: 0.61 (0.37 – 0.99)), whereas dabigatran 110 mg did not (HR: 0.98 (0.63 – 1.51)), and both markedly reduced the risk for ICH (HR_{110}: 0.37 (0.16 – 0.83); HR_{150}: 0.37 (0.16 – 0.84)) [26]. These results

are in line with our results, a similar stroke reduction with NOAC treatment, but with a lower risk for ICH. The current study adds to the knowledge that NOAC treatment does not substantially increase the risk for an ICH compared to no treatment, while VKA treatment does. This yielded a positive net clinical benefit of treating patients with a NOAC compared to no treatment and compared to VKA treatment.

To the best of our knowledge, we are the first to investigate the question whether moderate-risk patients would benefit from treatment with a NOAC, a VKA, or no treatment. Prior to the NOAC introduction it was uncertain whether VKA or no treatment should be recommended in moderate-risk patients. There was already compelling evidence that NOACs are safer and more effective than VKAs in the general AF population, but it has previously not been shown that this would also shift the balance towards a positive net clinical benefit in moderate-risk patients, indicating that these patients may benefit from being treated with a NOAC.

Our study has some limitations. First, the results were based on an observational study, which can suffer from confounding. We used IPTW to correct for this but, as always, residual confounding may still be present. The falsification endpoints showed no significant association with any of the treatments, indicating that confounding by non-specific factors such as frailty or frequent physician contacts is less likely to be present. In addition, there are no clear recommendations whether to treat a patient or not in this population, which also reduces the chances for confounding. However, the strongly increased risk for death in the no treatment group is probably partly explained by confounding. Near the end of life of a patient, it is likely that treatment is withheld and thus we saw such a markedly increased risk for mortality in untreated patients. Therefore, we have not considered this composite in the interpretation of our results comparing no treatment to NOAC and VKA treatment. Second, only one database had access to primary care diagnoses. Since several covariates from the CHA_2DS_2-VASc score are often only diagnosed in primary care, such as hypertension and diabetes, we might have missed those and underestimated the true CHA_2DS_2-VASc score and included patients who actually had a higher risk score [15]. We tried to avoid this by adding diagnoses based on an algorithm that searched for prescriptions for hypertension and diabetes drugs in the years before the cohort entry date, and validated this procedure in the Stockholm database, which had access to primary care data. In addition, we have performed an additional analysis in which we removed the primary care data from the Stockholm database, and this yielded similar results as the analysis with primary care data.

Our study also has some strengths. First, the study relies on data from four countries, which adds to the generalizability of the results. Second, we performed multiple additional analyses which all yielded similar results, indicating that the results in this study are robust to several changes in study design choices. In addition, the number of events per person year were similar to those found in the randomized trials, indicating the validity of the outcomes in our study [25, 26].

In conclusion, in 59 076 patients with AF at moderate stroke-risk from four countries, the absolute risk for both strokes and bleeds was low. This study indicates that NOAC treatment was associated with a positive net clinical benefit compared to no treatment and VKA treatment. Compared to no treatment, NOAC treatment was associated with a reduced stroke risk, without an increased ICH risk, and compared to VKA treatment, NOAC treatment was associated with similar stroke risk, but a lower ICH risk.

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APPENDICES

Appendix table 1. Description of databases.

	Origin	Data available from	Sample / full population	Sample size
Stockholm Healthcare Database	Stockholm County	July 2010	Full population	2.3 million
Danish National Registries	Denmark	1995	Full population	5.6 million
Norwegian National Registries	Norway	2004	Full population	5.3 million
Scotland	NHS Scotland	January 2009 (until 12.2017)	Full population	5.3 million

	Pharmacy data coding	Dispensing / Prescribed	Diagnostic data	Primary and/or secondary care
Stockholm Healthcare Database	ATC code	Dispensed medication	ICD	Primary and secondary (inpatient and outpatient)
Danish National Registries	ATC code	Dispensed medication	ICD	Secondary (inpatient and outpatient)
Norway	ATC code	Dispensed medication	ICD10	Secondary (inpatient and outpatient)
Scotland	BNF code (manually added ATC code)	Dispensed medication	ICD10	Secondary care (inpatient and outpatient)

	Typical prescription length	Medication Reimbursement
Stockholm Healthcare Database	90 days	Fully reimbursed, after yearly co-payment
Danish National Registries	90-120 days	Increasing reimbursement with additional purchases. Maximum yearly self-payment of ~500€.
Norway	90 days	Initially ~62% reimbursement then fully reimbursed when yearly patient co-payment limit reached (~210 Euro in 2018 for all expenses on drugs, physician visits)
Scotland	30-90 days (depending on whether the GP wants to check in with the patient more frequently for any reason)	There is no co-payment, all services – including prescription drugs – are free of charge (patients have to pay for OTC drugs if they don't have a prescription though).

Appendix table 2. ICD-10 and ATC-codes

Outcome	ICD-10 code beginning with
Ischemic stroke	I63
Major bleed	K25 – K28 (subcode 0, 2, 4, 6 only), K625, K922, I60, I61, I62, S064, S065, S066, D500, D62, J942, I312, H431, H356
Gastrointestinal bleed	K25 – K28 (subcode 0, 2, 4, 6 only), K625, K922
Intracranial bleed	I60, I61, I62, S064, S065, S066
Falsification endpoint	J01, J02, J03, J04, J05, J06, M15, M16, M17, M18, M19
Comorbidity	ICD-10 code beginning with
Alcohol abuse	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90, Y91, Z502, Z714, E529
Anemia	D50, D51, D52, D53, D54, D55, D56, D57, D58, D59, D60, D61, D62, D63, D64
Prior Bleed	I60, I61, I62, S064, S065, S066, I850, I983, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K922, D62, S063C, K920, I312, J942, K661, N02, R04, R31, R58
Diabetes	E10, E11, E12, E13, E14, G590, G632, H280, H360, N083, O240, O241, O242, O243; ATC codes: A10A, A10B
Heart Failure	I43, I50, I110, I130, I132, I255, I420, I425, I426, I427, I428, I429
Hypertension	I10, I11, I12, I13, I14, I15, I16; ATC codes: C03A, C08C, C08D, C09A-D
stroke/TIA/embolism	I63, I64, I679, I693, I694, I698, I679, I69, G451, G452, G453, G458, G459, I74
Liver disease	K70, K71, K72, K73, K74, K75, K76, K77
Renal disease	N183, N184, N185, N189, E102, E112, E122, E132, E142, I12, N03, N083, N085, N118, N14, N150, N16, N19, N26, P960, Q601, Q602, Z992
Cancer	C1, C2, C3, C4, C5, C6, C7, C8, C9, C0
COPD	J43, J44
Dementia	F00, F01, F02, F03
Vascular disease	I20, I21, I22, I23, I24, I25, I70, I739
Exclusion Criteria	ICD-10
Mitral Stenosis or Mechanical	'Z952', 'I050', 'I052', 'I342'
Heart Valve	Procedure codes for mechanical heart valve differ per country

Medication	ATC code beginning with
Apixaban	B01AF02
Dabigatran	B01AE07
Edoxaban	B01AF01
Rivaroxaban	B01AF03
Vitamin K antagonist	B01AA
Antiplatelets	B01AC
NSAIDS	M01A
Corticosteroids	H02AB
Diuretics	C03A, C03B, C03C, C03D, C03E
Beta blocker	C07A, C07B, C07C, C07D, C07E, C07F
Ca channel blocker	C08C, C08D, C08E, C08G
RAAS inhibitor	C09A, C09B, C09C, C09D, C09X

Appendix table 2. (continued)

Medication	ATC code beginning with
Statin	C10AA
Oral antidiabetics	A10B
Insulin	A10A
PPIs	A02BC
Antidepressants	N06A

Appendix table 3. Hazard ratios of different sensitivity analyses. First the analysis with time varying exposure, second the analysis censored at one-year follow-up, third the analysis from the Stockholm database with and without access to primary care.

	NOAC vs VKA	NOAC vs none	VKA vs none
Time varying exposure			
Stroke	1.00 (0.73-1.36)	0.75 (0.59-0.95)	0.84 (0.62-1.14)
Bleed	0.87 (0.69-1.09)	1.31 (1.06-1.63)	1.53 (0.95-2.47)
GIB	1.22 (0.85-1.75)	1.59 (1.16-2.18)	1.10 (0.74-1.63)
ICH	0.62 (0.40-0.97)	0.89 (0.60-1.33)	1.39 (0.88-2.18)
Stroke/bleed/death	0.96 (0.84-1.10)	0.37 (0.34-0.41)	0.38 (0.33-0.43)
One-year follow-up			
Stroke	0.90 (0.63-1.28)	0.71 (0.51-0.98)	0.90 (0.62-1.31)
Bleed	0.83 (0.63-1.10)	1.17 (0.89-1.55)	1.38 (0.62-3.07)
Results Stockholm with and without primary care			
Stroke with primary care	0.32 (0.10-1.05)	0.20 (0.06-0.67)	0.69 (0.30-1.60)
Stroke without primary care	0.18 (0.05-0.65)	0.13 (0.03-0.55)	0.78 (0.34-1.75)
Bleed with primary care	0.54 (0.26-1.09)	1.42 (0.59-3.40)	2.82 (1.35-5.92)
Bleed without primary care	0.65 (0.34-1.24)	1.37 (0.52-3.64)	2.84 (1.39-5.81)

APPENDIX METHODS 1

Testing different approaches to identify patients with hypertension and diabetes

In the Stockholm healthcare database, we had access to diagnosis from both primary and secondary care. Therefore, we were able to find all patients diagnosed with hypertension and diabetes, also if this was only treated in primary care. Through this, we could assess what the best approach would be to identify patients with hypertension and diabetes using concomitant treatment for these diseases, in the case of only having access to secondary care data. We tested several approaches, and calculated the positive predictive value, the negative predictive value, the sensitivity, and the specificity. We considered looking for diagnoses in both secondary and primary care as the golden standard.

We tested several different approaches. First, we varied by looking for ICD-10 codes in secondary care or not. Second, we used different strings of ATC-codes. Third, we used several look-back approaches to find the ATC-codes.

Hypertension: Including patients with an ICD-code and patients with claimed prescriptions. Using ATC-codes from Hellfritzsch et al. Europace 2017 (C03A, C08C, C08D, C09A-D)

	PPV	NPV	Sens	Spec
1 prescription in 5 years prior	68.2	96.1	92.7	80.5
3 prescriptions in 5 years prior	79.8	94.4	88.2	89.9
2 different ATC in 5 years prior (full ATC code)	91.2	91.2	79.3	96.6
2 different ATC classes in 5 years prior (first 3 positions ATC code)	94.4	90.8	78.0	97.9

Hypertension: Including only patients based on claimed prescriptions. Using ATC-codes from Hellfritzsch et al. Europace 2017 (C03A, C08C, C08D, C09A-D)

	PPV	NPV	Sens	Spec
1 prescription in 5 years prior	63.0	87.1	73.5	80.5
3 prescriptions in 5 years prior	72.4	82.9	58.8	89.9
2 different ATC in 5 years prior (full ATC code)	81.0	76.0	32.4	96.6
2 different ATC classes in 5 years prior (first 3 positions ATC code)	85.9	75.2	28.2	97.9

Hypertension: Including patients with an ICD-code and patients with claimed prescriptions. Using ATC-codes from Olesen et al. BMJ 2011 (C02A-C-DA-DB-DD-DG-L, C03A-B-D-E-X, C04, C05, C07, C08, C09)

	PPV	NPV	Sens	Spec
1 prescription in 5 years prior	40.6	98.0	98.4	35.2
3 prescriptions in 5 years prior	56.3	96.3	94.2	67.0
2 different ATC in 5 years prior (full ATC code)	61.3	94.8	90.9	74.1
2 different ATC classes in 5 years prior (first 3 positions ATC code)	64.5	94.6	90.1	77.7

Hypertension: Including only patients based on claimed prescriptions. Using ATC-codes from Olesen et al. BMJ 2011 (C02A-C-DA-DB-DD-DG-L, C03A-B-D-E-X, C04, C05, C07, C08, C09)

	PPV	NPV	Sens	Spec
1 prescription in 5 years prior	38.3	88.2	89.5	35.2
3 prescriptions in 5 years prior	51.5	87.0	77.8	67.0
2 different ATC in 5 years prior (full ATC code)	55.3	85.0	70.9	74.1
2 different ATC classes in 5 years prior (first 3 positions ATC code)	58.1	84.7	68.7	77.7

Diabetes: Including patients with an ICD-code and patients with claimed prescriptions. ATC code A10

	PPV	NPV	Sens	Spec
1 prescription in 5 years prior	86.5	99.7	89.4	99.6
3 prescriptions in 5 years prior	93.3	99.6	86.5	99.8
2 different ATC in 5 years prior (full ATC code)	96.0	99.5	81.2	99.9
2 different ATC classes in 5 years prior (first 3 positions ATC code)	NA	NA	NA	NA

Diabetes: Including only patients with claimed prescriptions. ATC code A10

	PPV	NPV	Sens	Spec
1 prescription in 5 years prior	83.3	99.1	69.7	99.6
3 prescriptions in 5 years prior	90.4	98.8	59.1	99.8
2 different ATC in 5 years prior (full ATC code)	92.0	98.3	38.5	99.9
2 different ATC classes in 5 years prior (first 3 positions ATC code)	NA	NA	NA	NA

APPENDIX METHODS 2

Rationale for study design

Ideally, when performing a comparative effectiveness study, one tries to emulate a target trial, which follows patients with an intention to treat analysis. However, in clinical practice, a patient is not randomized to a certain treatment strategy at the time a patient is diagnosed with atrial fibrillation, and thus patients might initiate treatment at a later stage. Potentially even more so in the case of patients with a low CHA_2Ds_2-VASc score, in which treatment is not as clearly recommended. In our data, we found that 30% of the patients started OAC treatment after the treatment allocation window during follow-up (i.e., between cohort entry date and 2.5 years of follow-up). We could choose to start follow-up at more than 14 days after the AF diagnosis at, for example, 60 days, to allocate more patients to their actual treatment, but through this we would miss all outcomes occurring in the 60 days after the AF diagnosis. Therefore, we decided not to use a classical intention-to-treat analysis, as it is known beforehand that a substantial number of patients is switching from untreated to treated over time.

Instead, we have chosen a modified intention-to-treat analysis, accompanied with an on-treatment analysis. The modified intention-to-treat analysis gives the patients the chance to change from untreated to treated status once during follow-up. Through this, we are still capturing the actual intended treatment strategy, namely, to treat the patient with an OAC, even though the patient may not start this treatment directly after the AF diagnosis.

The downside of this approach is that only untreated patients can switch to another treatment, which can ultimately introduce bias. Namely, there will be an overrepresentation of early follow-up time in the non-treated person time. This has to do with the fact that some patients will switch from untreated to treated. These patients will add person-time to the untreated group in their early days after the index date, and person time to the treated group later, yielding more early days in the untreated group. If then the rate of outcomes would be higher or lower shortly after the index date compared to longer after the index date, we could see an over- or underestimation of the risk in the untreated patients. However, supplementary analyses have shown that the rates of outcomes are equally distributed during follow-up; the median time to stroke was 438 days with an interquartile range of 206 to 605 days. Given the follow-up time of 2.5 years, which is 913 days, the median time to stroke is approximately half of the follow-up time. Therefore, we believe this approach will be unbiased in this regard.

Besides the modified intention-to-treat analysis, we have chosen to perform an on-treatment analysis. This analysis tries to follow the actual treatment status of a patient over time, through taking into account that a patient may stop treatment. Through this analysis, we will be able to analyse the treatment effect in patients that are actually on treatment, taking switching and non-persistence into account.

Finally, we did perform a true intention to treat analysis, comparing NOAC users to VKA users. As there is a clear point at which the treatment starts for those patients (and thus no chance for immortal time bias), we were able to follow these patients from the first prescription until censoring.

3.2

CONCOMITANT ANTICOAGULANT AND ANTIDEPRESSANT THERAPY IN ATRIAL FIBRILLATION PATIENTS AND RISK OF STROKE AND BLEEDING

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ABSTRACT

We aimed to quantify the effects of antidepressant (AD) use in oral anticoagulant (OAC) treated patients with atrial fibrillation (AF). Using the Stockholm Healthcare database, we analyzed AF patients initiated with an OAC. Outcomes were severe bleeds and strokes and were analyzed using Cox models. We included 17 210 patients claiming warfarin and 13 385 claiming a non-vitamin K OAC (NOAC). 4 303 claimed an AD during follow-up. Concomitant OAC and AD use was associated with increased rates of severe bleeds (4.7 vs 2.7 per 100 person years) compared to OAC treatment alone (aHR 1.42, CI: 1.12 to 1.80), but not significantly associated with increased stroke rates (3.5 vs 2.1 per 100 person years, aHR 1.23, CI: 0.93 to 1.62). No significant differences in risks were observed between different OAC classes or different AD classes. In conclusion, concomitant use of an OAC and an AD is associated with an increased bleeding risk.

INTRODUCTION

Antidepressants (ADs) are among the most frequently prescribed medications for a variety of psychiatric indications, especially depression and anxiety [1]. Almost all ADs share the feature of having a direct influence on serotonin neurotransmission by influencing serotonin levels and serotonin receptor signaling [2]. Besides the beneficial effects on a patient's well-being, serotonin inhibition also affects platelet function [3, 4]. By decreasing platelet serotonin or inhibiting serotonin receptors, platelet aggregation may become compromised, which results in impaired hemostasis [4, 5]. Numerous studies have reported on the increased bleeding risk that is associated with AD use [6–8]. Several studies have reported an increased risk for ischemic stroke in patients receiving ADs as well [7, 9–11]. It is hypothesized that ADs cause vasoconstriction in cerebral arteries due to serotonergic activation, causing an increased risk for ischemic stroke [12, 13]. However, it cannot be ruled out that this observed association is due to confounding by indication, since depression is a known risk factor for stroke [11, 14].

In patients with atrial fibrillation (AF), treatment with oral anticoagulants (OACs) is effective in reducing the risk of having a stroke, but also increases the risk of having a severe bleed [15–17]. Since OACs in general, and especially non-vitamin K antagonist oral anticoagulants (NOACs), are widely used in clinical practice [18, 19], there is need for a deeper understanding of their potential drug-drug interactions to further optimize antithrombotic treatment. The interaction with ADs is of key importance since both bleeding and stroke risks might be influenced. The combination of vitamin K antagonists such as warfarin and ADs has been studied previously, and is associated with an approximately 30% increased risk for severe bleeds [20–23]. However, neither the stroke risk for any combination of OACs and ADs nor the risk for severe bleeding with the combination of NOACs and ADs have been studied before.

The aim of the present study was therefore to assess the effects of combined use of different ADs with OAC therapy in the NOAC era on both bleeding and stroke risk in patients with AF.

METHODS

Data source

For this population based cohort study, we used the VAL database, which is the Stockholm Healthcare Database, containing pseudonymized information on all 2.3 million inhabitants in the Stockholm region [24, 25]. The individual level information consists of data regarding demographics, medical information, and prescription claims. This gives the opportunity to have complete healthcare data for follow-up of all inhabitants in the region.

The medical information in VAL covers both primary and secondary care, and diagnoses and interventions are registered as ICD-10 codes. Data for primary care have been available since 2003, and for secondary care since 1993. Information is available on migration and death for all individuals. Data from different databases are linked through a unique Personal Identification Number [26]. The VAL database is updated monthly and we had data available until December 2017 at the time of data extraction.

In the database, prescription claims data contain drugs claimed in any pharmacy in Sweden, and are derived from the national prescribed drug registry and registered as ATC codes [27]. Data on claimed drugs are available in the VAL database from July 2010. The drug information registered consists of amounts, dosages, expenditures, reimbursement, age and gender of the patient, co-payment, and prescriber category.

The study was approved by the Regional Ethical Review Board in Stockholm (EPN 2015/579-31/2)

Patient selection

From the VAL database, we selected all patients with a diagnosis code for atrial fibrillation (I48) from 2003 until 2016. Validation studies have shown a positive predictive value of 97% for this diagnosis [28]. Among the AF patients, we selected all patients with a new prescription for either a NOAC or warfarin from July 2011 until the end of 2016. We defined a prescription as a new prescription if the patient had no prescription for any OAC during the year prior to inclusion. The date of the first prescription of the OAC was considered the index date.

Follow-up and censoring

After inclusion, we followed patients for a maximum of one year during the study period which was from July 2011 until December 2017. During this year of follow-up, patients remained in the cohort as long as they claimed new prescriptions for a NOAC or warfarin. If they did not claim their previously prescribed OAC, we censored the patients at the estimated end of the duration covered by the last claimed prescription. Follow-up ended when a patient claimed a prescription for another oral anticoagulant class (i.e., switch from warfarin to NOAC or vice versa), when a patient experienced an outcome of interest (for ICD-10 codes see Appendix Table 1), when a patient emigrated from the county, or when a patient died.

Exposure definition

We included all claims for an AD from the index date until the end of follow-up to identify treatment episodes with ADs during follow-up. We looked for AD prescriptions one year prior to the index date to identify potential AD treatment episodes that overlapped the index date. We defined a treatment episode from the claim of an AD prescription until the calculated end of the treatment period, and these periods were considered current use periods. We calculated this using the number of pills claimed and the common dose for the antidepressant. We classified ADs into three classes: SSRIs, TCAs, and other ADs. For ATC-codes see Appendix Table 1.

Outcome definitions

For bleeding risk, we assessed the occurrence of a severe bleed, using ICD-10 codes as described in Appendix Table 1. We included the first registration of a bleed requiring acute somatic care in inpatient or outpatient hospital based care, starting from the day after inclusion in the cohort [29, 30]. The primary outcome was the occurrence of any severe bleed. Secondary outcomes were GIB,

intracranial hemorrhage, and other severe bleeds (see Appendix Table 1). Validation studies have shown a positive predictive value of 95.5% and sensitivity of 100% for these diagnoses [29].

For stroke risk, we assessed the occurrence of a composite endpoint of a transient ischemic attack (TIA), ischemic stroke, and unspecified stroke, using ICD-10 codes as described in Appendix Table 1 as primary outcome. We included the first registration in acute somatic inpatient care starting from the day after inclusion in the cohort. Only the primary or first secondary diagnosis was used as has been previously done [30, 31]. The secondary outcome was the occurrence of ischemic stroke. Validation studies have shown a positive predictive value of 98.6% for the combined stroke/TIA diagnosis and a sensitivity of 93.5% [32].

Comedication and comorbidity definition

We defined baseline drug use as claims in the six months prior to the index date (Table 1). We included claims of drugs that are known to influence the risk for bleeding and/or stroke, as they can introduce confounding. In addition, we assessed if patients had AD prescription in the year prior to inclusion. We also included comorbidities registered in the database before inclusion of the patient (Table 1). For anemia, a prior bleed, and a prior stroke/TIA/embolism, we also specifically assessed diagnoses recorded in the three months before inclusion and the year before inclusion, to further identify high-risk patients. Finally, we calculated the years between the first AF diagnosis and index date for each patient.

Statistical analyses

We used descriptive statistics to present baseline characteristics and to calculate IRs per 100 person-years. We used a Cox proportional hazards model to calculate HRs with 95% confidence intervals (CIs), and to control for potential confounders. The primary outcomes, severe bleed and stroke, were analyzed in separate models. We used the aHR to calculate an adjusted IR in patients on current AD treatment, in order to estimate an adjusted risk difference. To test to the robustness of our findings, we conducted several sensitivity analyses, including a propensity score matched analysis. SAS Enterprise Guide 7.1 was used for all statistical analyses.

Cox proportional hazards model

We used a Cox proportional hazards model to assess the association between current AD use and risk for severe bleed and stroke compared to patients without current AD use. In the models, we adjusted for age, sex, OAC class (i.e. warfarin or NOAC), year of inclusion, years since AF diagnosis, baseline medication and comorbidities as presented in Table 1. We used age and years since AF diagnosis as continuous variables. In the model, AD use was included as a time-dependent variable and we compared person-time with AD treatment to person-time without current AD treatment.

Besides the main model, which included any OAC treatment, we constructed two models, one with only warfarin users and one with only NOAC users. In the NOAC model, we also included a variable for the dose of the NOAC (i.e., standard or reduced). These models were analyzed similarly to the main analyses, to gain insight in potential differences between NOACs and warfarin.

Table 1. Baseline characteristics of patients receiving an antidepressant during follow-up and patients not receiving an antidepressant during follow-up. *[1] Other antidepressants are: bupropion, duloxetine, mianserin, mirtazapine, and moclobemide. AD: antidepressant, COPD: chronic obstructive pulmonary disease, NSAID: non-steroidal anti-inflammatory drug, RAAS: renin-angiotensin-aldosterone-system, SSRI: selective serotonin reuptake inhibitor, TCA: tricyclic antidepressant, TIA: transient ischemic attack.

	Baseline cohort	
	Patients without AD	**Patients with AD**
n	26291	4304
Age at index, years (mean (sd))	73.09 (11.1)	75.62 (10.8)
Female	10 957 (42%)	2 499 (58%)
Warfarin treatment	14 789 (56%)	2 300 (53%)
NOAC treatment	11 502 (44%)	2 004 (47%)
Reduced dose NOAC treatment	3447 (13%)	823 (19%)
Years since first AF date (mean (sd))	1.65 (3.1)	1.75 (3.2)
Valvular AF	334 (1%)	67 (2%)
AD class		
SSRI	N/A	2 625 (61%)
TCA	N/A	487 (11%)
Other *[1]	N/A	1 192 (28%)
Antidepressant use in year prior to inclusion	548 (2%)	3 218 (75%)
Aspirin	11 525 (44%)	2 014 (47%)
NSAID	3 177 (12%)	620 (14%)
Clopidogrel	1 120 (4%)	284 (7%)
Other antiplatelets	562 (2%)	156 (4%)
Corticosteroids	2 035 (8%)	419 (10%)
Diuretics	6 999 (27%)	1 445 (34%)
Beta blocker	14 963 (57%)	2 617 (61%)
Calcium channel blocker	7 002 (27%)	1 157 (27%)
RAAS inhibitor	12 333 (47%)	2 073 (48%)
Lipid lowering agent	8 105 (31%)	1 503 (35%)
Antidiabetic drug	3 093 (12%)	582 (14%)
Gastro protective agent	4 795 (18%)	1 368 (32%)
Anemia < 3 months	344 (1%)	80 (2%)
Major bleeding < 3 months	153 (1%)	34 (1%)
Stroke/TIA/embolism <3 months	1 652 (6%)	3 94 (9%)
Anemia 3 - 12 months	380 (1%)	105 (2%)
Major bleeding 3 - 12 months	180 (1%)	55 (1%)
Stroke/TIA/embolism 3 - 12 months	422 (2%)	148 (3%)
Anemia ≥ 12 months	2 939 (11%)	762 (18%)
Major bleeding ≥ 12 months	1 447 (6%)	427 (10%)
Stroke/TIA/embolism ≥ 12 months	2 424 (9%)	747 (17%)
Alcoholism	1 065 (4%)	384 (9%)
Hypertension	17 689 (67%)	3 223 (75%)
Abnormal liver function	613 (2%)	119 (3%)
Renal disease	2 041 (8%)	498 (12%)

Table 1. (continued)

	Baseline cohort	
	Patients without AD	**Patients with AD**
Heart failure	5 996 (23%)	1 280 (30%)
Diabetes	4 780 (18%)	961 (22%)
Vascular disease	7 047 (27%)	1 415 (33%)
Cancer	5 596 (21%)	1 104 (26%)
COPD	2 382 (9%)	651 (15%)
≥ 2 Falls	2 954 (11%)	803 (19%)
Dementia, delirium, or other mental disorders due to known physiological condition.	995 (4%)	556 (13%)
Mental disorder due to psychoactive substance use	1 518 (6%)	519 (12%)
Schizophrenia	139 (1%)	79 (2%)
Mood disorder	1655 (6%)	1 993 (46%)
Anxiety	2 397 (9%)	1 516 (35%)
Behavioral syndromes	2 218 (8%)	814 (19%)
Disorder in personality and behavior	52 (0%)	40 (1%)
Unspecified mental disorder	116 (0%)	63 (1%)
Year of index date		
2011	2 172 (8%)	286 (7%)
2012	4 517 (17%)	617 (14%)
2013	3 487 (13%)	494 (11%)
2014	6 305 (24%)	1 059 (25%)
2015	5 016 (19%)	935 (22%)
2016	4 794 (18%)	913 (21%)

Stratified analyses

We tested for significant interaction terms and conducted stratified analyses to assess if an association was modified by the following pre-specified subgroups; gender, age <80 or ≥80 years, type of AD (SSRI, TCA, other), AD use in the year prior to inclusion, and type of OAC (NOAC or warfarin).

Sensitivity analyses

Propensity score matching

In order to further address potential confounding, we calculated propensity scores for the probability of receiving an AD during the year of follow-up. To calculate the propensity score we performed a logistic regression conditional on age, gender, OAC class, year of inclusion, years since AF diagnosis, and baseline medication and comorbidities as presented in Table 1. With the Greedy matching algorithm [33], we matched each patient receiving an AD during follow-up to one patient not receiving an antidepressant during follow-up, based on the propensity score. Matching was done using calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score. We considered matching successful if the SMD for all covariates was below 0.1.

We also used propensity score matching to analyze the risks in different OAC treatment groups. For this, we conducted separate matching procedures for the two OAC treatment groups. When matching NOAC patients, we also included a variable for the dose of the NOAC (i.e., standard or reduced) in the logistic regression to calculate the propensity score.

Falsification endpoint

We analyzed a falsification endpoint to assess whether our results could be due to residual and unmeasurable confounding [34, 35]. We used a composite endpoint of acute upper respiratory infection, influenza, and pneumonia, registered in secondary inpatient or outpatient care, and requiring acute somatic care (i.e. all ICD-10 codes starting with J0 and J1). ADs are not believed to increase the risk for these diseases, but they could be related to residual and unmeasurable confounding (e.g. socioeconomic status, lifestyle factors, etc.). We analyzed the composite falsification endpoint with the same definitions as the main analyses, with the assumption of similar confounders for the falsification endpoint as for the study endpoints.

Former-users and never-users

We conducted sensitivity analyses by comparing person-time of current AD use with never-use person-time (i.e., person-time from patients never receiving an AD during follow-up). We also compared never-use person-time with former-use person-time (i.e., the unexposed person-time after an AD prescription has ended, but before follow-up has ended).

With this analysis, we can assess potential residual confounding due to unknown confounders that are more frequently present in AD users, regardless of receiving an AD at that time.

Exposure definitions

We used alternative definitions for the AD exposure since this definition can influence the results. We constructed AD treatment episodes with a grace period for non-compliance of 20% and by calculating the expected treatment duration using the DDD.

Censoring

We added two additional censoring moments in the main Cox model with all patients. First, we censored patients when they claimed a prescription for any antiplatelet agent, second, we censored patients when they claimed a prescription for any non-steroid anti-inflammatory drug, since antiplatelet and non-steroid anti-inflammatory drug therapy influence the risk for both stroke and bleeds [36].

RESULTS

A total of 134 016 patients had a diagnosis code for AF in the Stockholm healthcare database (Vårdanalysdatabasen, VAL). Of these, 30 595 received a new prescription for any OAC within the study period and were included in the cohort, 17 089 with warfarin and 13 506 with a NOAC. A total of 4 303 (14.1%) of these patients claimed a prescription for an AD during the year of

follow-up, yielding 2 226 person-years of current AD treatment, and 22 860 person-years of no current AD treatment.

AD use occurred slightly more often in the NOAC treated group (13.5% with warfarin vs 14.8% with a NOAC) and SSRIs were the most commonly used ADs (61.0%). Table 1 shows the baseline characteristics of the cohort. Patients receiving an AD during follow-up were older (75.6 vs. 73.1 years of age), more often female (58% vs 42%), had more comorbidities, and used more comedication compared to the patients not receiving an AD.

A total of 712 severe bleeds and 551 strokes occurred during the year of follow-up (Table 2). The most frequently occurring type of bleed was a gastrointestinal bleed (GIB) (50.9%) and ischemic strokes accounted for 63.5% of the composite stroke endpoint.

Bleeding risk

The incidence rate (IR) of severe bleeds during person-time with current AD use was 4.7 per 100 person years, compared to 2.7 per 100 person years during person-time without current AD use. After adjustment, this yielded an adjusted hazard ratio (aHR) of 1.42 (1.12 to 1.80) (Table 2). Based on the adjusted IR of severe bleeds per 100 person years we estimated a risk difference of 1.1 bleeds per 100 person-years during concomitant AD use (see Figure 1).

Table 2 also shows the aHR for different types of bleeds; both GIBs (aHR 1.42; 1.02 to 1.98) and other severe bleeds (aHR 1.75; 1.09 to 2.79) were significantly increased. The risk of intracranial bleeds was not associated with AD use (aHR 1.09; 0.66 – 1.80).

In the separate models for warfarin and NOAC users, we found similar results as in the main model. Both for NOAC and warfarin users the risk was increased, but non-significant in warfarin users (aHR 1.29; 0.92 to 1.81). When checking for an interaction in the model, this was non-significant (p=0.730), meaning no statistically significant difference in risk between warfarin and NOACs.

Stroke risk

The IR of the stroke endpoint during AD use was 2.5 per 100 person years, compared to 2.1 per 100 person years during episodes without AD use (see Figure 1). After adjustment, this yielded an aHR of 1.23 (0.93 to 1.62) (Table 2). The aHR was 1.31 (0.89 to 1.93) in NOAC treated patients and 1.12 (0.75 to 2.24) in warfarin treated patients. The secondary outcome ischemic stroke was not significantly increased.

Stratified analyses

Analyses stratified on sex, age-group, type of AD (i.e., selective serotonin reuptake inhibitor, tricyclic antidepressant, or other), or AD use in the year prior to inclusion yielded no statistically significant different results in any subgroup, i.e., there were no significant interactions (Table 3). Stratification based on OAC class (i.e., NOAC or warfarin) yielded a p for interaction of 0.730 for severe bleeds and 0.201 for the stroke endpoint, indicating no different effects in the two OAC classes (aHRs shown in table 2).

Table 2. Number of events per treatment group, adjusted hazard ratios, and absolute risk difference of bleeds and stroke. Hazard ratios adjusted age, sex, OAC class, year of inclusion, years since AF diagnosis, and comorbidities and comedication as presented in Table 1. AD: antidepressant, CI: confidence interval, GIB: gastrointestinal bleed, aHR: adjusted hazard ratio, NOAC: non-vitamin K oral anticoagulant, OAC: oral anticoagulant, TIA: transient ischemic attack.

		Number of outcomes		Adjusted HR	
		AD non-users	AD users	(95% CI)	Risk difference
All OAC	Person Years	22860	2226		
Bleeds	Severe bleed	607	105	1.42 (1.12 – 1.80)	1.1
	GIB	309	54	1.42 (1.02 – 1.98)	0.6
	Intracranial bleed	160	23	1.09 (0.66 – 1.80)	0.1
	Other severe bleed	138	28	1.75 (1.09 – 2.79)	0.5
Strokes	TIA/Ischemic Stroke/ Unspecified	474	77	1.23 (0.93 – 1.62)	0.5
	Ischemic Stroke	298	52	1.29 (0.92 – 1.81)	0.4
NOAC	Person Years	10305	1084		
Bleeds	Severe bleed	253	55	1.58 (1.12 – 2.21)	1.4
	GIB	142	29	1.32 (0.83 – 2.10)	0.4
	Intracranial bleed	57	8	1.02 (0.45 – 2.34)	0.0
	Other severe bleed	54	18	3.02 (1.62 – 5.64)	1.1
Strokes	TIA/Ischemic Stroke/ Unspecified	199	42	1.31 (0.89 – 1.93)	0.6
	Ischemic Stroke	132	28	1.25 (0.78 – 2.02)	0.3
Warfarin	Person Years	12555	1142		
Bleeds	Severe bleed	354	50	1.29 (0.92 – 1.81)	0.8
	GIB	167	25	1.57 (0.97 – 2.54)	0.8
	Intracranial bleed	103	15	1.08 (0.58 – 2.01)	0.1
	Other severe bleed	84	10	1.02 (0.49 – 2.12)	0.0
Strokes	TIA/Ischemic Stroke/ Unspecified	275	35	1.12 (0.75 – 2.24)	0.3
	Ischemic Stroke	166	24	1.35 (0.83 – 2.19)	0.5

Sensitivity analyses

Propensity score matching

Using propensity score matching, 3 802 patients receiving an AD during follow-up were matched to the same number of patients not receiving an AD. Baseline characteristics after matching were almost identical and all standardized mean differences (SMDs) were below 0.1, indicating successful matching (Appendix Table 2).

For severe bleeds, the results were similar as with the main analysis (Appendix Table 3). For stroke, the model yielded a HR of 1.47 (1.08 to 2.02).

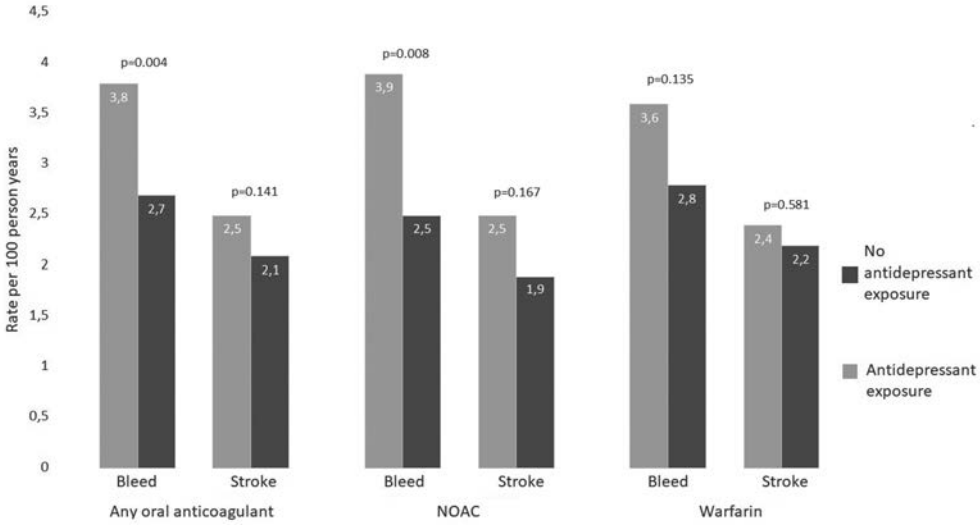

Figure 1. Rates of stroke and bleed per 100 person-years after adjustment for confounders for patients with concomitant antidepressant use and for patients with anticoagulant therapy alone. Rates are shown for all oral anticoagulants and stratified for non-vitamin K oral anticoagulants and warfarin. NOAC: non-vitamin K oral anticoagulant

Falsification endpoint

The composite falsification endpoint of acute upper respiratory infection, influenza, and pneumonia showed an aHR of 1.08 (0.78 to 1.48) in the Cox regression model, showing no indication of residual confounding in this analysis (Appendix Table 4). None of the subgroup analyses showed any significantly increased risk.

Former-users and never-users

Comparing person-time of current use with person-time for individuals who never used an AD yielded similar results as the main analyses; an increased risk for severe bleeds and not for stroke.

Comparing person-time of former users of ADs with person-time of non-users yielded non-significant aHRs of 1.11 (0.73 to 1.69) for severe bleeds and 0.59 (0.33 to 1.07) for stroke, showing no indication for residual confounding (Appendix Table 5).

Exposure definitions

Using different exposure definitions of AD treatment (i.e., using the defined daily dose (DDD) to create exposure periods, and including a 20% grace period for non-compliance) yielded similar results as the main analysis (Appendix Table 6).

Censoring

Censoring the patients when they received antiplatelet therapy or non-steroid anti-inflammatory drug therapy yielded similar results as the main analysis (Appendix Table 6).

Table 3. Adjusted hazard ratios for severe bleeds and stroke risk, stratified by sex, age (<80 and ≥80 years of age), antidepressant class, and prior antidepressant use. Other antidepressants are: bupropion, duloxetine, mianserin, mirtazapine, and moclobemide. Hazard ratios adjusted age, sex, OAC class, year of inclusion, years since AF diagnosis, and comorbidities and comedication as presented in Table 1. AD: antidepressant, CI: confidence interval, aHR: adjusted hazard ratio, SSRI: selective serotonin reuptake inhibitor, TCA: tricyclic antidepressant

	Bleed		Stroke	
	Adjusted HR (95% CI)	**p for interaction**	**Adjusted HR (95% CI)**	**p for interaction**
Sex				
Male	1.57 (1.07 – 2.32)	0.578	1.53 (0.97 – 2.40)	0.668
Female	1.40 (0.98 – 2.00)		1.37 (0.91 – 2.08)	
Age				
<80	1.46 (1.00 – 2.12)	0.940	1.35 (0.87 – 2.09)	0.623
≥80	1.48 (1.03 – 2.13)		1.52 (1.00 – 2.32)	
AD class				
SSRI	1.30 (0.90 – 1.88)	0.393	1.13 (0.73 – 1.75)	0.085
TCA	1.53 (0.74 – 3.17)		1.44 (0.58 – 3.60)	
Other *[1]	1.73 (1.17 – 2.55)		1.92 (1.25 – 2.95)	
AD use in year prior to index date				
Yes	1.89 (1.14 – 3.15)	0.382	1.28 (0.88 – 1.88)	0.110
No	1.50 (1.09 – 2.08)		2.04 (1.18 – 3.52)	

DISCUSSION

In the current population-based cohort study, we found an increased risk for severe bleeds in OAC treated AF patients with concomitant AD therapy. We found a non-significant trend towards an increased risk of stroke. The observed risks were similar for NOAC and warfarin treatment, and different ADs (i.e., SSRI, TCA, or other ADs). Increases in bleeding risk were significant for GIBs and other severe bleeds but not for intracranial bleeds. Sensitivity analyses added to the robustness of our findings and showed no indication for residual and unmeasured confounding. However, in a sensitivity analysis using propensity score matching the stroke risk was significantly increased.

Study strengths

This is to our knowledge the first study to investigate both stroke and bleeding risk when combining ADs with OACs, as well as describing bleeding risk when combining ADs with NOACs. We addressed a clinically relevant research question for which evidence has been very limited so far. Both AF and OAC and AD use are increasing [1, 37–39], which will result in higher numbers of patients receiving this combination. A major strength of this study is the completeness of the VAL database, which contains full healthcare coverage of an entire healthcare region, resulting in high external validity of our findings. The other major strength of this study is the robustness of our design. We used different approaches to test our hypotheses and validated our results by several sensitivity analyses and additional tests to check for residual confounding. The sensitivity analyses yielded similar results

and additional tests all showed no signs of major residual confounding, which supports the validity of our results.

Study limitations

Our study has some limitations. First, this is an observational study, and despite all efforts, one can never completely rule out unmeasured confounding. Depression is a known risk factor for stroke and could act as a confounder, even after adjusting for it, since diagnoses for depression might be lacking. There is no evidence that depression is a risk factor for severe bleeds, and therefore these results are not potentially biased by depression as confounder. Second, one is never sure if a patient actually takes the medication as prescribed. Sensitivity analyses by defining AD treatment episodes in different ways yielded similar results, but uncertainty still exists whether patients took their prescribed medication at the time of an event. Third, we used a conservative approach in defining outcomes, especially for strokes. With that, we avoid misclassification, but also probably underestimate the incidence of strokes. Fourth, the VAL database lacks information on lifestyle factors such as smoking.

Previous studies

Previous studies have reported an approximate 30% increase in the risk for severe bleeds when combining warfarin treatment with ADs [20–23]. Our study confirmed these findings, and showed a similarly increased risk when combining ADs with NOACs. Contrasting to previous work, we found a similarly increased risk for all AD classes, while others found an increased risk only for SSRIs in combination with warfarin. There is, however, evidence suggesting an increased bleeding risk independent of AD class in patients in general [7, 8], or in patients on concomitant non-steroid anti-inflammatory drug treatment [40]. One recent meta-analysis of observational studies showed an increased bleeding risk for mirtazapine and bupropion, both of which have very little or no influence on the serotonin transporter [41]. For mirtazapine, it is hypothesized the 5HT-2A receptor affinity increases the risk for bleeding [42], as serotonin mediated enhancement of platelet activation in whole blood is mediated by 5HT-2A receptors [43]. For bupropion, it is hypothesized that the effects on dopamine and noradrenaline neurotransmission increase the risk for bleeding [41]. These findings are supported by the new insights from our study and suggest that TCAs or other antidepressants are not safer alternatives to SSRIs in OAC treated patients.

We are, to our knowledge, the first to report on the association between concomitant OAC and AD use regarding the risk of suffering ischemic stroke. Studies have shown an increased risk for ischemic stroke with AD use in general, but this was without concomitant OAC treatment [7, 9–11]. Our data suggests an increased risk of stroke when combining OACs and ADs, and in the propensity score matched model this increase was statistically significant. A study in another larger database may confirm these signals. Depression appears to increase the risk of suffering stroke [14], but it is noteworthy that AD treatment may counterbalance the beneficial effects of OAC treatment in the prevention of stroke in AF patients.

We found no difference in the results with warfarin or NOAC treatment strategies or for different AD classes. Therefore, we cannot recommend any combination to be the safest should a patient have indications for both treatments. We have shown an increased risk for severe bleeds in all patients, and therefore increased awareness is recommended when prescribing any of the studied combinations. A critical consideration for the need of an AD is recommended when it is combined with OAC therapy.

Conclusion

In this study of a complete healthcare region we found that AD use in OAC treated AF patients was associated with an increased risk for severe bleeds. In addition, we found suggestions of an increased risk for stroke that merit further investigations. We found no differences between OAC treatment strategies, or between different AD classes. Increased awareness and careful follow-up of patients receiving this combination is warranted.

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APPENDICES

Appendix table 1. The used ATC-codes for prescription claims and the used ICD-10 codes for comorbidities and outcomes.

Diagnosis	ICD-code beginning with
Alcohol abuse	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714
Anemia	D50-64
Any severe bleed	I60-62, I690-I692, S064-S066, I850, I983, K25-28 (subcodes 0-2 and 4-6 only), K625, K922, D500, D629, J942, I312, H431, H356
Atrial fibrillation	I48
Behavioral syndromes	F50-59
Cancer	entire C-series
COPD/Emphysema	J43-44
Dementia	F00-F03
Diabetes	E10-E14
Disorder in personality and behavior	F60-69
Frequent falls (more than one registration)	W00-19
Heart failure	I50
Hypertension	I10-I15
Ischemic stroke, arterial embolism, and stroke, unspecified	I63, I64, I679, I693, I694, I698, I67-, I69-, Z866A, Z866B, Z867C, G450, G451, G452, G453, G458, G45.9, G45-, I74
Intracranial bleeding	I60-I62, I690-I692, S064-S066
Liver disease	K70-77
Obesity	E65-66
Renal disease	N17, N183, N184, N185, N189
Unspecified mental disorder	F90-99
Vascular disease	I20-I25, I70, I739
Venous thromboembolism	I26, I80-I82
Valvular AF	Procedure codes: FCA60, FDC10, FGE00, FGE96, FJF00, FJF96, FKD00, FKD96, FMD00, DMF96. ICD-10: Z952, I050, I052, I342

Treatment	ATC-code beginning with
Acetylsalicylic acid (aspirin)	B01AC06
Apixaban	B01AF02
Beta Blockers	C07
Calcium Channel Blockers	C08
Clopidogrel	B01AC04
Corticosteroids	H02A
Dabigatran	B01AE07
Diabetic Drugs	A10A, A10B
Diuretics	C03A, C03B, C03C, C03D, C03E
Gastro protective agents	A02B
Lipid Lowering Agents	C10A, C10B

Appendix table 1. (continued)

Treatment	ATC-code beginning with
NSAIDs	M01A
Other antiplatelets	B01AC07, B01AC08, B01AC22, B01AC24
Other antidepressants	N06AX11, N06AX03, N06AX12, N06AG02, N06AX21
RAAS inhibitors	C09
Rivaroxaban	B01AF01,B01AX06
SSRIs	N06AB10, N06AX16, N06AB04, N06AB06, N06AB03, N06AB05
TCAs	N06AA09, N06AA10, N06AA21, N06AA04
Warfarin	B01AA
Outcomes	**ICD-10 code beginning with**
Any severe bleed	I60-62, S064-S066, I850, I983, K25-28 (subcodes 0-2 and 4-6 only), K625, K922, D500, D629, J942, I312, H431, H356
Gastrointestinal bleed	K25-28 (subcodes 0-2 and 4-6 only), K625, K922
Intracranial bleed	I60-I62, S064-S066
TIA/ischemic stroke/stroke unspecified	I63, I64, G450, G451, G452, G453, G458, G459
Ischemic stroke	I63

Appendix table 2. Baseline characteristics and standardized mean differences after propensity score matching. The left column after matching all patients, middle after matching only NOAC patients, right column after matching only warfarin patients. SMD: standardized mean difference, AD: antidepressant, SSRI: selective serotonin reuptake inhibitor, TCA: tricyclic antidepressant, NSAID: non-steroidal anti-inflammatory drug, RAAS: renin-angiotensin-aldosterone-system, TIA: transient ischemic attack, COPD: chronic obstructive pulmonary disease.

	Baseline after matching			Baseline NOAC patients after matching			Baseline warfarin patients after matching		
	Without AD	**With AD**	**SMD**	**Without AD**	**With AD**	**SMD**	**Without AD**	**With AD**	**SMD**
n	3802	3802		1743	1743		2047	2047	
Mean age at index	75.51	75.26	0.015	76,08	75,55	0.036	74,74	75,17	0.02
Female	58%	56%	0.033	60%	58%	0.062	57%	55%	0.016
NOAC treatment	46%	46%	0.002	100%	100%	0	0%	0%	0
Reduced dose NOAC	19%	18%	0.03	41%	40%	0.032	0%	0%	0
Years since AF diagnosis (mean)	1,77	1,74	0.008	2,02	1,95	0.02	1,49	1,56	0.025
AD class									
SSRI	N/A	60%	N/A	N/A	58%	N/A	N/A	63%	N/A
TCA	N/A	12%	N/A	N/A	12%	N/A	N/A	13%	N/A
Other	N/A	27%	N/A	N/A	30%	N/A	N/A	24%	N/A
Concomitant drug use									
Aspirin	46%	46%	0.016	44%	44%	0.02	49%	48%	0.006
NSAID	15%	14%	0.011	16%	16%	0.034	14%	13%	0
Clopidogrel	6%	6%	0.021	5%	6%	0.023	6%	6%	0.004
Other antiplatelets	3%	3%	0.01	3%	3%	0.043	4%	4%	0.008
Corticosteroids	11%	10%	0.02	9%	9%	0.016	11%	10%	0.039
Diuretics	35%	33%	0.036	33%	30%	0.025	36%	35%	0.032
Beta blocker	61%	60%	0.012	60%	59%	0.015	61%	61%	0.011
Calcium channel blocker	27%	27%	0.015	26%	27%	0.008	27%	28%	0.013
RAAS inhibitor	48%	48%	0.011	47%	47%	0	48%	48%	0.015
Lipid lowering agent	35%	35%	0.018	32%	31%	0.007	37%	37%	0.016
Antidiabetic drug	14%	13%	0.005	13%	12%	0.023	14%	15%	0.031
Gastro protective agent	31%	30%	0.005	29%	30%	0.029	30%	29%	0.01

Appendix table 2. (continued)

	Baseline after matching			Baseline NOAC patients after matching			Baseline warfarin patients after matching		
	Without AD	With AD	SMD	Without AD	With AD	SMD	Without AD	With AD	SMD
Comorbidities									
Anemia < 3 months	2%	2%	0.002	3%	2%	0.009	2%	2%	0
Major bleeding < 3 months	1%	1%	0.003	1%	1%	0.019	1%	1%	0
Stroke/TIA/embolism <3 months	9%	9%	0.037	9%	8%	0.004	10%	10%	0.011
Anemia 3 - 12 months	2%	2%	0	2%	2%	0.012	2%	2%	0.015
Major bleeding 3 - 12 months	1%	1%	0.007	1%	1%	0	1%	1%	0.009
Stroke/TIA/embolism 3 - 12 months	3%	3%	0.016	3%	3%	0	3%	4%	0.003
Anemia ≥ 12 months	17%	17%	0.016	18%	17%	0.029	17%	17%	0.004
Major bleeding ≥ 12 months	10%	9%	0.006	11%	10%	0.048	9%	8%	0.007
Stroke/TIA/embolism ≥ 12 months	16%	16%	0.004	18%	15%	0.01	17%	16%	0.016
Alcoholism	8%	8%	0.018	8%	9%	0.01	7%	7%	0.008
Hypertension	75%	74%	0.024	75%	74%	0.007	73%	74%	0.011
Abnormal liver function	3%	3%	0.008	3%	3%	0.01	3%	3%	0.018
Renal disease	11%	11%	0.011	10%	10%	0.008	12%	12%	0.015
Heart failure	29%	29%	0.025	26%	26%	0.018	32%	31%	0.017
Diabetes	22%	22%	0.013	22%	21%	0.001	23%	23%	0.022
Vascular disease	33%	32%	0.013	30%	29%	0.008	36%	35%	0.015
Cancer	26%	25%	0.002	26%	25%	0.014	25%	25%	0.02
Mental disorder due to known physiological condition	11%	10%	0.009	12%	13%	0.01	9%	9%	0.007
Mental disorder due to psychoactive substance use	11%	11%	0.011	11%	11%	0.002	10%	10%	0.003
Schizophrenia	1%	1%	0.016	2%	2%	0.022	1%	1%	0.004
Mood disorder	38%	39%	0.022	38%	40%	0.033	38%	38%	0.026
Anxiety	30%	30%	0.007	33%	33%	0.004	28%	27%	0.032
Behavioral syndromes	17%	17%	0.007	17%	17%	0.009	17%	17%	0.01

Appendix table 2. (continued)

	Baseline after matching			Baseline NOAC patients after matching			Baseline warfarin patients after matching		
	Without AD	**With AD**	**SMD**	**Without AD**	**With AD**	**SMD**	**Without AD**	**With AD**	**SMD**
Disorder in personality and behavior	1%	1%	0.012	1%	1%	0.006	1%	1%	0.011
Unspecified mental disorder	1%	1%	0.019	1%	1%	0.005	1%	1%	0.014
COPD	14%	14%	0.028	14%	14%	0.005	13%	14%	0.014
≥ 2 Falls	17%	17%	0.008	21%	20%	0.009	15%	15%	0.005
Year of index date									
2011	7%	7%	0.018	1%	1%	0.008	12%	13%	0.016
2012	14%	15%	0.021	4%	4%	0.012	25%	24%	0.002
2013	11%	12%	0.003	7%	7%	0.013	15%	15%	0.001
2014	25%	24%	0.008	21%	20%	0.006	28%	28%	0.035
2015	21%	21%	0.014	31%	32%	0.01	13%	13%	0.01
2016	21%	21%	0.001	36%	37%	0.006	7%	7%	0.05

Appendix table 3. Results from the sensitivity analyses with propensity score matched cohorts. Number of events per treatment group, crude incidence rates per 100 person years, hazard ratios, and absolute excess risks of bleeds and stroke. AD: antidepressant, CI: confidence interval, IR: incidence rate, OAC: oral anticoagulant, GIB: gastro intestinal bleed, TIA: transient ischemic attack, NOAC: non-vitamin K oral anticoagulant.

		Number of outcomes		Incidence rate			
		AD non-users	AD users	AD non-users	AD users	Hazard ratio (95% CI)	Risk difference
All OAC	Person Years	4163	1939				
Bleeds	Severe bleed	124	83	3.0	4.3	1.44 (1.09 – 1.90)	1.3
	GIB	67	41	1.6	2.1	1.31 (0.89 – 1.93)	0.5
	Intracranial bleed	29	20	0.7	1.0	1.51 (0.85 – 2.66)	0.4
	Other severe bleed	28	22	0.7	1.1	1.69 (0.97 – 2.96)	0.5
Strokes	TIA/Ischemic Stroke/Unspecified	96	66	2.3	3.4	1.47 (1.08 – 2.02)	1.1
	Ischemic Stroke	58	46	1.4	2.4	1.71 (1.16 – 2.52)	1.0
NOAC	Person Years	1979	927				
Bleeds	Severe bleed	56	45	2.8	4.9	1.71 (1.15 – 2.53)	2.0
	GIB	31	21	1.6	2.3	1.46 (0.84 – 2.54)	0.7
	Intracranial bleed	14	8	0.7	0.9	1.20 (0.50 – 2.86)	0.1
	Other severe bleed	11	16	0.6	1.7	3.05 (1.42 – 6.58)	1.1
Strokes	TIA/Ischemic Stroke/Unspecified	44	33	2.2	3.6	1.60 (1.02 – 2.52)	1.3
	Ischemic Stroke	29	21	1.5	2.3	1.55 (0.88 – 2.72)	0.8
Warfarin	Person Years	2170	1006				
Bleeds	Severe bleed	77	44	3.5	4.4	1.25 (0.86 – 1.81)	0.9
	GIB	31	23	1.4	2.3	1.60 (0.93 – 2.75)	0.9
	Intracranial bleed	26	13	1.2	1.3	1.12 (0.57 – 2.17)	0.1
	Other severe bleed	20	8	0.9	0.8	0.86 (0.38 – 1.96)	-0.1
Strokes	TIA/Ischemic Stroke/Unspecified	40	32	1.8	3.2	1.72 (1.08 – 2.74)	1.3
	Ischemic Stroke	24	23	1.1	2.3	2.08 (1.17 – 3.68)	1.2

Appendix table 4. Results from the analyses on the falsification endpoint. Number of events per treatment group and adjusted hazard ratios. Hazard ratios adjusted age, sex, OAC class, year of inclusion, years since AF diagnosis, and comorbidities and comedication as presented in Table 1. AD: antidepressant, HR: hazard ratio, CI: confidence interval, IR: incidence rate, OAC: oral anticoagulant, NOAC: non-vitamin K oral anticoagulant.

		Number of outcomes			
All OAC	**Falsification**	**AD non-users**	**AD users**	**Crude HR**	**adjusted HR (95% CI)**
	Composite	385	55	1.35	1.08 (0.78 – 1.48)
	Acute upper resp infection	111	13	1.28	0.85 (0.44 – 1.63)
	Influenza and pneumonia	329	42	1.37	1.17 (0.81 – 1.69)
NOAC	Falsification				adjusted HR (95% CI)
	Composite	203	26	1.15	0.81 (0.51 – 1.28)
	Acute upper resp infection	49	3	0.56	0.32 (0.09 – 1.10)
	Influenza and pneumonia	154	23	1.33	1.00 (0.61 – 1.65)
Warfarin	Falsification				adjusted HR (95% CI)
	Composite	182	29	1.59	1.42 (0.90 – 2.24)
	Acute upper resp infection	49	10	2.05	1.69 (0.75 – 3.77)
	Influenza and pneumonia	133	19	1.42	1.31 (0.75 – 2.28)

Appendix table 5. Results from the sensitivity analyses comparing former use with non-use and current use with non-use. HR: hazard ratio, CI: confidence interval, NOAC: non-vitamin K oral anticoagulant.

	All adjusted HR (95% CI)	NOAC adjusted HR (95% CI)	Warfarin adjusted HR (95% CI)
Bleed			
Former use vs non use	1.11 (0.73 – 1.69)	0.90 (0.45 – 1.79)	1.27 (0.75 – 2.16)
Current use vs non use	1.36 (1.06 – 1.74)	1.53 (1.08 – 2.16)	1.23 (0.86 – 1.74)
Stroke			
Former use vs non use	0.59 (0.33 – 1.07)	0.39 (0.14 – 1.07)	0.80 (0.38 – 1.67)
Current use vs non use	1.11 (0.83 – 1.48)	1.18 (0.79 – 1.76)	1.02 (0.68 – 1.54)

Appendix table 6. Results from the sensitivity analyses using different exposure definitions and with censoring patients at NSAID treatment or antiplatelet treatment. HR: hazard ratio, CI: confidence interval, NSAID: non-steroidal anti-inflammatory drug, DDD: defined daily dose.

	Bleed Adjusted HR (95% CI)	Stroke Adjusted HR (95% CI)
Main analysis	1.42 (1.12 – 1.80)	1.23 (0.93 – 1.62)
Sensitivity analyses		
Censoring at NSAID treatment	1.38 (1.09 – 1.76)	1.23 (0.93 – 1.62)
Censoring at antiplatelet treatment	1.39 (1.09 – 1.76)	1.23 (0.93 – 1.62)
Exposure with DDD method	1.34 (1.04 – 1.75)	1.09 (0.80 – 1.49)
Exposure with 20% grace period	1.34 (1.06 – 1.70)	1.17 (0.89 – 1.53)

3.3

NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANT AND PROTON-PUMP INHIBITOR COTREATMENT IN RELATION TO UPPER GASTROINTESTINAL BLEEDS IN PATIENTS WITH ATRIAL FIBRILLATION: A MULTI-DATABASE COHORT STUDY

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ABSTRACT

Aim

To evaluate if proton pump inhibitor (PPI) treatment reduce the risk for upper gastrointestinal bleeding (UGIB) in patients with atrial fibrillation (AF) treated with non-vitamin K antagonist oral anticoagulants (NOACs).

Methods and Results

We used a common protocol, common data model approach to conduct a cohort study including AF patients initiated on a NOAC in Stockholm, Denmark, and the Netherlands from April 2011 until July 2018. The outcome of interest was a UGIB diagnosed in a secondary care inpatient setting. We used an inverse probability weighted (IPW) Poisson regression to calculate incidence rate ratios (IRRs), contrasting PPI use to no PPI use periods.

In 164 290 NOAC users with AF, providing 272 570 years of follow-up and 39 938 years of PPI exposure, 806 patients suffered from a UGIB. After IPW, PPI use was associated with lower UGIB rates (IRR: 0.75; 95%-CI: 0.59–0.95). On an absolute scale, the protective effect was modest, and was found to be largest in high risk patients, classified as age 75–84 (number needed to treat for one year (NNTY): 787), age ≥85 (NNTY: 667), HAS-BLED score ≥3 (NNTY: 378), or on concomitant antiplatelet therapy (NNTY: 373). Stratifying by NOAC yielded an IRR of 0.67 for apixaban, 0.64 for dabigatran, and 1.03 for rivaroxaban.

Conclusion

Concomitant treatment with a PPI in NOAC treated AF patients is associated with a reduced risk for severe UGIB. This indicates that PPI cotreatment can be considered, in particular among those with highest baseline risk of UGIB.

INTRODUCTION

Pooled results from clinical trials showed that treatment with non-vitamin K antagonist oral anticoagulants (NOACs) significantly increased the risk for upper gastro-intestinal bleeds (UGIB) compared to warfarin [1]. Proton pump inhibitors (PPI) reduce gastric acid production and prevent ulcer recurrence [2]. In patients on aspirin treatment, which increases the risk for GIB [3], PPIs have been shown to reduce the risk of GIB [4]. Therefore, PPI use is recommended in patients on aspirin treatment with certain comorbidities and comedications [5]. Since clinical trials show an overall increased risk for UGIB associated with NOAC treatment, it is hypothesized that cotreatment with PPI could decrease the risk of UGIB in NOAC users as well.

An observational study from the US showed markedly reduced risks for UGIB associated with PPI use in patients treated with NOACs [6]. In contrast, the COMPASS trial showed no protective effect with respect to GI bleeding overall, while a sub-analysis on gastroduodenal bleeding showed a clearly reduced risk [7]. However, this trial was in patients with stable cardiovascular disease and peripheral artery disease receiving a lower dose of rivaroxaban than in AF (5mg twice daily).

In the absence of convincing results, the guidelines state that PPI treatment *may be* considered to reduce the risk for GIB, especially in those with a history of GI bleeding or ulcer and patients requiring concomitant use of (dual) antiplatelet therapy [8], a statement that was, however, removed in the most recent guidelines [9]. As there is currently limited evidence from randomized studies regarding the effect of PPIs on UGIB in NOAC treated AF patients, observational data is the main source of guidance for this clinically relevant topic. Therefore, the aim of the current study was to assess the association between PPI use and UGIBs in AF patients treated with a NOAC in three Western-European countries.

METHODS

Database

For this population-based cohort-study, we used three different databases; the Swedish Healthcare database in the Stockholm region (complete population, n = 2.3 million), the nationwide Danish health registers (complete population, n = 5.8 million), and the PHARMO-database (random sample from the Dutch population, n = 4 million). The databases are described in detail elsewhere [10–12]. All three databases contain prescription claims data from community pharmacies, registered by ATC codes, and all three databases contain medical diagnostic data from secondary care, registered by ICD-10 codes. In addition, the Stockholm-database also contains medical diagnostic data from primary care, also registered by ICD-10 codes. We used a common protocol and a common data model to combine the data from the different databases.

Study population

From each database, we included all patients dispensed a NOAC with a known history of AF, defined by a registration of the ICD-10 code I48 any time prior to or within 90 days after the first NOAC dispensing, to account for diagnostic lag [13]. Patients entered the cohort at the date of their first ever NOAC prescription (cohort entry date), and we included patients from April 2011 until July

2018. We considered a patient to be on continued NOAC treatment when the patient claimed a prescription for a NOAC within 30 days after the calculated end of the previous prescription (see Appendix Figure 1). We censored patients at an outcome of interest, at the calculated end of their last prescription, when they died, moved out of the region or database, or switched to warfarin treatment. Patients could re-enter the cohort after they stopped their treatment if restarting NOAC therapy, and follow-up was defined in a similar manner after re-entering the cohort. All patients had to have at least three years of follow-up time prior to cohort entry, in order to adequately assess baseline characteristics.

3.3

Exposure definition

During follow-up, patients were considered exposed to PPIs when they claimed a PPI prescription (see Appendix Figure 1). They were considered exposed until the end of the duration of their last consecutive PPI prescription. We considered PPI treatment to be consecutive if a new prescription was claimed within the duration the prior prescription, with another 30-day grace period added to account for irregular fill patterns and minor non-compliance. We calculated the duration of the prescription using the number of tablets dispensed, thus assuming a one tablet a day dosing regimen. To avoid bias from reversed causality (i.e., that patients receive a PPI because of suspected or early symptoms of a UGIB), we used a lag time of 7 days after a first PPI prescription before we considered a patient exposed to PPI.

Outcome definition

The outcome of interest was a diagnosis code indicating a severe UGIB (see Appendix Table 1 for ICD-10 codes). We defined a severe UGIB as a registration of such a bleed in secondary inpatient care. Using this approach for the outcome, validation studies have shown a positive predictive value (PPV) of 98.1 and sensitivity of 82.3% for the Stockholm database [14], and a PPV of 98.0 and a sensitivity of 89.5% for the Danish database [12].

Covariate assessment

Given the non-random allocation of PPIs, potentially introducing confounding by indication, adjustment was needed. We adjusted for age, sex, year of inclusion, days from cohort entry date as well as relevant baseline comorbidities, time-varying comorbidities, and time-varying comedications.

Baseline covariates included comorbidities in the HAS-BLED score (except labile INR): hypertension, renal disease, liver disease, stroke history, prior bleeding or anemia, and alcohol abuse; and comorbidities in the CHA_2DS_2-VASc score, not represented in the HAS-BLED score: heart failure, vascular disease, and diabetes (see Appendix Table 1 for ICD-10 codes). We searched for registrations of relevant diagnosis codes in the three years prior to each patient's cohort entry date.

Time-varying comorbidities included: peptic ulcer, GI cancer, gastritis, esophagitis, gastro esophageal reflux disease (GERD) or dyspepsia, abdominal pain, lower GI problems, and other GI problems (see Appendix Table 1 for ICD-10 codes). As these comorbidities might be markers for an already present UGIB, we added a 7-day lag period to the actual registration date of the diagnosis,

to avoid reverse causality in the assessment of covariates. In addition, as these confounders might change over time, and affect both the risk for UGIB and the chance of PPI prescription, we partitioned follow-up time into 91-day periods, with the individual patient's initial cohort entry date as starting point. We searched for registrations of these diagnosis codes in the three years prior to the first day of the 91-day period. We defined the time-varying comorbidities as acute if the code was registered in the 30 days prior to the first day, as current if it was registered in the 30 – 90 days prior to the first day, as recent if it was registered in the 90 – 365 days prior to the first day, and as long-term if it was registered in the 365 days – three years prior to the first day.

The comedications assessed were aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), clopidogrel, other antiplatelets, oral corticosteroids, diuretics, beta blockers, calcium channel blockers, renin angiotensin aldosterone system (RAAS) inhibitors, statins, oral antidiabetic drugs, insulins, and antidepressants (see Appendix Table 1 for ATC codes). As comedications may change over time, we used the same 91-day periods as for the time-varying confounders. We looked for a prescription in the 180 days prior to the first day of the 91-day period.

Statistical analysis

We used descriptive statistics to present baseline characteristics for each database. To describe PPI users and non-users, we defined patients as users of a PPI if they received a PPI at some point during follow-up. This division was only done to describe the cohorts, as for all other analyses we used time-varying exposure definitions to define PPI exposed periods in order to avoid immortal time bias [15].

Given the time-varying exposure and time-varying covariates, we used time-varying Poisson regression to calculate adjusted incidence rate ratios (IRR) with 95% confidence intervals (CI) for the association between PPI use and UGIB. We used time-varying inverse probability weights (IPWs) to account for confounding introduced by the included covariates. We calculated 90-day period specific probabilities of receiving PPI treatment conditional on the aforementioned covariates using a logistic regression model. The time-varying covariates were included as categorical variables, with the timing of the diagnoses considered, as described above. For each 91-day period, the IPW was calculated by dividing the prevalence of observed PPI treatment during follow-up by the probability of receiving treatment, to obtain a stabilized IPW. All statistical analyses were performed with statistical software R version 4.0.0 and RStudio Desktop version 1.1.463.

Meta-analysis

The analyses could not be conducted centrally on a pooled database due to privacy regulations but was performed locally and separately in the three databases. All study centers used the same protocol, same programming code, and same ICD-10 codes for outcomes and comorbidity codes through a common data model. For all analysis, the results from each database were pooled using a meta-analysis. We performed a Cochran's Q statistic to test for heterogeneity across the databases and used a fixed effects meta-analysis based on the results from this test.

Supplementary analyses

In addition to the main analyses, we performed several stratified analyses. First, we stratified by sex, age-groups (0-64, 65 – 74, 75 – 85, >85), and bleeding risk (HAS-BLED 0-2 and ≥3). Second, we stratified by concomitant antiplatelet and concomitant NSAID use. Third, we stratified by the individual NOACs apixaban, dabigatran, and rivaroxaban (edoxaban was not considered due to the very small sample size). We included an interaction term in our models and used the likelihood ratio test to test whether the interaction terms were significant. As it is not possible to pool results from different likelihood ratio tests through a meta-analysis, we considered a subgroup as an effect-modifier if the likelihood ratio test was significant in two or more databases. In each subgroup, we calculated the number needed to treat for one year (NNTY), by taking the multiplicative inverse of the absolute risk reduction. The absolute risk reduction was estimated with the incidence rate from the untreated group and the adjusted IRR.

Sensitivity analyses

We conducted several sensitivity analyses to test the robustness of our findings. First, we calculated E-values to identify the minimum strength of association that an unmeasured confounder would need to have with both PPI use and UGIB, conditional on the measured confounders, to explain away the observed associations [16]. Second, we tested the association between PPI use and non-GI major bleeds. As PPI use should not affect the risk for those bleeds, they could serve as falsification endpoints and we could assess potential residual confounding [17]. Third, we assessed how the results would be affected by including information on primary care diagnostic data by assessing the association between PPI use and UGIB in the Stockholm healthcare database with and without restricting the analyses to only secondary care data. Fourth, we conducted an analysis in which we had a maximum follow-up of one year. Fifth, we conducted an analysis in which we kept all covariates fixed at baseline. Finally, we conducted an analysis in which we excluded all patients suffering from the outcome of interest in the year prior to inclusion to remove high risk patients and an analysis where we excluded all patients suffering from any bleed or anemia in the year prior to inclusion.

To assess for each covariate how it influenced the exposure-outcome association, and thus what the effect of confounding adjustment is per covariate, we performed an additional analysis in which we created several adjusted Poisson regression models (i.e., without taking IPW into account). In these models we first: added each aforementioned covariate univariately, but still time-dependently; second: added groups of covariates (i.e., age-sex, CHADsVASc- and HAS-BLED comorbidities, GI comorbidities, comedication), and third: performed a full time-dependent covariate adjusted Poisson regression model.

RESULTS

Cohort characteristics

In total, we included 164 290 NOAC users with AF in the study, of whom 46 708 (28%) used a PPI at some point during follow-up (see Table 1 for a summary and Appendix Table 2 for all baseline characteristics). The mean age of the PPI users was slightly higher than for non-users, and women

Table 1. Summary of the baseline characteristics of PPI users compared to PPI non-users stratified by database. The full baseline characteristics are in Appendix table 2.

	Stockholm Total (N=35 031)		Denmark Total (N = 110 225)		PHARMO Total (N=19 034)	
	PPI-user	**PPI non-user**	**PPI-user**	**PPI non-user**	**PPI-user**	**PPI non-user**
Number of patients	11 682	23 349	26 220	84 005	8 806	10 228
Follow-up (Person years)	9 993	45 586	21 762	169 226	8 183	17 820
Age, sex, risk scores						
Female, n (%)	5 771 (49.6%)	10 028 (42.9%)	12 323 (47.0%)	36 962 (44.0%)	3 954 (44.9%)	4 146 (40.5%)
Age, mean (sd)	75.31 (10.36)	74.30 (11.07)	75.83 (10.19)	74.50 (11.11)	73.26 (10.11)	70.97 (10.96)
CHADsVASc, mean (sd)	3.77 (1.84)	3.29 (1.78)	3.22 (1.68)	2.83 (1.66)	2.85 (1.66)	2.37 (1.63)
HAS-BLED, mean(sd)	2.55 (1.22)	2.16 (1.14)	2.19 (1.16)	1.86 (1.12)	1.89 (1.12)	1.52 (1.09)
≥1 GI comorbidity, n (%)	2 330 (20.0%)	1 951 (8.4%)	2 944 (11.2%)	5 159 (6.1%)	562 (6.4%)	450 (4.4%)
NOAC						
Apixaban, n (%)	7 154 (61.5%)	15 876 (68.0%)	8 299 (31.7%)	28 439 (33.9%)	2 072 (23.5%)	2 548 (24.9%)
Dabigatran, n (%)	2 526 (21.7%)	3 930 (16.8%)	9 154 (34.9%)	23 957 (28.5%)	3 673 (41.7%)	3 711 (36.3%)
Rivaroxaban, n (%)	1 929 (16.6%)	3 486 (14.9%)	8 506 (32.4%)	30 295 (36.1%)	2 649 (30.1%)	3 362 (32.9%)
Edoxaban, n (%)	19 (0.2%)	57 (0.2%)	261 (1.0%)	1314 (1.6%)	412 (4.7%)	607 (5.9%)

used PPIs more often in all three databases. In Stockholm, apixaban was the most frequently used NOAC (>60%), while in Denmark and PHARMO all NOACs, except edoxaban, were used to approximately the same extent during the study period. Both the mean HAS-BLED and CHA_2DS_2-VASc scores were higher in PPI users compared to non-users. Patients receiving PPIs more often had GI comorbidities. In total, the cohorts accumulated 272 570 person years of NOAC use of which 39 938 person years were exposed to PPIs. PPIs were most commonly used in the PHARMO database with 31% of all follow-up time being exposed to PPI, while this was 11% in Denmark and 18% in Stockholm. In Stockholm, omeprazole was the most frequently used PPI (72%), while in Denmark this was pantoprazole (60%), and in the PHARMO both were used approximately equally (51% pantoprazole and 41% omeprazole).

Associations PPI use and UGIB

A total of 806 severe UGIBs occurred during 272 570 person-years of follow-up yielding an overall IR of 0.30%/person year (py). The pooled unadjusted (crude) IRR for exposed vs. non-exposed person-time was 1.06 (95% CI: 0.86 – 1.30). The cohorts were however imbalanced on several baseline characteristics. After IPW all covariates had an SMD below 0.1, indicating successful weighting (Appendix Figures 2A-C). Taking the time varying IPW into account, the pooled IRR for UGIB was 0.75 (95% CI: 0.59 – 0.95), indicating a protective effect of PPIs on UGIBs (see Figure 1). The adjusted IRRs were consistent in all three databases; 0.79 (95% CI: 0.49 – 1.26) in Stockholm, 0.72 (CI: 0.53 – 0.97) in Denmark, and 0.85 (CI: 0.39 – 1.85) in PHARMO.

Supplementary results

The incidence of UGIB increased with increasing age groups, as did the protective effect of PPIs, which was greatest in patients above the age of 75 (75-84 IPW IRR: 0.60; 95%-CI: 0.39 – 0.93, ≥85 IPW IRR: 0.64; 95%-CI: 0.40 – 1.03). The NNTY in these groups were 788 and 668, respectively. Patients with a HAS-BLED score of 3 or more experienced twice as many UGIBs as patients with a score below 3 (0.52%/py versus 0.22 %/py), and the protective effect of PPIs was largest in this group as well (IPW IRR 0.51; 95%CI: 0.35 – 0.77, NNTY: 378). Patients with concomitant antiplatelet use had the highest crude rate of UGIB (0.64%/py) and the protective effect of PPI treatment was significantly

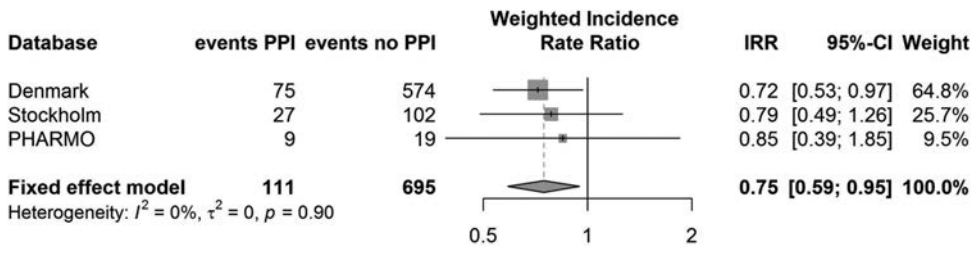

Figure 1. Results from the meta-analysis on the inverse probability weighted incidence rate ratio of upper gastrointestinal bleeds.

greater than in patients without concomitant antiplatelet use (IPW IRR: 0.64; 95%-CI: 0.39 – 1.05, NNTY: 374). Stratifying by sex and concomitant NSAID use yielded no statistically different results.

The protective effect of PPIs on UGIB was only present in patients receiving apixaban or dabigatran (IPW IRR: 0.65; 95%-CI: 0.43 – 0.98 and 0.65; 95%CI: 0.39 – 1.08, respectively) but not in patients receiving rivaroxaban (1.06; 95%-CI: 0.73 – 1.54) (see Table 2).

Sensitivity analysis

The E-value for the point estimate for UGIB was 2.01. This indicates that a potential unobserved confounder would have required a relative risk of 2.01 with both the outcome and PPI use to move the point estimate to neutral.

We found a neutral association between PPI use and the first falsification endpoint of non-GI major bleed (IRR: 1.04; CI: 0.89 – 1.23). Censoring patients after one year of follow-up yielded similar results as in the main analysis (IRR: 0.72; CI: 0.54 – 0.96), as did excluding patients with a UGIB in the year prior to inclusion (IRR: 0.76; CI: 0.60 – 0.97) and exclusion of patients with any bleed or

Table 2. Number of events, follow-up time, incidence rate, crude incidence rate ratio, and inverse probability weighted incidence rate ratio of PPI vs no PPI exposure in different subgroups. NSAID: non-steroidal anti-inflammatory drug; AP: antiplatelet.

	n events	Follow-up time (person years)	Incidence rate (%/y)	Crude IRR (95%-CI)	IPW IRR (95%-CI)	LRT significant *
Age						*2 out of 3*
0 - 64	53	43 542	0.12	2.55 (1.33-4.88)	1.09 (0.48-2.48)	
65 - 74	252	101 012	0.25	1.50 (1.06-2.11)	0.99 (0.65-1.49)	
75 - 84	294	87 954	0.33	0.71 (0.49-1.03)	0.58 (0.37-0.89)	
≥ 85	207	40 063	0.52	0.74 (0.49-1.12)	0.67 (0.42-1.07)	
Sex						0 out of 3
Female	457	149 597	0.31	1.02 (0.77-1.34)	0.66 (0.47-0.92)	
Male	349	122 974	0.28	1.12 (0.83-1.51)	0.88 (0.62-1.24)	
HAS-BLED						*3 out of 3*
Low (0-2)	472	209 553	0.23	1.14 (0.86-1.52)	0.95 (0.7-1.29)	
High (≥ 3)	334	63 018	0.53	0.76 (0.57-1.03)	0.54 (0.36-0.8)	
Concomittant NSAID					1 out of 3	
No	691	249 520	0.28	1.01 (0.81-1.27)	0.74 (0.57-0.96)	
Yes	115	23 050	0.50	1.15 (0.72-1.86)	0.84 (0.46-1.54)	
Concomittant AP					*2 out of 3*	
No	585	239 339	0.24	1.10 (0.87-1.4)	0.80 (0.61-1.06)	
Yes	221	33 232	0.67	0.79 (0.54-1.16)	0.63 (0.38-1.04)	
NOAC						*2 out of 3*
Apixaban	282	93 566	0.30	0.93 (0.67-1.31)	0.67 (0.45-1.01)	
Dabigatran	240	100 105	0.24	1.06 (0.71-1.58)	0.64 (0.39-1.07)	
Rivaroxaban	278	76 842	0.36	1.29 (0.92-1.80)	1.03 (0.71-1.50)	

* The number of databases in which the likelihood ratio test (LRT) was significant. If this test was significant in two or more databases, we considered a subgroup as a relevant effect-modifier.

anemia in the year prior to the event (IRR: 0.78; CI 0.60 – 1.01). Keeping the covariates fixed at baseline yielded no different results (IRR: 0.81; CI 0.64 – 1.03).

Baseline characteristics were comparable to those observed in the main analysis when analyzing only secondary care data (Appendix Table 3). We found comparable results when we used only data from secondary care in Stockholm (IRR: 0.67; CI: 0.34 – 1.20), compared to data from both primary and secondary care (IRR: 0.79; CI: 0.49 – 1.26).

The stepwise adjusted models showed that anemia had the largest univariate effect when adjusting the models, followed by vascular disease and diuretics, and all three moved the point estimate towards a protective effect (Appendix Table 4). All groups of covariates were effective in removing confounding, but no group was as effective as the fully adjusted model and the full IPW model, indicating that adjustment for all covariates was needed. The fully adjusted models showed a larger protective effect compared to the IPW model.

DISCUSSION

In this large multi-country population-based study, covering 162 333 NOAC treated AF patients, we found that PPI use was associated with a 25% reduced risk for UGIB during NOAC treatment. This result was consistent in all three databases. The protective effect was most pronounced in high risk patients, i.e., patients above the age of 75, and patients with a HAS-BLED score of three or higher and/or on concomitant antiplatelet therapy. Interestingly, the protective effect of PPIs was only observed in those treated with apixaban or dabigatran and not in those treated with rivaroxaban.

Our results are in line with what was found in prior observational research and evidence from the single randomized controlled trial available[6, 7]. The COMPASS trial, comparing pantoprazole to placebo in patients treated with rivaroxaban 5mg twice daily, reported a hazard ratio of 0.93 (CI: 0.60 – 1.47) for all upper GI events, while for an upper GI bleeding confirmed by endoscopy or radiography, the HR was 0.25 (CI: 0.07 – 0.89) [7]. However, these results were from patients with stable cardiovascular disease instead of AF patients, and using a lower dose of rivaroxaban than recommended in AF (5mg twice daily instead of 15-20mg once daily). A recent large observational study from the United States reported an adjusted IRR of 0.66 (CI: 0.52 – 0.85) for UGIB in OAC treated AF patients using PPIs, however, this study also included patients on warfarin therapy [6]. In line with our findings, this study also reported the largest risk reduction in patients receiving apixaban and dabigatran (adjusted IRRs of 0.50 and 0.51, respectively), but contrary to our findings, they also found a protective effect in patients receiving rivaroxaban (IRR 0.68).

Clinical implications

As there is currently no randomized trial assessing the efficacy of PPIs in NOAC treated AF patients, and our results are in line with the COMPASS trial and another large observational study [6, 7], we believe that PPI co-treatment can be considered for the prevention of UGIBs in high risk NOAC treated AF-patients (age above 75, a HAS-BLED score above two, and/or receiving concomitant antiplatelet therapy). The numbers needed to treat for one year were 788 (age 75-84), 668 (age ≥85), 378 (HAS-BLED >2), and 374 (antiplatelet). Given that NOAC treatment is lifelong, more realistic

NNTs might be for a five-year period, which would yield NNTs of 158, 134, 76, and 75, respectively. In addition, we used a conservative endpoint by only including specific ICD-10 codes in hospitalized patients. Therefore, the absolute risk for UGIB in our study was low (approximately three times lower than in the clinical trials [1]) and with that, the absolute risk reduction could potentially be higher if the absolute risks were as high as in the clinical trials. It is also conceivable that our results are to some extent affected by residual confounding, since PPIs were primarily channeled to high-risk patients. However, this implies that the true effect is most likely larger than what we could demonstrate.

There has been debate about the risk for adverse cardiovascular events with PPI use [16], but results from a randomized trial showed no increased risk for such events with PPI use compared to placebo [17]. Therefore, we believe that cardiovascular safety is not a reason to refrain from treating high risk NOAC treated AF patients with PPIs for gastroprotection. But, as in line with the most recent ESC guidelines, patient preference should be an important factor when deciding on PPI co-treatment [9].

Limitations

Our study has several limitations. First, despite using time varying IPW, there is still the potential for residual confounding, for example due to lifestyle factors such as smoking. Second, there was potential misclassification of exposure, as we used prescription claims data, which has potentially biased the point estimate towards a neutral association [18]. In addition, in all three settings, PPIs can be bought over-the-counter. Therefore, we might have classified some patients as non-users, while in reality they were using over-the-counter PPIs. Third, we used a conservative approach to define the outcome of interest and might therefore underestimate the true number of events. On the other hand, a conservative approach leads to a higher positive predictive value for the outcome and a lower risk of detection bias. Fourth, NOACs can also be prescribed for other indications than AF, and we have not included patients with those diagnoses.

Strengths

Our study has several strengths. First, we used data from unselected populations from three different European countries, yielding generalizable results to similar populations, especially since the results were consistent in all databases. Second, our results were robust to all sensitivity analyses, indicating that our study results are independent of the analytic choices we made. Third, this is the first study addressing this clinically important question in a European healthcare setting, where prescribing patterns are probably different than in a US setting. In addition, there is currently no randomized trial data addressing the clinical question of the efficacy of PPI in NOAC users and thus observational research can provide guidance.

Conclusion

We found an association between PPI use and a lower risk for severe UGIB in an unselected NOAC treated AF population, which was consistent in three different Northern European healthcare settings. Based on these findings, as well as the results of other studies, we believe PPIs can be useful to reduce the risk of UGIBs in NOAC treated AF patients with a high risk for bleeds.

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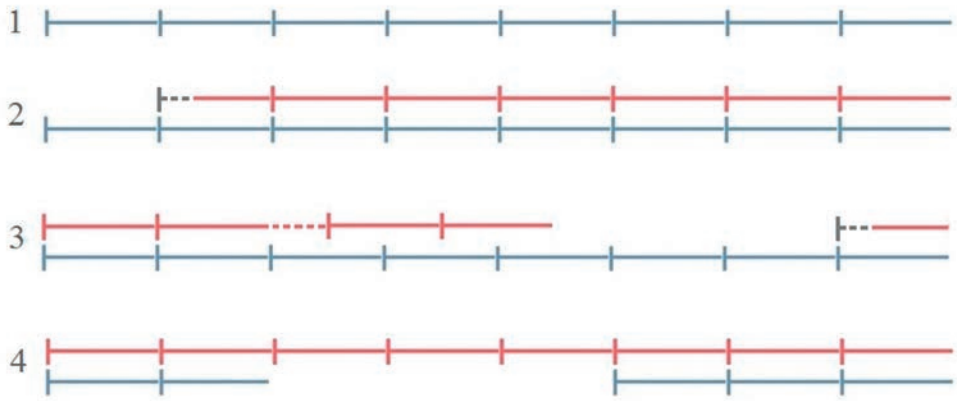
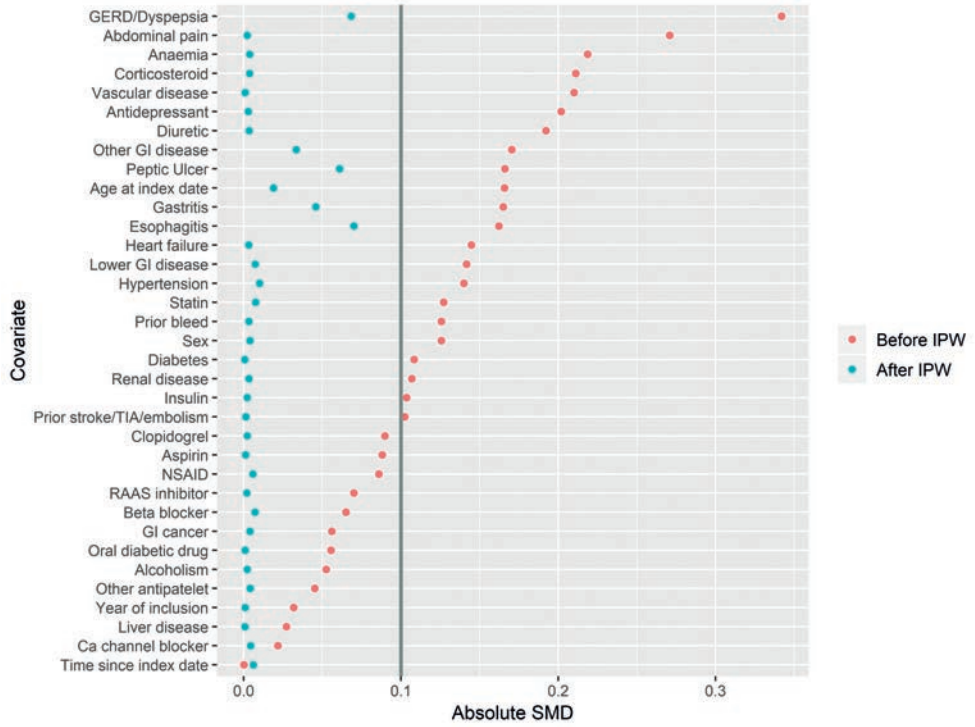
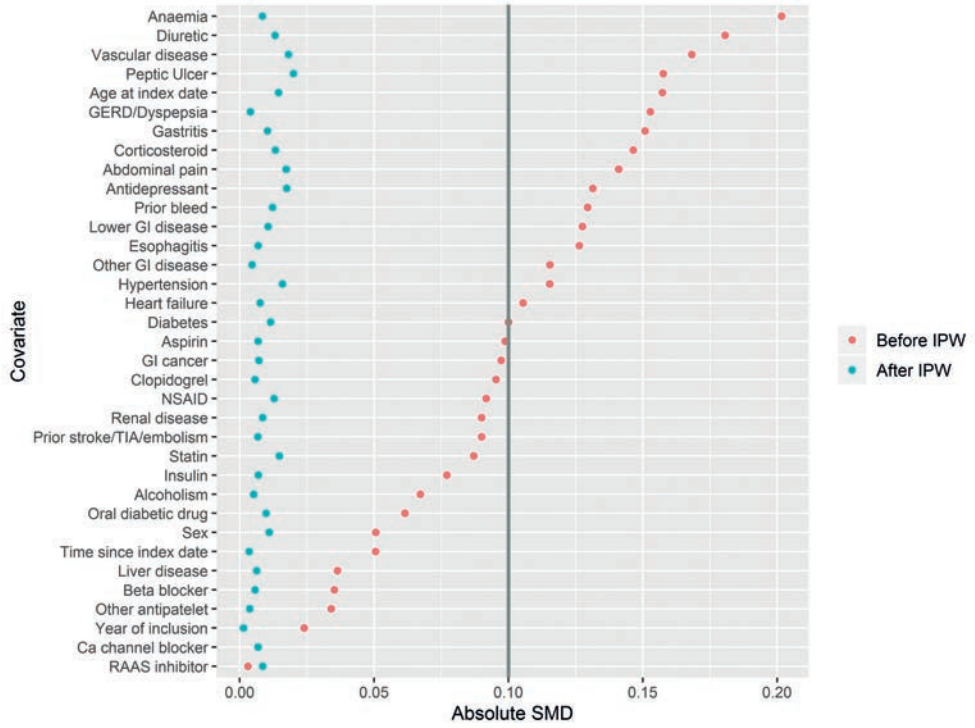


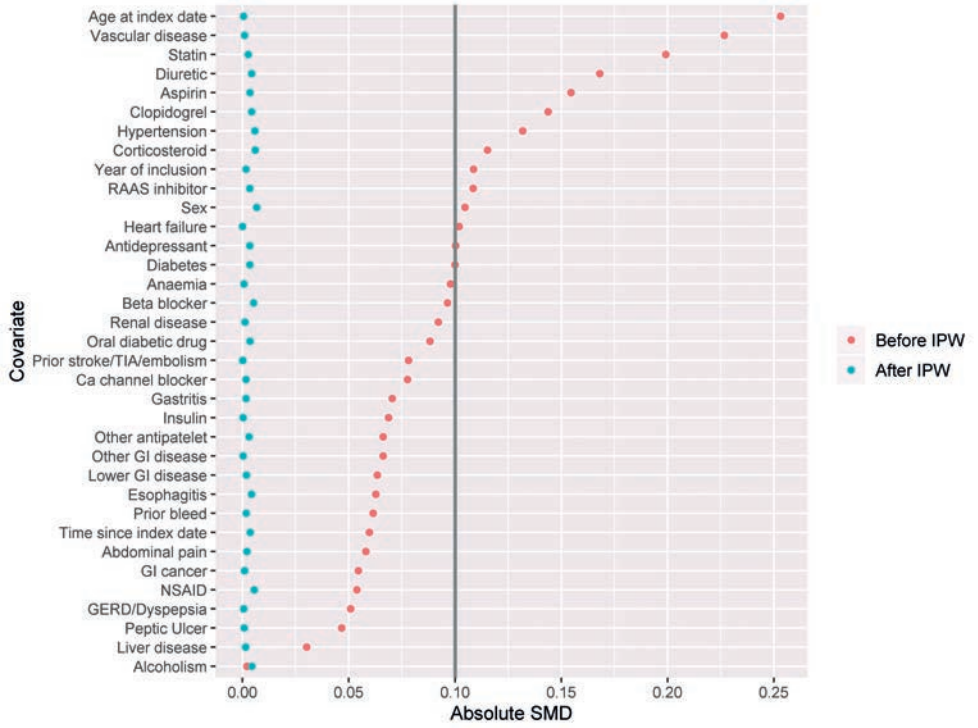
Appendix figure 1. Graphical presentation of four hypothetical patients with different exposure patterns. The vertical lines indicate that a patient claims a prescription and the horizontal lines indicate the duration of a prescription. A blue line is for a NOAC prescription and a red line is for a PPI prescription. Patient 1 is exposed to a NOAC the whole period and is therefore in the cohort the whole time, without any PPI exposure. Patient 2 claims a PPI prescription in the second period, and after a wash-in of 7 days (the grey area), the patient is considered exposed to a PPI the rest of the study period. Patient 3 is taking a PPI from the beginning of the study and is considered exposed to a PPI from the start. After the second PPI prescription, the patient claims a new PPI prescription after the calculated end of the second prescription, but within the 30-day grace period for non-compliance and, therefore, the patient is considered exposed to PPI treatment during that whole period. After the fourth PPI prescription, the patient fails to claim a new prescription within the 30-day grace period and is therefore considered unexposed from the end of the calculated end of the fourth prescription. At the end the patient claims a new PPI prescription and after a wash-in of 7 days the patient is considered exposed to PPI treatment. Patient 4 is taking a PPI from the beginning of the study and is considered exposed to a PPI from the start. After the second NOAC prescription, the patient fails to claim a new NOAC prescription within the 30-day grace period and, therefore, the patient is removed from the cohort during that period. After the patient claims a new NOAC prescription, the patient is once again included in the cohort.



Appendix figure 2a. Standardized mean differences of covariates before and after applying inverse probability weighting in the Stockholm database.



Appendix figure 2b. Standardized mean differences of covariates before and after applying inverse probability weighting in the Denmark database.



Appendix figure 2c. Standardized mean differences of covariates before and after applying inverse probability weighting in the PHARMO database.

Appendix table 1. ATC and ICD-10 codes

Outcome definition	ICD-code beginning with
Upper GI bleed	K25-K28 (sub codes 0, 2, 4, and 6 only) K290, K228, K298, I864
Baseline comorbidities	ICD-code beginning with
Hypertension	I10-I16
Renal disease	N183, N184, N185, N189, E102, E112, E122, E132, E142, I12, N03, N083, N085, N118C, N14, N150, N16, N19, N26, P960, Q601, Q602, Z992
Liver disease	K70-77
Stroke/TIA/embolism	I63, I64, I679, I693, I694, I698, I69, G453, G458, G459, I74, I26, I80, I81, I82
Prior bleed	I60, I61, I62, S064, S065, S066, I850, I983, K25-K28 (sub codes 0, 2, 4, and 6 only) K290, K228, K298, I864, K625, K922, D62, S063C, K920, G951A, I312, J942, K638B, K638C, K661, K868G, N02, R04, R31, R58
Anaemia	D50-59, D60-64
Alcohol abuse	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, T51, Y90, Y91, Y91, Z502, Z714, E529A
Heart failure	I50, I099A, I971A, O754C, O291A, O742A, O754D, O891A, I30, Z035EA
Vascular disease	I20, I21, I22, I23, I24, I25, I70, I739
Diabetes	E10, E11, E12, E13, E14, G590, G632, H280, H360, N083, O240, O241, O242, O243
Peptic ulcer	K25-K28 (sub codes 1, 3, 5, 7, and 9 only)
GI cancer	C15-26
Gastritis	K29
Esophagitis	K20, K220, K2210, K222-229
GERD/dyspepsia	K21, K30
Abdominal pain	R10, R12
Lower GI problems	K57, K60-64
Other GI problems	K31, R11
Medication	**ATC code beginning with**
Apixaban	B01AF02
Dabigatran	B01AE07
Rivaroxaban	B01AF01
Edoxaban	B01AF03
PPI	A02BC
Aspirin	B01AC06
NSAID	M01A
Clopidogrel	B01AC04
Other antiplatelet	B01AC22, B01AC24, B01AC07
Corticosteroids	H02AA01, H02AA02, H02AA03, H02AB
Diuretic	C03A, C03B, C03C, C03D, C03E
Beta blocker	C07A, C07B, C07C, C07D, C07E, C07F
Ca channel blocker	C08C, C08D, C08E, C08G
RAAS inhibitor	C09A, C09B, C09C, C09D, C09X
Statin	C10AA
Oral antidiabetic drug	A10B
Insulin	A10A
Antidepressant	N06A
Falsification endpoint	**ICD code beginning with**
Non GI major bleed	I60, I61, I62, S064, S065, J942, I312, H431, H351

Appendix table 2. Full baseline characteristics per database

	Stockholm Total (N=34977)		Denmark Total (N = 108322)		PHARMO Total (N=19034)	
	PPI user	PPI non-user	PPI user	PPI non-user	PPI user	PPI non-user
n	11 682	23 349	26 220	84 005	8 806	10 228
Person time (years)	9993	45586	21762	169226	8183	17820
Age, sex, risk scores						
Female	5771 (49.6%)	10028 (42.9%)	12323 (47.0%)	36962 (44.0%)	3954 (44.9%)	4146 (40.5%)
Age	75.31 (10.36)	74.30 (11.07)	75.83 (10.19)	74.50 (11.11)	73.26 (10.11)	70.97 (10.96)
CHADsVASc (mean (sd))	3.77 (1.84)	3.29 (1.78)	3.22 (1.68)	2.83 (1.66)	2.85 (1.66)	2.37 (1.63)
HAS-BLED (mean(sd))	2.55 (1.22)	2.16 (1.14)	2.19 (1.16)	1.86 (1.12)	1.89 (1.12)	1.52 (1.09)
≥1 GI comorbidity, n (%)	2330 (20.0%)	1951 (8.4%)	2944 (11.2%)	5159 (6.1%)	562 (6.4%)	450 (4.4%)
NOAC						
Apixaban	7154 (61.5%)	15876 (68.0%)	8299 (31.7%)	28439 (33.9%)	2072 (23.5%)	2548 (24.9%)
Dabigatran	2526 (21.7%)	3930 (16.8%)	9154 (34.9%)	23957 (28.5%)	3673 (41.7%)	3711 (36.3%)
Rivaroxaban	1929 (16.6%)	3486 (14.9%)	8506 (32.4%)	30295 (36.1%)	2649 (30.1%)	3362 (32.9%)
Edoxaban	19 (0.2%)	57 (0.2%)	261 (1.0%)	1314 (1.6%)	412 (4.7%)	607 (5.9%)
Main comorbidities						
Hypertension	7966 (68.5%)	14393 (61.6%)	9558 (36.5%)	25212 (30.0%)	2912 (33.1%)	2737 (26.8%)
Renal disease	906 (7.8%)	1135 (4.9%)	1142 (4.4%)	2460 (2.9%)	610 (6.9%)	522 (5.1%)
Liver disease	140 (1.2%)	189 (0.8%)	268 (1.0%)	580 (0.7%)	148 (1.7%)	124 (1.2%)
Prior stroke/TIA/embolism	2624 (22.6%)	4270 (18.3%)	5408 (20.6%)	14471 (17.2%)	1023 (11.6%)	994 (9.7%)
Alcoholism	368 (3.2%)	601 (2.6%)	677 (2.6%)	1423 (1.7%)	112 (1.3%)	127 (1.2%)
Prior bleed	1692 (14.6%)	2316 (9.9%)	3190 (12.2%)	6691 (8.0%)	410 (4.7%)	335 (3.3%)
Anaemia	1791 (15.4%)	1699 (7.3%)	2426 (9.3%)	3539 (4.2%)	720 (8.2%)	548 (5.4%)
Heart failure	3065 (26.4%)	4850 (20.8%)	4351 (16.6%)	11131 (13.3%)	1221 (13.9%)	1121 (11.0%)
Vascular disease	3031 (26.1%)	3755 (16.1%)	6228 (23.8%)	14048 (16.7%)	2188 (24.8%)	1459 (14.3%)
Diabetes	2414 (20.8%)	3895 (16.7%)	3459 (13.2%)	8566 (10.2%)	1362 (15.5%)	1237 (12.1%)

Appendix table 2. (continued)

	Stockholm Total (N=34977)		Denmark Total (N = 108322)		PHARMO Total (N=19034)	
	PPI user	PPI non-user	PPI user	PPI non-user	PPI user	PPI non-user
GI comorbidities						
Peptic ulcer	189 (1.6%)	42 (0.2%)	309 (1.2%)	191 (0.2%)	13 (0.1%)	3 (0.0%)
Gastrointestinal cancer	124 (1.1%)	149 (0.6%)	414 (1.6%)	765 (0.9%)	141 (1.6%)	109 (1.1%)
Gastritis	199 (1.7%)	72 (0.3%)	294 (1.1%)	265 (0.3%)	41 (0.5%)	16 (0.2%)
Esophagitis	136 (1.2%)	37 (0.2%)	227 (0.9%)	221 (0.3%)	36 (0.4%)	26 (0.3%)
GERD/dyspepsia	530 (4.6%)	188 (0.8%)	370 (1.4%)	495 (0.6%)	40 (0.5%)	16 (0.2%)
Abdominal pain	1028 (8.8%)	881 (3.8%)	857 (3.3%)	1868 (2.2%)	92 (1.0%)	77 (0.8%)
Lower GI problems	611 (5.3%)	681 (2.9%)	949 (3.6%)	2019 (2.4%)	193 (2.2%)	183 (1.8%)
Other GI problems	276 (2.4%)	184 (0.8%)	242 (0.9%)	402 (0.5%)	104 (1.2%)	81 (0.8%)
Comedication						
Aspirin	3837 (33.0%)	5892 (25.2%)	8748 (33.4%)	22930 (27.3%)	2448 (27.8%)	1680 (16.4%)
Vitamin K antagonist	1978 (17.0%)	2438 (10.4%)	6525 (24.9%)	19625 (23.4%)	2371 (26.9%)	2984 (29.2%)
Clopidogrel	560 (4.8%)	600 (2.6%)	2536 (9.7%)	6816 (8.1%)	734 (8.3%)	531 (5.2%)
Other antiplatelets	241 (2.1%)	253 (1.1%)	773 (2.9%)	1614 (1.9%)	348 (4.0%)	189 (1.8%)
NSAID	1380 (11.9%)	1737 (7.4%)	4467 (17.0%)	9975 (11.9%)	1164 (13.2%)	939 (9.2%)
Corticosteroid	1708 (14.7%)	1375 (5.9%)	3207 (12.2%)	6364 (7.6%)	1237 (14.0%)	983 (9.6%)
Diuretic	3663 (31.5%)	5492 (23.5%)	11557 (44.1%)	30465 (36.3%)	2904 (33.0%)	2624 (25.7%)
Beta blocker	7302 (62.8%)	13445 (57.6%)	12591 (48.0%)	36831 (43.8%)	5166 (58.7%)	5395 (52.7%)
Calcium channel blocker	3089 (26.6%)	5932 (25.4%)	7425 (28.3%)	21921 (26.1%)	2196 (24.9%)	2163 (21.1%)
RAAS inhibitor	5312 (45.7%)	9599 (41.1%)	12466 (47.5%)	37509 (44.7%)	4522 (51.4%)	4425 (43.3%)
Statin	4161 (35.8%)	6864 (29.4%)	10788 (41.1%)	30781 (36.6%)	4139 (47.0%)	3676 (35.9%)
Diabetic drug	1199 (10.3%)	2036 (8.7%)	3641 (13.9%)	9917 (11.8%)	1394 (15.8%)	1256 (12.3%)
Insulin	806 (6.9%)	1089 (4.7%)	1280 (4.9%)	3225 (3.8%)	481 (5.5%)	451 (4.4%)
Antidepressant	1978 (17.0%)	2438 (10.4%)	4147 (15.8%)	10768 (12.8%)	783 (8.9%)	657 (6.4%)

Appendix table 3. Baseline characteristics of the Stockholm cohort with and without access to primary care data

	Primary + Secondary	Secondary only
Characteristic		
Female	15799 (45.2%)	12472 (46.6%)
Age	74.64 (10.85)	75.50 (11.05)
CHADsVASc (mean (sd))	3.45 (1.81)	3.25 (1.82)
HAS-BLED (mean(sd))	2.29 (1.18)	2.02 (1.15)
≥1 GI comorbidity	4281 (12.2%)	2302 (8.6%)
NOAC		
Apixaban	23030 (65.8%)	17335 (64.8%)
Dabigatran	6456 (18.5%)	5197 (19.4%)
Rivaroxaban	5415 (15.5%)	4156 (15.5%)
Edoxaban	76 (0.2%)	58 (0.2%)
Comorbidities		
Hypertension	22359 (63.9%)	12864 (48.1%)
Renal disease	2041 (5.8%)	1312 (4.9%)
Liver disease	329 (0.9%)	166 (0.6%)
Prior stroke/TIA/embolism	6894 (19.7%)	4776 (17.9%)
Alcoholism	969 (2.8%)	552 (2.1%)
Prior bleed	4008 (11.5%)	1921 (7.2%)
Anaemia	3490 (10.0%)	2035 (7.6%)
Heart failure	7915 (22.6%)	6100 (22.8%)
Vascular disease	6786 (19.4%)	4503 (16.8%)
Diabetes	6309 (18.0%)	3808 (14.2%)
GI comorbidities		
Peptic ulcer	231 (0.7%)	159 (0.6%)
Gastrointestinal cancer	273 (0.8%)	190 (0.7%)
Gastritis	271 (0.8%)	91 (0.3%)
Esophagitis	173 (0.5%)	84 (0.3%)
GERD/dyspepsia	718 (2.1%)	125 (0.5%)
Abdominal pain	1909 (5.5%)	212 (0.8%)
Lower GI problems	1292 (3.7%)	395 (1.5%)
Other GI problems	460 (1.3%)	130 (0.5%)
Comedication		
Aspirin	9729 (27.8%)	6783 (25.4%)
Vitamin K antagonist	4416 (12.6%)	3302 (12.3%)
Clopidogrel	1160 (3.3%)	822 (3.1%)
Other antiplatelets	494 (1.4%)	330 (1.2%)
NSAID	3117 (8.9%)	2150 (8.0%)
Corticosteroid	3083 (8.8%)	2647 (9.9%)
Diuretic	9155 (26.2%)	8157 (30.5%)
Beta blocker	20747 (59.3%)	17015 (63.6%)
Calcium channel blocker	9021 (25.8%)	6643 (24.8%)
RAAS inhibitor	14911 (42.6%)	11966 (44.7%)
Statin	11025 (31.5%)	8638 (32.3%)
Diabetic drug	3235 (9.2%)	2522 (9.4%)
Insulin	1895 (5.4%)	1655 (6.2%)
Antidepressant	4416 (12.6%)	3823 (14.3%)

Appendix table 4. Effect of adjustment on association per covariate or set of covariates. First three columns are for the databases separately, and the final column is for the pooled analysis.

	Stockholm	Denmark	PHARMO	Pooled
Model	IRR	IRR	IRR	IRR
Main analysis (IPW)	0,79 (0,48-1,23)	0,72 (0,53-0,96)	0,85 (0,37-1,78)	0,75 (0,59-0,95)
Full covariate adjustment	0,72 (0,45-1,13)	0,67 (0,52-0,86)	0,74 (0,30-1,66)	0,69 (0,56-0,85)
Unadjusted	1,21 (0,77-1,82)	1,02 (0,79-1,28)	1,03 (0,44-2,22)	1,06 (0,86-1,30)
Age sex adjusted	1,12 (0,72-1,82)	0,96 (0,74-1,27)	0,99 (0,42-2,23)	0,99 (0,81-1,29)
Age	1,11 (0,71-1,67)	0,95 (0,74-1,20)	0,97 (0,41-2,10)	0,99 (0,81-1,21)
Sex	1,21 (0,77-1,82)	1,02 (0,79-1,29)	1,06 (0,46-2,29)	1,06 (0,87-1,30)
HASBLED CHADSVASC adjustment	0,98 (0,62-1,49)	0,83 (0,64-1,05)	0,89 (0,38-1,94)	0,86 (0,70-1,06)
Hypertension	1,17 (0,75-1,77)	0,99 (0,78-1,26)	0,99 (0,43-2,14)	1,03 (0,84-1,27)
Renal disease	1,15 (0,74-1,73)	1,02 (0,79-1,28)	1,04 (0,45-2,24)	1,05 (0,85-1,28)
Liver disease	1,21 (0,78-1,82)	1,00 (0,78-1,27)	1,04 (0,45-2,23)	1,05 (0,86-1,29)
Stroke/TIA/Embolism	1,15 (0,74-1,73)	1,00 (0,78-1,27)	1,03 (0,44-2,21)	1,03 (0,84-1,27)
Alcoholism	1,18 (0,76-1,78)	0,99 (0,77-1,25)	1,03 (0,44-2,22)	1,03 (0,84-1,26)
Prior bleed	1,14 (0,73-1,71)	1,00 (0,78-1,26)	0,99 (0,43-2,14)	1,03 (0,84-1,26)
Anaemia	1,02 (0,65-1,55)	0,91 (0,71-1,16)	0,89 (0,38-1,94)	0,94 (0,76-1,15)
Heart failure	1,11 (0,71-1,68)	0,98 (0,77-1,24)	1,00 (0,43-2,15)	1,01 (0,83-1,24)
Vascular disease	1,11 (0,71-1,67)	0,97 (0,75-1,22)	0,91 (0,39-1,98)	0,99 (0,81-1,22)
Diabetes	1,19 (0,76-1,79)	0,99 (0,77-1,25)	0,98 (0,42-2,11)	1,03 (0,84-1,27)
GI covariate adjustment	1,08 (0,68-1,65)	0,94 (0,73-1,19)	0,94 (0,40-2,05)	0,97 (0,78-1,19)
Peptic ulcer	1,14 (0,73-1,73)	0,98 (0,76-1,24)	1,03 (0,44-2,22)	1,02 (0,83-1,25)
GI cancer	1,21 (0,77-1,82)	1,00 (0,78-1,27)	1,04 (0,45-2,23)	1,05 (0,86-1,29)
Gastritis	1,19 (0,76-1,79)	1,01 (0,79-1,28)	0,99 (0,42-2,14)	1,05 (0,86-1,29)
Esophagitis	1,11 (0,71-1,69)	0,99 (0,77-1,25)	0,99 (0,42-2,14)	1,02 (0,83-1,25)
GERD/Dyspepsia	1,18 (0,76-1,79)	1,02 (0,79-1,28)	1,00 (0,43-2,15)	1,05 (0,86-1,29)
Abdominal pain	1,24 (0,79-1,86)	1,00 (0,78-1,26)	1,04 (0,45-2,23)	1,05 (0,86-1,29)
Lower GI disease	1,18 (0,76-1,78)	1,01 (0,79-1,27)	1,03 (0,44-2,21)	1,05 (0,85-1,28)
Other GI disease	1,22 (0,78-1,83)	1,00 (0,78-1,27)	1,04 (0,45-2,23)	1,05 (0,86-1,29)
Full drug adjustment	0,98 (0,62-1,49)	0,83 (0,64-1,05)	0,89 (0,38-1,94)	0,86 (0,70-1,06)
Aspirin	1,15 (0,74-1,74)	0,96 (0,75-1,21)	1,00 (0,43-2,17)	1,00 (0,82-1,23)
NSAID	1,20 (0,77-1,81)	0,99 (0,77-1,25)	1,01 (0,43-2,16)	1,03 (0,84-1,27)
Clopidogrel	1,18 (0,75-1,78)	0,98 (0,77-1,24)	1,08 (0,47-2,33)	1,03 (0,84-1,26)
Other antiplatelets	1,21 (0,78-1,83)	1,00 (0,78-1,27)	1,04 (0,45-2,24)	1,05 (0,86-1,29)
Corticosteroids	1,23 (0,79-1,86)	0,97 (0,76-1,23)	1,03 (0,44-2,22)	1,03 (0,84-1,26)
Diuretics	1,10 (0,70-1,65)	0,94 (0,73-1,18)	0,93 (0,40-2,01)	0,97 (0,79-1,19)
Beta blocker	1,21 (0,78-1,83)	1,02 (0,80-1,29)	1,05 (0,45-2,26)	1,06 (0,87-1,30)
Ca channel blocker	1,20 (0,77-1,81)	1,02 (0,79-1,28)	1,00 (0,43-2,16)	1,05 (0,86-1,29)
RAAS inhibitor	1,19 (0,76-1,79)	0,98 (0,76-1,24)	0,99 (0,42-2,13)	1,03 (0,84-1,26)
Statin	1,19 (0,76-1,79)	1,02 (0,80-1,29)	1,03 (0,44-2,23)	1,06 (0,86-1,30)
Oral diabetic drug	1,21 (0,77-1,82)	1,01 (0,79-1,27)	0,96 (0,41-2,07)	1,05 (0,85-1,28)
Insulin	1,13 (0,73-1,71)	1,01 (0,78-1,27)	1,02 (0,44-2,20)	1,04 (0,84-1,27)
Antidepressant	1,13 (0,72-1,70)	1,00 (0,78-1,26)	0,99 (0,43-2,15)	1,02 (0,84-1,26)
Vitamin K antagonist	1,21 (0,77-1,82)	1,01 (0,79-1,27)	1,03 (0,44-2,22)	1,05 (0,86-1,29)

3.4

ASSOCIATION OF PRECEDING ANTITHROMBOTIC THERAPY IN ATRIAL FIBRILLATION PATIENTS WITH ISCHEMIC STROKE, INTRACRANIAL HEMORRHAGE, OR GASTROINTESTINAL BLEED AND MORTALITY

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ABSTRACT

Aim

To analyze 90-day mortality in AF patients after a stroke or a severe bleed and assess associations with the type of antithrombotic treatment at the event.

Methods and Results

From the Stockholm Healthcare database, we selected 6 017 patients with a known history of AF who were diagnosed with ischemic stroke, 3 006 with intracranial hemorrhage, and 4 291 with a severe gastrointestinal bleed (GIB). The 90-day mortality rates were 25.1% after ischemic stroke, 31.6% after intracranial hemorrhage, and 16.2% after severe GIB. We used Cox regression and propensity score matched analyses to test the association between antithrombotic treatment at the event and 90-day mortality. After intracranial hemorrhage, there was a significantly higher mortality rate in warfarin compared to NOAC treated patients (adjusted hazard ratio (aHR): 1.36 CI: 1.04 – 1.78). After an ischemic stroke and a severe GIB, patients receiving antiplatelets or no antithrombotic treatment had significantly higher mortality rates compared to patients on NOACs, but there was no difference comparing warfarin to NOACs (aHR 0.84 CI: 0.63 – 1.12 after ischemic stroke, aHR 0.91 CI: 0.66 – 1.25 after severe GIB). Propensity score matched analysis yielded similar results.

Conclusion

Mortality rates were high in AF patients suffering from an ischemic stroke, an intracranial hemorrhage, or a severe GIB. NOAC treatment was associated with a lower 90 day mortality after intracranial hemorrhage than warfarin.

INTRODUCTION

Non-vitamin K oral anticoagulants (NOACs) have been shown to be at least as safe and efficacious as warfarin [1], and superior to aspirin in preventing stroke in patients with atrial fibrillation (AF) [2]. In particular, NOACs markedly reduce the risk for intracranial hemorrhage compared to warfarin. Overall, oral anticoagulant (OAC) and aspirin treatment increase the risks of bleeding similarly [2, 3], but misconceptions about the safety of aspirin have most likely contributed to undertreatment with OACs and overtreatment with aspirin in AF patients [4]. In line with the emerging evidence, the recent guidelines advocate increasing OAC treatment, preferably with NOACs [5, 6]

Previous studies have found associations between antithrombotic treatment at the time of an ischemic stroke or an intracranial hemorrhage and in-hospital mortality [7, 8]. Work by Hylek et al. showed that mortality in the 30 days post-discharge is as large as the in-hospital mortality in AF patients suffering from an ischemic stroke [9]. Studies with a longer follow-up, capturing both in-hospital and early out-of-hospital mortality after an ischemic stroke or intracranial hemorrhage in the NOAC era have not been reported. Studies describing the outcomes of AF patients suffering from a severe gastrointestinal bleed (GIB) even appear to be lacking.

The aims of the current study were therefore to analyze the 90 day mortality in patients suffering from an ischemic stroke, an intracranial hemorrhage, or a severe GIB, and to assess if this is associated with the type of antithrombotic treatment at the time of the event.

MATERIAL AND METHODS

Database

The Stockholm Healthcare Database (Vårdanalysdatabasen, VAL-database) which contains pseudonymized information on demographics, claimed prescriptions, and medical information for all 2.3 million inhabitants in the Stockholm region [10].These individual-level data provide the opportunity to have complete healthcare data for follow-up of all patients in the region.

The medical information in the VAL database comes from both primary and secondary care and is registered with ICD-10 codes. Diagnoses and procedures from secondary care have been available since 1993 and from primary care since 2003. The claimed prescription data in the database contain information on drugs claimed in any pharmacy in Sweden and is registered with ATC codes. Data on claimed prescriptions have been included in the VAL database since July 2010 [11]. Linkage within the database is done using the Swedish unique personal identifier [12].

Patient selection

From this database, we created three cohorts: one with patients with ischemic stroke, one with patients with intracranial hemorrhage, and one with patients with a severe GIB, registered between July 2011 and June 2018. All patients had a prior diagnosis for AF (I48). (see Appendix Table 1 for ICD-10 codes). Patients could be included in more than one cohort. We only included diagnoses recorded in a hospital care setting requiring acute somatic care. For ischemic strokes we only included diagnoses registered as primary or secondary diagnosis in inpatient care. For intracranial hemorrhage and severe GIBs the diagnoses could be in any position and could be recorded

in inpatient care or at an acute hospital-based emergency visit [13]. Validation studies in the same database have shown a positive predictive value of 98.6% for ischemic stroke, 97.7% for intracranial hemorrhage, and 98.1% for gastrointestinal bleeds [13, 14]. The study was approved by the Regional Ethical Review Board in Stockholm (EPN 2015/579-31/2).

Follow-up, outcome, and censoring

We defined the date of the qualifying event as the index date, and followed patients for a maximum of 90 days. The outcome of interest during follow-up was all cause mortality, registered at Statistics Sweden. Patients were censored if they moved out from the region during follow-up.

Baseline treatment assessment

Baseline treatment at the time of the bleed or stroke could be any of the following four classes: NOAC, warfarin, antiplatelet, or no treatment (see Appendix Table 1). NOAC treatment included all four NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban), and the antiplatelet treatment was low-dose aspirin and/or $P2Y_{12}$ antagonist treatment (clopidogrel, ticagrelor, and prasugrel).

We searched for a claimed prescription of any of the treatments that was theoretically available for the patient at the time of the bleed or stroke. For the NOACs and antiplatelets we calculated the end of a prescription by assessing the amount of drug dispensed. For warfarin, we used a 90 day period as the duration for a prescription, given the diversity in warfarin dosing. If the qualifying bleed or stroke was within the duration of the prescription, we allocated the patient to that treatment class.

Baseline exposure to any of the drugs was mutually exclusive, where NOAC or warfarin treatment overruled antiplatelet therapy. Therefore, if a patient had a prescription for both an antiplatelet and a NOAC or warfarin at the time of inclusion, the patient was allocated to the NOAC or warfarin group. However, we assessed the proportion receiving combination therapy at the time of the events. If the patient had a prescription for both a NOAC and warfarin at the time of inclusion, the patient was allocated to the last of the two drugs claimed. If a patient had no treatment available at the time of the bleed or stroke, the patient was considered to have no treatment.

Baseline comedication and comorbidity definition

We defined baseline comedication as prescriptions claimed during six months prior to inclusion, i.e. the bleed or stroke. We searched for prescriptions for diuretics, beta-blockers, calcium channel blockers, RAAS inhibitors, statins, oral antidiabetic drugs, insulins, antidepressants, digoxin, rhythm control drugs, NSAIDs, corticosteroids, and proton pump inhibitors (see Appendix Table 1 for ATC codes).

We defined baseline comorbidity as all recorded diagnoses in the five years prior to inclusion (see Appendix Table 1 for ICD codes). We assessed the comorbidities of the Charlson Comorbidity Index, the CHA_2DS_2-VASc score, and the modified HAS-BLED score [15–17]. Comorbidities that occurred in more than one score, were counted only once. The Charlson Comorbidity Index includes the following: myocardial infarction, heart failure, peripheral vascular disease, cerebral vascular

disease, dementia, COPD, peptic ulcer, rheumatoid arthritis, mild liver disease, uncomplicated diabetes, connective tissue disease, renal disease, complicated diabetes, cancer, moderate to severe liver disease, metastatic carcinoma, and HIV. For the CHA_2DS_2-VASc score, we also assessed hypertension and previous stroke, TIA, or embolism. For the modified HAS-BLED score, we assessed anemia, alcoholism and prior bleeds; PK(INR) values were not available.

Statistical analysis

We used basic descriptive statistics to present baseline characteristics of the three cohorts and to calculate the crude 90 day mortality rates. We used a Cox proportional hazards model to calculate hazard ratios (aHRs), adjusting for potential confounders [18]. In the Cox proportional hazards model, we adjusted for age, sex, the individual components of the Charlson Comorbidity Index, the CHA_2DS_2-VASc score, and the modified HAS-BLED score, for baseline medication as described above, and for the year of inclusion. We created models for several comparisons, to assess underlying relationships. We compared NOACs with warfarin, antiplatelets, and no treatment. We tested the proportional hazards assumptions of the Cox regression with Schoenfeld residuals [19].

In addition to the Cox regression, we performed propensity score matched analyses. We thus calculated the probability of receiving NOAC treatment using logistic regression, using the same explanatory variables as in the Cox regression. We matched NOAC to warfarin users, NOAC to antiplatelet users, and NOAC users to non-users on the propensity score. We used a 1:1 nearest neighbor matching method with a greedy matching procedure, using calipers of 0.2 of the standard deviation of the logit of the propensity score. After matching, we created Kaplan Meier curves and performed log rank tests, comparing patient groups that had on average the same distribution of characteristics that were included in the propensity score. Baseline characteristics were compared after the matching, and if all standardized mean differences (SMD) were below 0.1, the matching was considered successful. If not, we would re-estimate the propensity score and re-match the cohorts.

Data extraction was performed using SAS EG 7.1 (SAS Institute INC., Cary, NC), all statistical analyses were performed with statistical software R version 3.4.2 and RStudio Desktop version 1.1.463. The statistical packages 'survival' and 'MatchIt' were used for the survival analyses and the propensity score matching, respectively [20, 21].

Sensitivity analysis

First, to estimate the influence of unmeasured confounding on mortality, we performed sensitivity analyses based on an array approach according to Schneeweiss [22]. This analysis assesses both how strong the association of the confounder with the outcome must be, and how unequally the confounder must be distributed to fully explain the observed association. We used the analyses for both the weakest and the strongest significant associations.

Second, we conducted another propensity score matched analysis, but now with asymmetric propensity score trimming at cut points corresponding to the 5^{th} and 95^{th} percentiles of the propensity score distribution in the treated and untreated patients, respectively. This approach, as suggested

by Stürmer et al, will limit unmeasured confounding since patients in the upper and lower tails of the propensity score distribution are excluded [23].

Third, we performed sensitivity analyses in which we assumed a patient was exposed if any treatment was claimed in the 180 days before the event, to account for potential non-compliance.

Fourth, as bleeds recorded in an emergency hospital setting might be less severe than those recorded in an inpatient setting, we have performed an additional analysis where we only included patients with an intracranial hemorrhage or a GIB that was recorded as primary diagnosis in inpatient care.

Fifth, as patients receiving concomitant antiplatelet therapy might have different mortality rates, we performed an analysis where we excluded all patients receiving concomitant antiplatelet therapy.

RESULTS

Patient characteristics

A total of 105 313 patients in the Stockholm region were diagnosed with AF in the VAL database during the period of inclusion. Among these patients, 6 017 had an ischemic stroke, 3 006 an intracranial hemorrhage, and 4 291 a severe GIB after their diagnosis of AF. Patients suffering from an ischemic stroke were the oldest with a mean age of 81.6 years. The mean ages were 80.2 years for intracranial hemorrhage and 78.7 years for severe GIB.

Among the patients with ischemic stroke, 454 (7.5%) were using NOACs, 1 229 (20.4%) were using warfarin, 2 026 (33.7%) were using antiplatelets, and 2 308 (38.4%) had not claimed any antithrombotic treatment (see Table 1). The proportion of ischemic stroke patients without OAC treatment decreased from 80.2% in 2011 to 58.8% in 2018. Patients receiving antiplatelets were older and had higher risk scores than the other three groups, which were comparable.

Among the patients with intracranial hemorrhage, 311 (10.3%) were using NOACs, 1 028 (34.2%) were using warfarin, 595 (19.8%) were using antiplatelets, and 1 072 (35.7%) had not claimed any antithrombotic treatment (see Table 1). Among the patients with severe GIB, 652 (15.2%) were using NOACs, 1 293 (30.1%) warfarin, 893 (20.8%) antiplatelets, and 1 453 (33.9%) no treatment (see Table 1). Again, patients on antiplatelets were older and had higher risk scores, but patients on NOACs, warfarin, and no treatment were comparable also in the two cohorts with bleeds.

The proportion of NOAC patients treated with a low dose was 48.0% in the ischemic stroke group, 43.7% in the intracranial hemorrhage group, and 39.0% in the severe GIB group. The proportion of patients receiving combination therapy (i.e., OAC with antiplatelet or double antiplatelet therapy) was small; below 10% in all groups (see Table 1).

After propensity score matching, all covariates had a standardized mean difference below 0.1, indicating successful matching in all three cohorts (see Appendix Table 3a-c).

Mortality

The 90 day mortality was 25.1% after an ischemic stroke, 31.6% after an intracranial hemorrhage, and 16.2% after a severe GIB, regardless of antithrombotic treatment at the time of the event).

Table 1. Baseline characteristics of patients included after ischemic stroke, intracranial hemorrhage, and severe gastrointestinal bleed. Complete baseline tables with all comedication and comorbidities can be found in Appendix table 2a-c. Concomitant antiplatelet is either NOAC + antiplatelet, warfarin + antiplatelet, or double antiplatelet therapy ** For the no treatment group, this is the mean number of years since a last prescription, only among patients that ever received any antithrombotic treatment.

Baseline characteristics	NOAC	Warfarin	Antiplatelet	No treatment
Ischemic stroke (n = 6 017)				
Number of patients	454	1 229	2 026	2 308
Female sex, n (%)	237 (52.2%)	577 (46.9%)	1149 (56.7%)	1238 (53.6%)
Mean age (SD)	79.25 (9.35)	80.62 (8.45)	83.89 (9.24)	80.64 (10.60)
Mean Charlson Comorbidity Index (SD)	5.59 (2.35)	5.92 (2.40)	6.18 (2.39)	5.75 (2.59)
Mean CHA_2DS_2-VASc score (SD)	4.43 (1.68)	4.66 (1.64)	4.80 (1.69)	4.23 (1.84)
Mean HAS-BLED score (SD)	2.32 (0.88)	2.29 (0.84)	2.36 (0.95)	2.25 (1.06)
Concomitant antiplatelet*	37 (8.1%)	107 (8.7%)	49 (2.4%)	NA
Mean treatment duration (years (SD))**	1.2 (1.2)	2.9 (2.0)	2.7 (1.8)	0.8 (1.0)
Intracranial hemorrhage (n = 3 006)				
Number of patients	311	1 028	595	1 072
Female sex, n (%)	132 (42.4%)	415 (40.4%)	275 (46.2%)	442 (41.2%)
Mean age (SD)	80.02 (9.12)	79.62 (8.75)	83.02 (9.32)	79.32 (10.92)
Mean Charlson Comorbidity Index (SD)	5.83 (2.53)	5.80 (2.46)	6.52 (2.58)	5.93 (2.83)
Mean CHA_2DS_2-VASc score (SD)	4.33 (1.71)	4.31 (1.64)	4.75 (1.64)	4.07 (1.83)
Mean HAS-BLED score (SD)	2.35 (0.91)	2.26 (0.85)	2.51 (0.98)	2.36 (1.02)
Concomitant antiplatelet*	5 (1.6%)	25 (2.4%)	12 (2.0%)	NA
Mean treatment duration (years (SD))**	1.4 (1.3)	3.1 (2.1)	2.9 (2.0)	0.6 (0.7)
Severe gastrointestinal bleed (n = 4 291)				
Number of patients	652	1 293	893	1 453
Female sex, n (%)	300 (46.0%)	526 (40.7%)	412 (46.1%)	607 (41.8%)
Mean age (SD)	77.84 (9.36)	78.39 (9.60)	81.59 (10.40)	77.68 (11.43)
Mean Charlson Comorbidity Index (SD)	5.77 (2.63)	6.09 (2.65)	6.61 (2.68)	6.29 (3.09)
Mean CHA_2DS_2-VASc score (SD)	4.21 (1.81)	4.26 (1.65)	4.58 (1.74)	3.93 (1.86)
Mean HAS-BLED score (SD)	2.25 (0.93)	2.26 (0.92)	2.41 (1.02)	2.34 (1.17)
Concomitant antiplatelet*	41 (7.8%)	129 (8.1%)	54 (2.5%)	NA
Mean treatment duration (years (SD))**	1.3 (1.2)	2.9 (2.1)	3.0 (2.0)	0.8 (1.0)

Ischemic stroke

Both NOAC and warfarin treated patients had 90 day mortalities of 17.6%. For antiplatelet treated patients this was 29.8% and for patients without treatment 26.3% (see Table 2). After adjustment for confounders, patients receiving antiplatelets or no treatment had significantly higher mortality rates compared to patients on NOAC treatment (antiplatelet vs NOAC, aHR: 1.57 CI: 1.20 – 2.04; no treatment vs NOAC, aHR: 1.47 CI: 1.15 – 1.88, see Table 2). There was no statistically significant difference in mortality rates between warfarin and NOAC treated patients, either in the adjusted Cox regression or in the propensity score matched cohort (see Figure 1a).

Table 2. 90 day mortality rates in the different treatment groups after ischemic stroke, intracranial hemorrhage, and severe gastrointestinal bleed. Hazard ratios from the unadjusted and adjusted Cox regression models, adjusted for age, sex, the individual components of the Charlson Comorbidity Index, the CHA_2DS_2-VASc score, and the modified HAS-BLED score, for baseline medication, and for the year of inclusion. NOAC: Non-vitamin K oral anticoagulant. HR: hazard ratio. CI: 95% confidence interval.

	NOAC	Warfarin	Antiplatelet	No treatment
Ischemic stroke				
90 day mortality, n (%)	80 (17.6%)	216 (17.6%)	604 (29.8%)	608 (26.3%)
Unadjusted HR (CI)	Reference	1.00 (0.77 – 1.29)	1.84 (1.45 – 2.32)	1.58 (1.25 – 2.00)
Adjusted HR (CI)	Reference	0.84 (0.63 – 1.12)	1.57 (1.20 – 2.04)	1.47 (1.15 – 1.88)
Intracranial hemorrhage				
90 day mortality, n (%)	82 (26.4%)	333 (32.4%)	220 (37.0%)	315 (29.4%)
Unadjusted HR (CI)	Reference	1.30 (1.02 – 1.66)	1.49 (1.16 – 1.92)	1.13 (0.88 – 1.44)
Adjusted HR (CI)	Reference	1.36 (1.04 – 1.78)	1.16 (0.84 – 1.61)	1.02 (0.78 – 1.34)
Severe gastrointestinal bleed				
90 day mortality, n (%)	71 (10.9%)	147 (11.4%)	194 (21.7%)	284 (19.5%)
Unadjusted HR (CI)	Reference	1.05 (0.79 – 1.39)	2.13 (1.62 – 2.80)	1.89 (1.45 – 2.45)
Adjusted HR (CI)	Reference	0.91 (0.66 – 1.25)	1.56 (1.13 – 2.16)	1.51 (1.13 – 2.01)

Intracranial hemorrhage

Among patients with an intracranial hemorrhage, the lowest 90 day mortality was found in NOAC treated patients (26.4%), and the highest in patients receiving antiplatelets (37.0%). After adjusting for confounders, there was a significantly increased risk of dying among warfarin compared to NOAC treated patients (aHR: 1.36 CI: 1.04 – 1.78). In patients on antiplatelets and in patients without antithrombotic treatment, there were no significant differences in mortality risk compared to NOAC treated patients. The log-rank test in the propensity score matched cohorts yielded similar results (see Figure 1b).

Gastrointestinal bleeds

The lowest 90 day mortality was again found in NOAC treated patients (10.9%), while the mortality in antiplatelet treated patients was twice as high (21.7%). After adjustment for confounders, patients receiving antiplatelets or no treatment had significantly higher mortalities compared to NOACs (antiplatelet vs NOAC, aHR: 1.56 CI: 1.13 – 2.16; no treatment vs NOAC, aHR: 1.51 CI: 1.13 – 2.01). There was no statistically significant difference between NOAC and warfarin treated patients (aHR 0.96 CI: 0.72 – 1.29). The log-rank test in the propensity score matched cohorts again yielded similar results (see Figure 1c).

Sensitivity analyses

The array approach analyses showed that for the lowest significant association found (aHR: 1.36, warfarin vs NOAC after intracranial hemorrhage) there had to be an unmeasured confounder with a relative risk for mortality of 2.0, occurring 5 times more often in the warfarin group (i.e. 10%

in the NOAC group, 50% in the warfarin group) to move the hazard ratio to 1, or an unmeasured confounder with a relative risk for mortality of 3.0 occurring 3 times more often in the warfarin group (see Appendix Table 4). For the strongest association (aHR: 1.57, antiplatelet vs NOAC treatment after ischemic stroke), an unmeasured confounder with a relative risk of 3.0 for mortality had to occur 5 times more often in the antiplatelet group to move the hazard ratio below 1.

The propensity score matched analyses with asymmetric trimming yielded similar results as the main analyses, with all significant results from the main analysis remaining significant and indicating limited residual confounding (Appendix Figure 1a-c).

Considering a patient to be exposed if a drug was claimed 180 days before inclusion yielded similar results as the main analyses (Appendix Table 5).

When including only primary diagnosis from inpatient care, the mortality rates remained similar after intracranial hemorrhages, but increased slightly to 19.1% after gastrointestinal bleeds. The mortality rates in the different treatment groups increased non-differentially, and the associations are similar as in the main analysis (Appendix Table 6).

When excluding all patients receiving concomitant antiplatelet therapy, the mortality rates in the different treatment groups after the different events, remained practically unchanged (Appendix Table 7).

DISCUSSION

In this observational study covering a complete healthcare setting, we found high 90 day mortalities in AF patients suffering from an ischemic stroke, an intracranial hemorrhage, or a severe GIB, requiring acute hospital-based emergency care or inpatient care. The 90-day mortalities were 25.1%, 31.6%, and 16.2%, respectively, regardless of antithrombotic treatment at the time of the event. A high proportion of AF patients, i.e., approximately 2 out of 3 patients, were apparently without OAC treatment at the time of an ischemic stroke.

After an intracranial hemorrhage, the mortality was significantly lower among patients treated with a NOAC compared to those treated with warfarin, both in the adjusted Cox regression and in a propensity score matched analysis. A possible explanation could be that intracranial hemorrhages occurring during warfarin treatment are associated with larger expansion of hematoma volumes than those observed during NOAC treatment [24]. Warfarin acts on several coagulation factors and the brain is rich in subendothelial tissue factor which can generate thrombin locally; warfarin may thus counteract locally formed thrombin more effectively than the NOACs and cause more protracted bleeding [24]. The four pivotal clinical trials showed lower risks for intracranial hemorrhage with NOACs compared to warfarin [1]. Our study adds that patients also had a better survival after an intracranial hemorrhage when treated with a NOAC. Although intracranial hemorrhage is a rare complication, the favorable effects of NOACs on the risk of intracranial hemorrhage and the survival after intracranial hemorrhage may add to the improved overall survival that is suggested in the clinical trials.

For ischemic stroke and severe GIB, the mortality rates were similar in patients on warfarin and NOAC treatment, while mortality rates were significantly higher in patients receiving antiplatelets

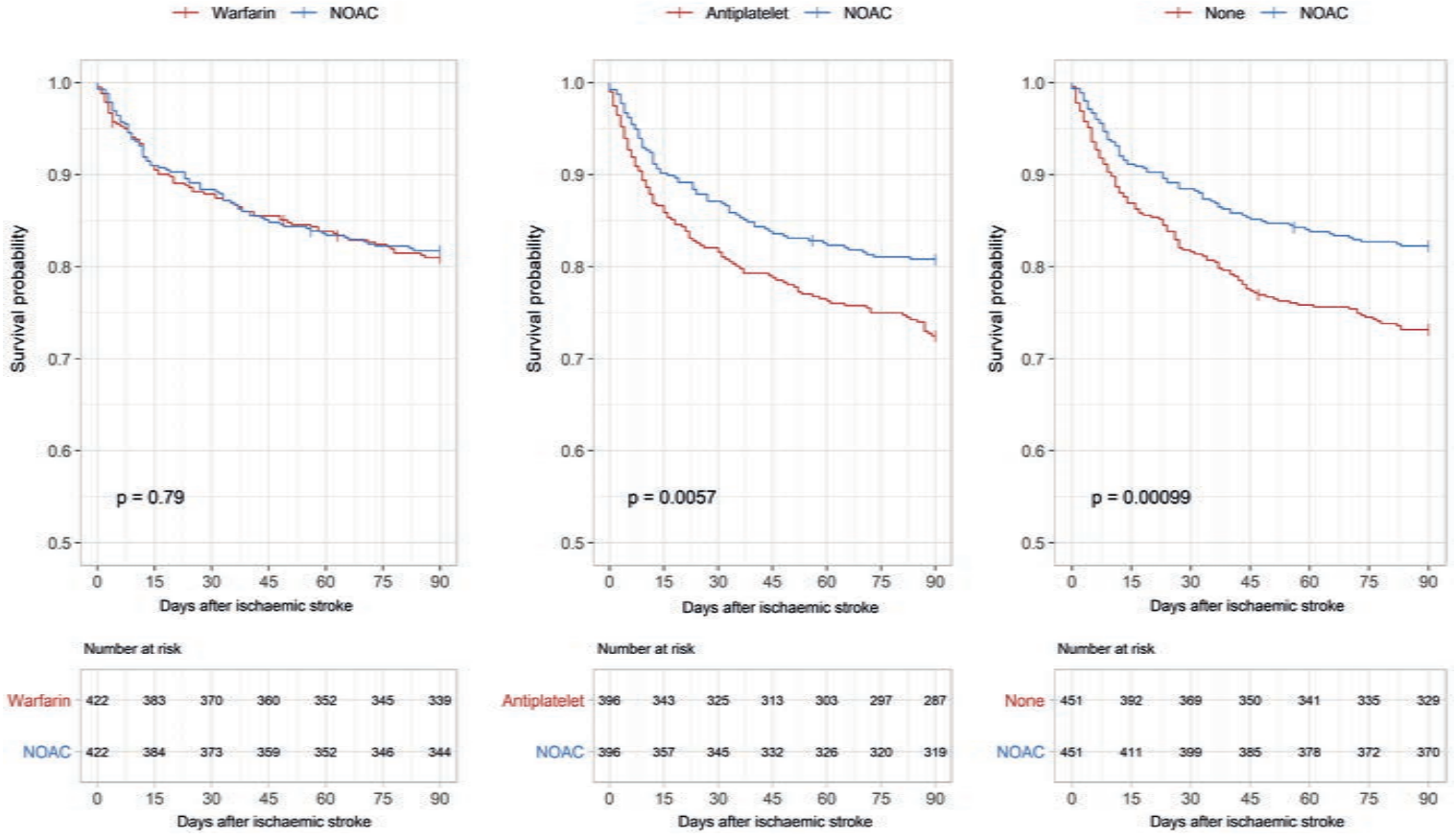

Figure 1a. 90 day mortality after ischemic stroke. Kaplan-Meier curves and p-values from the log-rank test in the propensity score matched cohorts after ischemic stroke. NOAC: Non-vitamin K oral anticoagulant

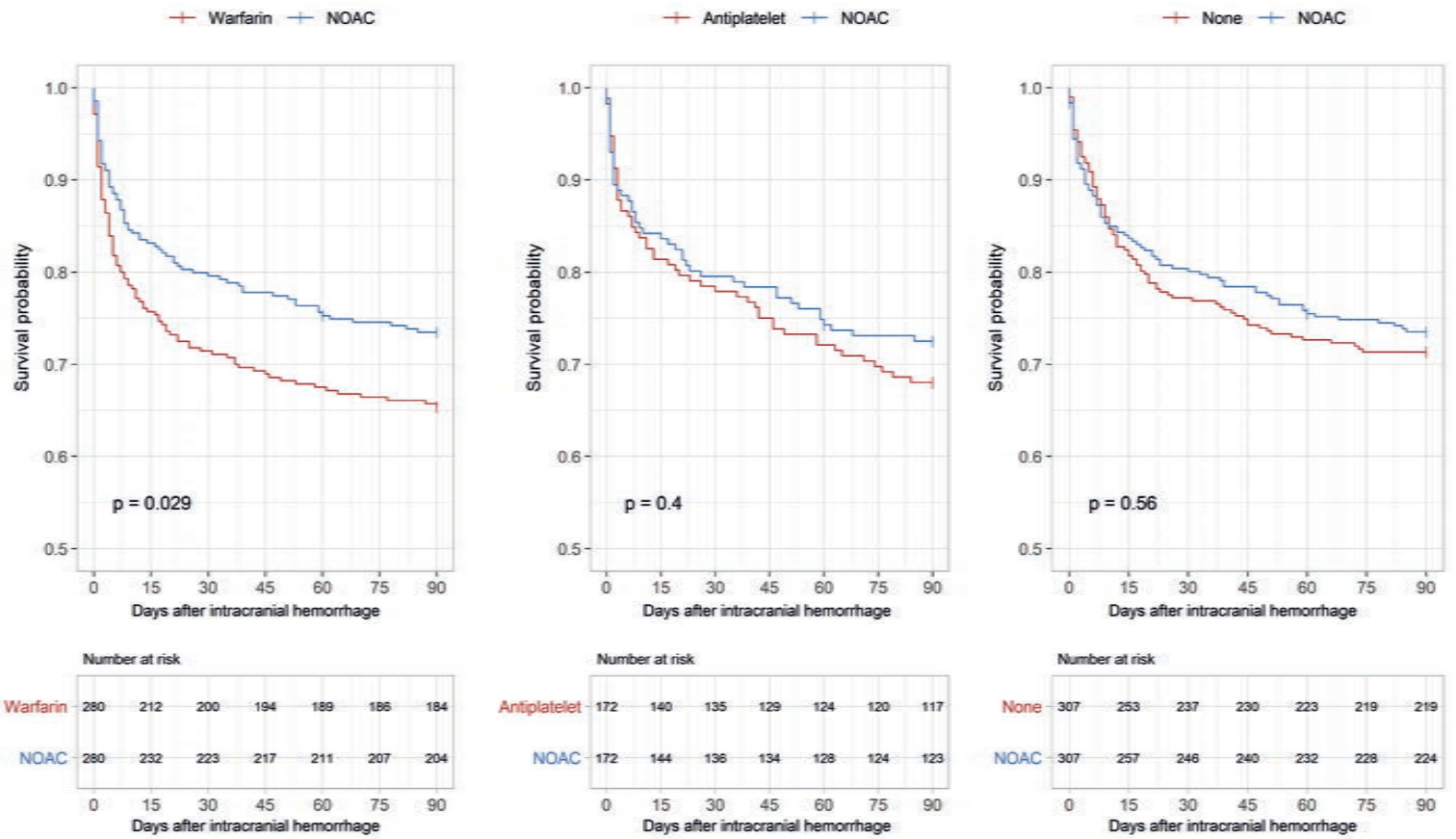

Figure 1b. 90 day mortality after intracranial hemorrhage. Caption: Kaplan-Meier curves and p-values from the log-rank test in the propensity score matched cohorts after intracranial hemorrhage. NOAC: Non-vitamin K oral anticoagulant.

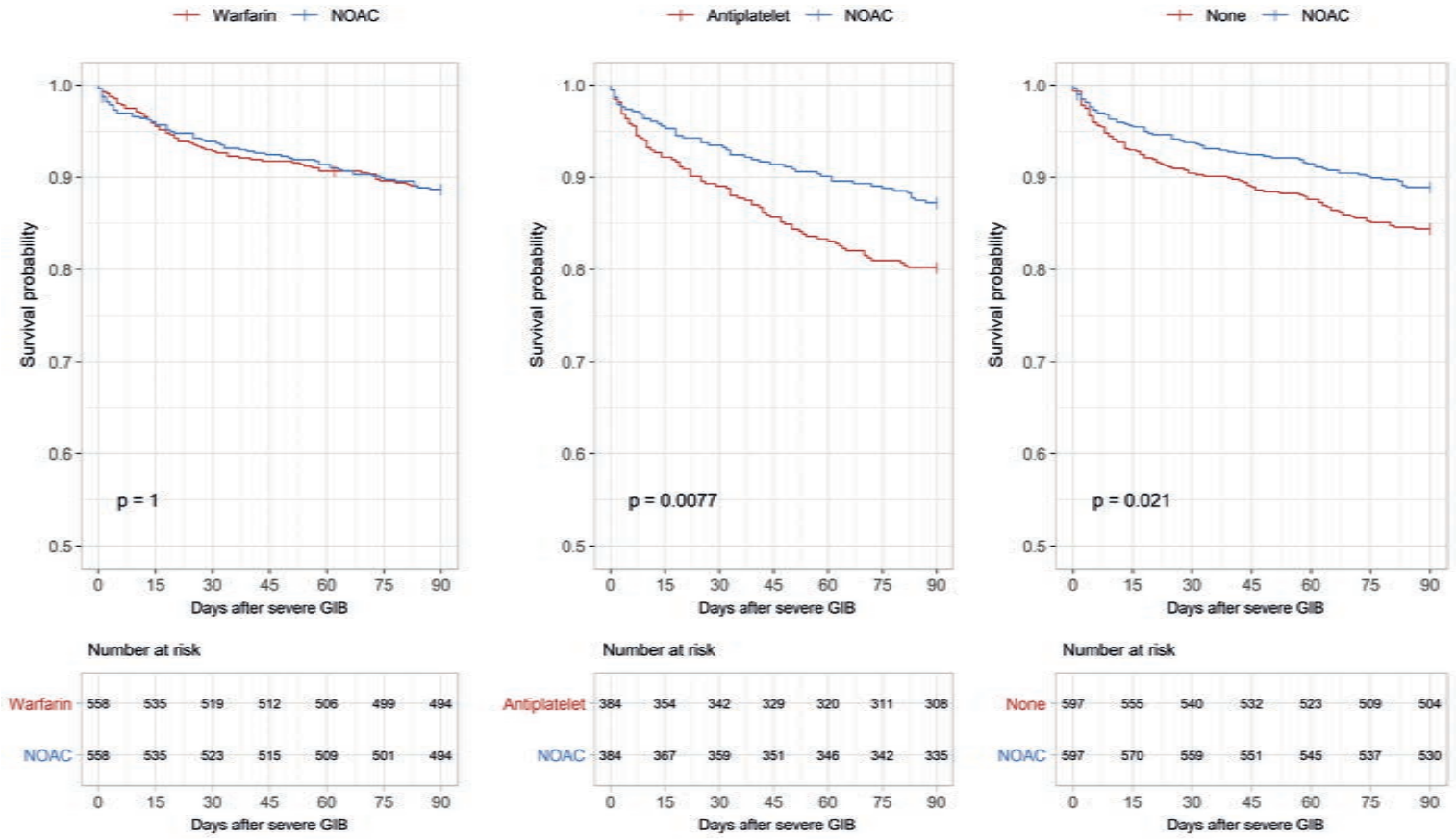

Figure 1c. 90 day mortality after severe gastrointestinal bleed. Caption: Kaplan-Meier curves and p-values from the log rank test in the propensity score matched cohorts after severe gastrointestinal bleed. NOAC: Non-vitamin K oral anticoagulant

or no antithrombotic therapy. The lower mortality rates after ischemic strokes occurring during OAC treatment compared to non-OAC treatment could potentially be explained by fewer thrombi from a cardiac source, smaller thrombi, or both [25, 26]. Lower mortality rates after a severe GIB during NOAC treatment could potentially be explained by less careful follow-up of patients treated with antiplatelets or no treatment and bleeds being discovered later. However, residual confounding might also be part of the explanation.

Other literature

Our findings are in line with previous publications with shorter follow-up which reported on in-hospital mortality rates only. Xian et al. reported similar in-hospital mortality rates after an ischemic stroke for NOAC and warfarin treated patients, while patients receiving no antithrombotic treatment had higher in-hospital mortality rates [8]. Studies conducted before NOACs were available also showed a lower in-hospital mortality when comparing warfarin with aspirin or no antithrombotic treatment in AF patients suffering from an ischemic stroke [9, 27]. In the current study we had no access to PK(INR) measurements while previous work showed that subtherapeutic warfarin is associated with worse outcomes after stroke and intracranial hemorrhage [7–9]. The difficulty of warfarin dosing is a drawback of the treatment and our results represent clinical practice. However, it has been reported that warfarin treatment is delivered with high quality and excellent time in therapeutic range values in Sweden and Stockholm [28, 29]

Inohara et al. found an increased in-hospital mortality after an intracranial hemorrhage in patients with warfarin compared to NOAC treatment, in agreement with our findings [7]. However, when comparing OACs versus no OACs, they found a reduced in-hospital mortality in patients without OAC treatment, while we found no such association. An explanation could be that we focused solely on AF patients, while Inohara et al. included all patients with an intracranial hemorrhage. As a result, the no OAC population in that study was approximately 10 years younger than the OAC population in our study (68 vs 78 years of age), and also 12 years younger than our intracranial hemorrhage cohort (68 vs 80 years of age).

Clinical implications

We are the first to address mortality after the occurrence of a severe GIB in an AF population, which was 16.2% overall after 90 days. For comparison, previous work in the Stockholm region showed a 1-year mortality rate in all AF patients of 8.4%, and in the elderly AF population (age ≥ 80 years) of 16.0% [30]. The present findings show that mortality rates in the 90 days after a severe GIB are as high as the 1-year mortality in the elderly AF population. Increased awareness and follow-up of these patients is warranted, especially during the first months after the event. In addition, we found that 72% of AF patients suffering from an ischemic stroke were not receiving OAC treatment. Even with prolonged exposure windows in the sensitivity analysis, 62% of those patients were not receiving OAC treatment. Not only does OAC treatment reduce the risk for an ischemic stroke, but mortality rates are also higher in patients without OAC treatment at the time of the ischemic stroke. Finally, guidelines have recommended NOACs above warfarin for stroke prevention in AF, partly due to

the reduced risk for intracranial hemorrhage. The current study adds that intracranial hemorrhages occurring while receiving NOAC treatment were also associated with lower mortality rates.

Strengths

Our study has several strengths. First, the VAL-database contains complete follow-up and healthcare utilization data for all patients in the region, giving a unique opportunity to study clinical practice based outcomes in patients suffering strokes or serious bleeds. Second, we used different analytical approaches and sensitivity analyses, all yielding similar results and confirming the robustness of our findings. Third, we are the first to address outcomes with a longer follow-up after an event. In comparison, we found 90 day mortalities of 31.6% after an intracranial hemorrhage and 27.0% after an ischemic stroke, while this was only 24% after intracranial hemorrhage and 8% after stroke in studies assessing only in-hospital mortality [7,8].

Limitations

Our study has some limitations. First, the study relies on pharmacy claims data, so we cannot be sure that the patients actually took the medication at the time of the event. Changing the exposure definition and defining a patient treated in the 180 days after a prescription reduced the proportion of untreated patients, but mortality rates remained unchanged, adding to the robustness of our findings. Second, no information is available on the use of reversing therapies after bleeding. Idarucizumab, a dabigatran antidote, became available during the study period, but only 1.9% of all ICH patients used dabigatran (18% of NOAC patients), and 4.0% of all severe GIB patients used dabigatran (26% of NOAC patients). Andexanet alfa, a factor Xa inhibitor antidote, was not available during the study period. Third, patients who died from the event before reaching the hospital were not captured in our database as causes of death were not available for this study. Furthermore, causes of death were not analyzed in the presently identified patients with events since the very low autopsy rates in Sweden most likely result in frequent misclassification [31]. Fourth, antithrombotic treatment after the event, which may have affected mortality, was not taken into account. Finally, despite the efforts made we cannot rule out residual confounding. However, we found that an unmeasured confounder needed an RR of 2.0 and occurring in 50% of the warfarin patients and only 10% of the NOAC patients to explain the association with mortality after an intracranial hemorrhage. It is unlikely that we, after adjusting for many known risk factors, have missed a confounder or group of confounders that is so strongly associated with mortality and so unevenly distributed. Therefore, the associations we observed are not likely to be explained by residual confounding.

We did not take adequacy of NOAC dose and PK(INR) into account in the current study. However, the study describes a clinical practice-based setting in which inadequacy of dosing and low TTRs are part of everyday treatment with oral anticoagulants. Therefore, the results of this study give a realistic picture of what mortality rates will look like in clinical practice. We did not study reinitiations of antithrombotic treatment after ischemic or bleeding events since it is impossible to determine if and when a patient with a drug supply from before the event used that after the event. Data on new prescriptions and claims after the event would be seriously confounded by concealed

use. We decided to analyze a relatively short follow-up, so that reinitiation of therapy would be expected to have a limited effect on mortality. However, future studies addressing post-event antithrombotic treatment are of interest and warranted.

Conclusion

In conclusion, the 90 day mortality was high among AF patients suffering from an ischemic stroke, an intracranial hemorrhage, or a severe GIB. Treatment at the time of the event was associated with 90 day mortality. After an intracranial hemorrhage, patients had better chances of surviving if they received NOAC treatment before the event as compared to warfarin treatment. After a severe GIB or an ischemic stroke, patients had lower mortality rates if they had received NOAC treatment compared to no OAC treatment. The results of this study support current guidelines that recommend NOACs as first line treatment in stroke prevention in AF.

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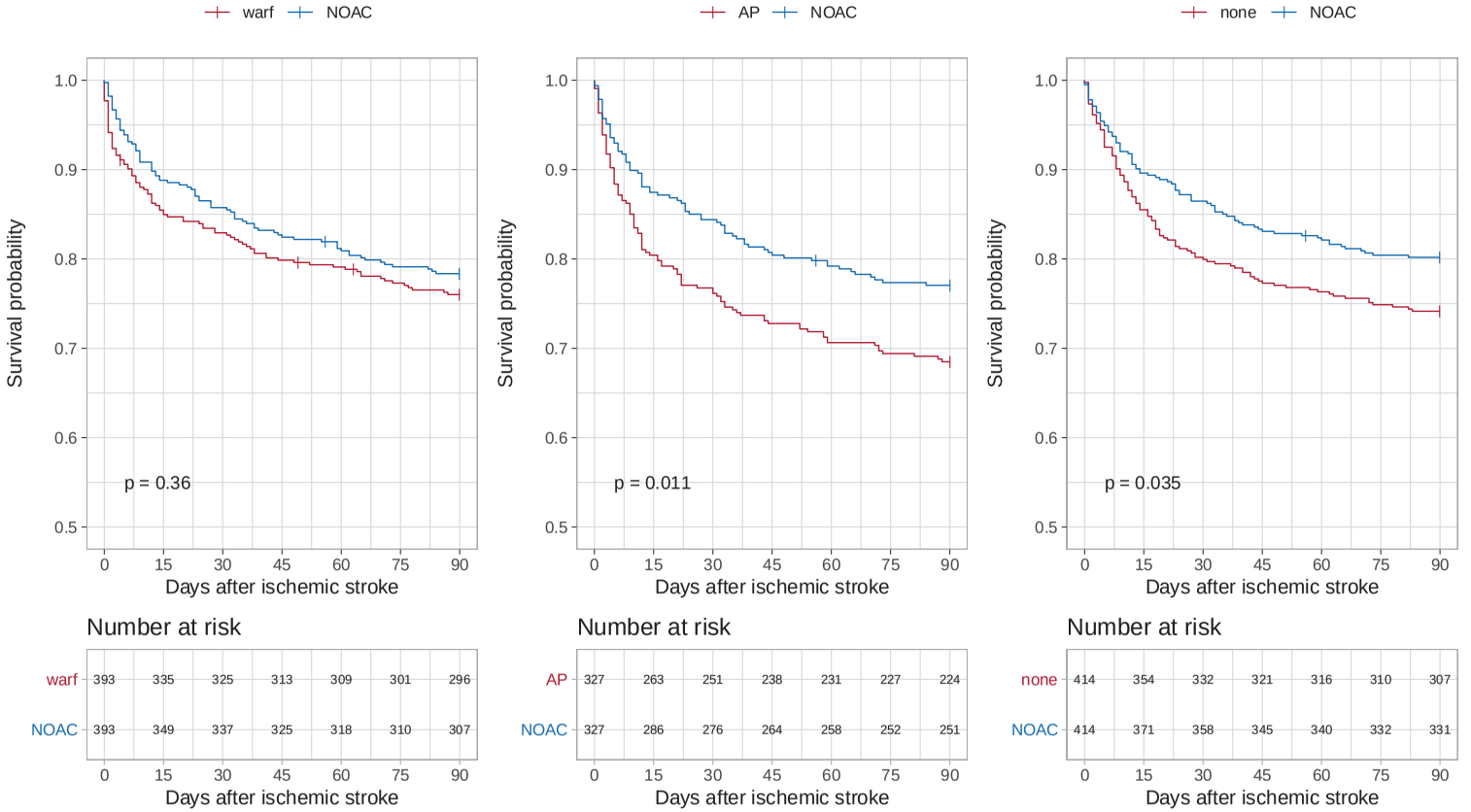
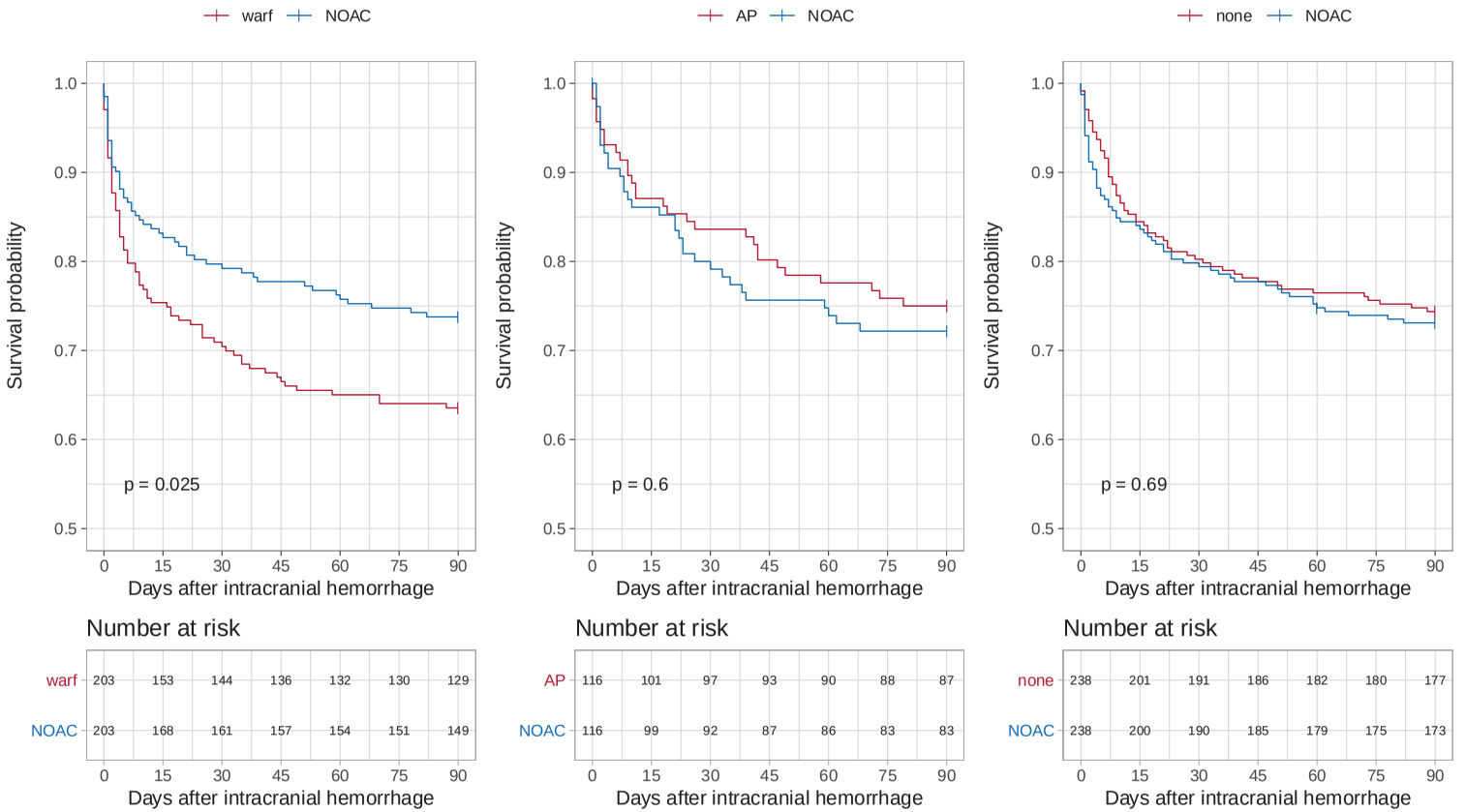
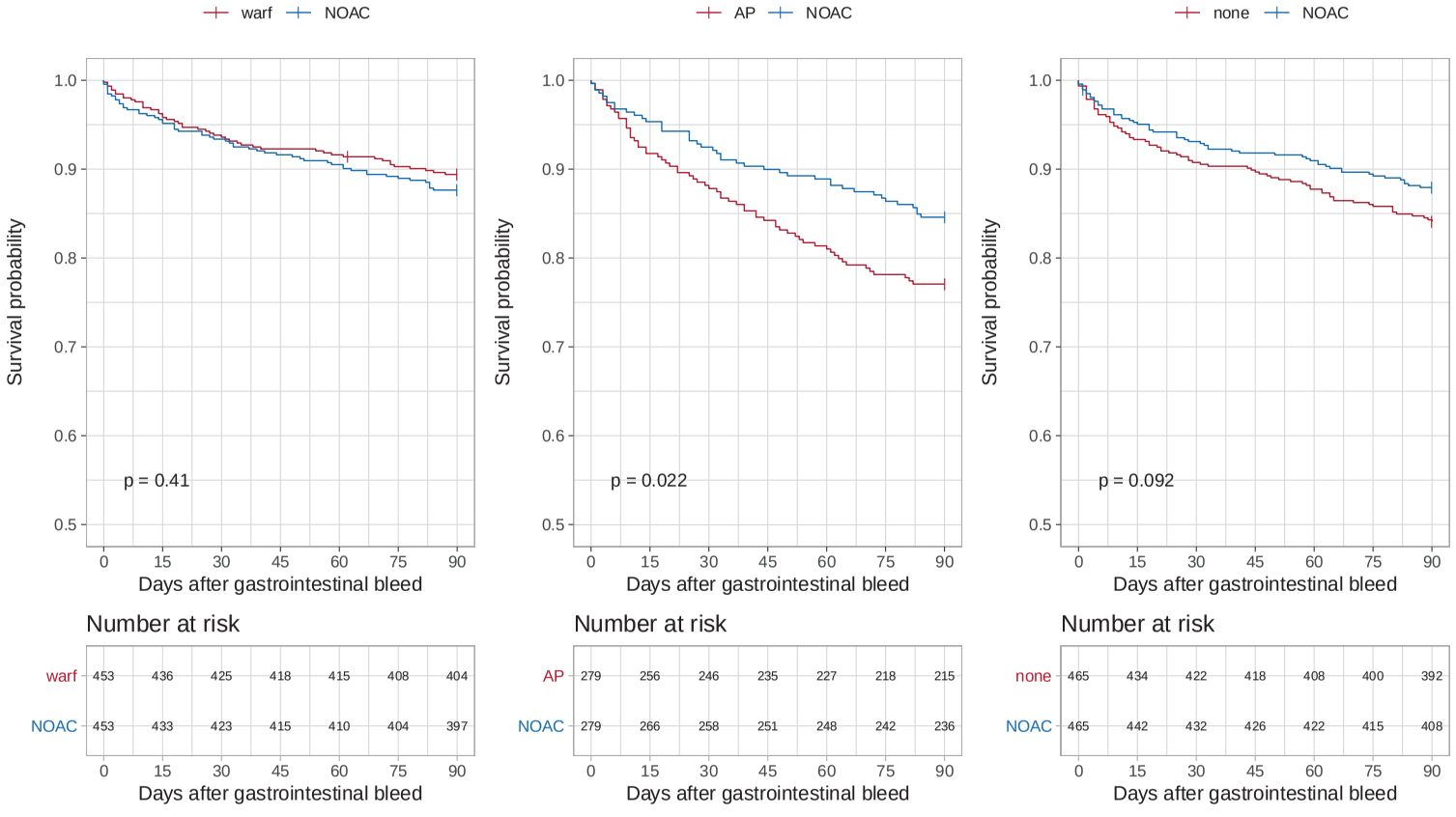
APPENDICES



Appendix figure 1a. Kaplan-Meier curves and p-values from the log-rank test in the trimmed propensity score matched cohorts after ischemic stroke.



Appendix figure 1b. Kaplan-Meier curves and p-values from the log-rank test in the trimmed propensity score matched cohorts after intracranial hemorrhage.



Appendix figure 1c. Kaplan-Meier curves and p-values from the log rank test in the trimmed propensity score matched cohorts after severe gastrointestinal bleed.

Appendix table 1. ICD-10 and ATC codes for inclusion, comorbidities, and medication

Diagnosis for inclusion	ICD-code beginning with
Ischaemic stroke	I63
Intracranial haemorrhage	I60, I61, I62, S064, S065, S066
Gastrointestinal bleed	K25-28 (subcodes 0-2 and 4-6 only), K625, K922
Baseline comorbidities	ICD-code beginning with
Myocardial infarction	I21, I22, I252
Heart failure	I43, I50, I099, I110, I130, I132, I255, I420, I425-429, P290
Peripheral vascular disease	I70, I71, I731, I738, I739, I711, I790, I792, K551, K558, K559, Z958, Z959
Cerebral vascular disease	G45, G46, I60-69, H340
Dementia	F00-03, G30, F051, G311
COPD	J40-47, J60-67, I278, I279, J684, J701, J703
Peptic ulcer	K25-28
Rheumatoid arthritis	M05, M06, M32-34, M315, M351, M353, M360
Mild liver disease	B18, K73, K74, K700, K701, K702, K703, K709, K717, K713, K714, K715, K760, K762, K763, K764, K768, K769, Z944
Uncomplicated diabetes	E100, E101, E106, E108-111, E118, E119, E120, E121, E126, E128-131, E136, E138-141, E146, E148, E149
Connective tissue disease	G81, G82, G041, G114, G801, G802, G830, G831, G832, G833, G834, G839
Renal disease	N18, N19, N052, N053, N054, N055, N056, N057, N250, I120, I131, N032, N033, N034, N035, N036, N037, Z490, Z491, Z492, Z940, Z992
Complicated diabetes	E102, E103, E104, E105, E107, E112, E113, E114, E115, E117, E122, E123, E124, E125, E127, E132, E133, E134, E135, E137, E142, E143, E144, E145, E147
Cancer	C0, C1, C20-26, C30-34, C37-39, C40-43, C45-49, C50-58, C6, C70-76, C81-85, C88, C90-97
Moderate to severe liver disease	K704, K711, K721, K729, K765, K766, K767, I850, I859, I864, I982
Metastatic carcinoma	C77-90
HIV	B20, B21, B22, B24
Hypertension	I10-I16
Previous stroke, TIA, or embolism	I63, I64, I679, I693, I694, I698, I67, I69, Z866, Z876, G453, G458, G459, I74
Anaemia	D50-59, D60-64
Alcoholism	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90, Y91, Y91, Z502, Z714
Prior bleed	I60, I61, I62, S064, S065, S066, I850, I983, K25-28 (subcodes 0-2 and 4-6 only), K625, K922, D62
Medication	**ATC code beginning with**
Warfarin	B01AA03
NOAC	B01AF02, B01AE07, B01AF03, B01AF01
Antiplatelet	B01AC06, B01AC04, B01AC24, B01AC22
Diuretic	C03A, C03B, C03C, C03D, C03E
Beta blocker	C07A, C07B, C07C, C07D, C07E, C07F
Ca channel blocker	C08C, C08D, C08E, C08G
RAAS inhibitor	C09A, C09B, C09C, C09D, C09X
Statin	C10AA
Oral antidiabetic drug	A10B
Insulin	A10A

Appendix table 1. (continued)

Medication	ATC code beginning with
Antidepressant	N06A
Digoxin	C01AA05
Rhythm control drug	C01B, C07AA07
Corticosteroids	H02A
PPI	A02BC

Appendix table 2a. Complete baseline characteristics ischemic stroke cohort.

Baseline characteristics of ischaemic stroke cohort	NOAC (N=454)	Warfarin (N=1229)	Antiplatelet (N=2026)	No treatment (N=2308)
Female sex, n (%)	237 (52.2%)	577 (46.9%)	1149 (56.7%)	1238 (53.6%)
Low dose NOAC	218 (48.0%)	NA	NA	NA
Mean duration (years (SD))**	1.2 (1.2)	2.9 (2.0)	2.7 (1.8)	0.8 (1.0)
Age				
Mean (sd)	79.25 (9.35)	80.62 (8.45)	83.89 (9.24)	80.64 (10.60)
0-65	27 (5.9%)	58 (4.7%)	82 (4.0%)	207 (9.0%)
66-75	110 (24.2%)	228 (18.6%)	261 (12.9%)	403 (17.5%)
76-85	180 (39.6%)	529 (43.0%)	571 (28.2%)	760 (32.9%)
86-95	132 (29.1%)	392 (31.9%)	992 (49.0%)	845 (36.6%)
95+	5 (1.1%)	22 (1.8%)	120 (5.9%)	93 (4.0%)
Charlson Comorbidity Index				
Mean (sd)	5.59 (2.35)	5.92 (2.40)	6.18 (2.39)	5.75 (2.59)
0-2	24 (5.3%)	40 (3.3%)	63 (3.1%)	172 (7.5%)
3-4	137 (30.2%)	324 (26.4%)	398 (19.6%)	596 (25.8%)
4+	293 (64.5%)	865 (70.4%)	1565 (77.2%)	1540 (66.7%)
CHA_2DS_2-VASc				
Mean (sd)	4.43 (1.68)	4.66 (1.64)	4.80 (1.69)	4.23 (1.84)
0-1	15 (3.3%)	24 (2.0%)	50 (2.5%)	171 (7.4%)
2-3	117 (25.8%)	276 (22.5%)	388 (19.2%)	617 (26.7%)
3+	322 (70.9%)	929 (75.6%)	1588 (78.4%)	1520 (65.9%)
HAS-BLED				
Mean (sd)	2.32 (0.88)	2.29 (0.84)	2.36 (0.95)	2.25 (1.06)
0-3	414 (91.2%)	1132 (92.1%)	1802 (88.9%)	2035 (88.2%)
3+	40 (8.8%)	97 (7.9%)	224 (11.1%)	273 (11.8%)
Comorbidities underlying scores, n (%)				
Myocardial infarction	56 (12.3%)	207 (16.8%)	403 (19.9%)	283 (12.3%)
Heart failure	153 (33.7%)	531 (43.2%)	805 (39.7%)	825 (35.7%)
Peripheral vascular disease	57 (12.6%)	150 (12.2%)	250 (12.3%)	240 (10.4%)
Cerebral vascular disease	135 (29.7%)	369 (30.0%)	678 (33.5%)	637 (27.6%)
Dementia	39 (8.6%)	69 (5.6%)	319 (15.7%)	251 (10.9%)
COPD	67 (14.8%)	233 (19.0%)	328 (16.2%)	350 (15.2%)
Peptic ulcer	17 (3.7%)	33 (2.7%)	71 (3.5%)	101 (4.4%)
Rheumatoid arthritis	27 (5.9%)	86 (7.0%)	122 (6.0%)	154 (6.7%)
Mild liver disease	4 (0.9%)	13 (1.1%)	35 (1.7%)	61 (2.6%)

Appendix table 2a. (continued)

Baseline characteristics of ischaemic stroke cohort	NOAC (N=454)	Warfarin (N=1229)	Antiplatelet (N=2026)	No treatment (N=2308)
Uncomplicated diabetes	98 (21.6%)	300 (24.4%)	433 (21.4%)	437 (18.9%)
Connective tissue disease	13 (2.9%)	17 (1.4%)	48 (2.4%)	54 (2.3%)
Renal disease	43 (9.5%)	130 (10.6%)	216 (10.7%)	257 (11.1%)
Complicated diabetes	37 (8.1%)	84 (6.8%)	142 (7.0%)	167 (7.2%)
Cancer	66 (14.5%)	195 (15.9%)	320 (15.8%)	378 (16.4%)
Moderate to severe liver disease	2 (0.4%)	5 (0.4%)	11 (0.5%)	14 (0.6%)
Metastatic carcinoma	8 (1.8%)	30 (2.4%)	41 (2.0%)	54 (2.3%)
HIV	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)
Hypertension	357 (78.6%)	973 (79.2%)	1540 (76.0%)	1595 (69.1%)
Previous stroke, TIA, or embolism	141 (31.1%)	383 (31.2%)	672 (33.2%)	605 (26.2%)
Anaemia	82 (18.1%)	220 (17.9%)	404 (19.9%)	531 (23.0%)
Alcoholism	13 (2.9%)	22 (1.8%)	77 (3.8%)	149 (6.5%)
Prior bleed	54 (11.9%)	100 (8.1%)	237 (11.7%)	353 (15.3%)
Comedication, n (%)				
Concomitant antiplatelet*	37 (8.1%)	107 (8.7%)	49 (2.4%)	NA
Diuretic	185 (40.7%)	597 (48.6%)	968 (47.8%)	868 (37.6%)
Beta blocker	347 (76.4%)	916 (74.5%)	1325 (65.4%)	1309 (56.7%)
Ca channel blocker	131 (28.9%)	324 (26.4%)	444 (21.9%)	446 (19.3%)
RAAS inhibitor	242 (53.3%)	702 (57.1%)	899 (44.4%)	873 (37.8%)
Statin	158 (34.8%)	473 (38.5%)	568 (28.0%)	468 (20.3%)
Oral antidiabetic drug	47 (10.4%)	128 (10.4%)	161 (7.9%)	157 (6.8%)
Insulin	35 (7.7%)	112 (9.1%)	183 (9.0%)	175 (7.6%)
Antidepressant	86 (18.9%)	160 (13.0%)	323 (15.9%)	334 (14.5%)
Digoxin	68 (15.0%)	249 (20.3%)	305 (15.1%)	281 (12.2%)
Rhythm control drug	18 (4.0%)	32 (2.6%)	42 (2.1%)	52 (2.3%)
NSAID	23 (5.1%)	47 (3.8%)	115 (5.7%)	121 (5.2%)
Corticosteroid	42 (9.3%)	113 (9.2%)	173 (8.5%)	179 (7.8%)
PPI	130 (28.6%)	280 (22.8%)	596 (29.4%)	552 (23.9%)

** For the no treatment group, this is the mean number of years since a last prescription, only of patients that ever received any antithrombotic treatment.

Appendix table 2b. Complete baseline characteristics intracranial hemorrhage cohort.

Baseline characteristics of intracranial haemorrhage cohort	NOAC (N=311)	Warfarin (N=1028)	Antiplatelet (N=595)	No treatment (N=1072)
Female sex, n (%)	132 (42.4%)	415 (40.4%)	275 (46.2%)	442 (41.2%)
Low dose NOAC	136 (43.7%)	NA	NA	NA
Mean duration (years (SD))**	1.4 (1.3)	3.1 (2.1)	2.9 (2.0)	0.6 (0.7)
Age				
Mean (sd)	80.02 (9.12)	79.62 (8.75)	83.02 (9.32)	79.32 (10.92)
0-65	17 (5.5%)	60 (5.8%)	28 (4.7%)	113 (10.5%)
66-75	65 (20.9%)	217 (21.1%)	88 (14.8%)	203 (18.9%)
76-85	128 (41.2%)	445 (43.3%)	183 (30.8%)	385 (35.9%)
86-95	88 (28.3%)	295 (28.7%)	261 (43.9%)	338 (31.5%)
95+	13 (4.2%)	11 (1.1%)	35 (5.9%)	33 (3.1%)
Charlson Comorbidity Index				
Mean (sd)	5.83 (2.53)	5.80 (2.46)	6.52 (2.58)	5.93 (2.83)
0-2	15 (4.8%)	38 (3.7%)	11 (1.8%)	79 (7.4%)
3-4	89 (28.6%)	295 (28.7%)	103 (17.3%)	278 (25.9%)
4+	207 (66.6%)	695 (67.6%)	481 (80.8%)	715 (66.7%)
CHA_2DS_2-VASc				
Mean (sd)	4.33 (1.71)	4.31 (1.64)	4.76 (1.64)	4.07 (1.83)
0-1	14 (4.5%)	30 (2.9%)	13 (2.2%)	86 (8.0%)
2-3	83 (26.7%)	308 (30.0%)	119 (20.0%)	330 (30.8%)
3+	214 (68.8%)	690 (67.1%)	463 (77.8%)	656 (61.2%)
HAS-BLED				
Mean (sd)	2.35 (0.91)	2.26 (0.85)	2.52 (0.98)	2.36 (1.02)
0-3	281 (90.4%)	961 (93.5%)	505 (84.9%)	932 (86.9%)
3+	30 (9.6%)	67 (6.5%)	90 (15.1%)	140 (13.1%)
Comorbidities underlying scores, n (%)				
Myocardial infarction	32 (10.3%)	140 (13.6%)	128 (21.5%)	141 (13.2%)
Heart failure	103 (33.1%)	421 (41.0%)	247 (41.5%)	358 (33.4%)
Peripheral vascular disease	29 (9.3%)	106 (10.3%)	84 (14.1%)	98 (9.1%)
Cerebral vascular disease	91 (29.3%)	285 (27.7%)	221 (37.1%)	339 (31.6%)
Dementia	39 (12.5%)	84 (8.2%)	123 (20.7%)	107 (10.0%)
COPD	64 (20.6%)	157 (15.3%)	96 (16.1%)	167 (15.6%)
Peptic ulcer	9 (2.9%)	32 (3.1%)	26 (4.4%)	48 (4.5%)
Rheumatoid arthritis	20 (6.4%)	62 (6.0%)	35 (5.9%)	54 (5.0%)
Mild liver disease	4 (1.3%)	15 (1.5%)	9 (1.5%)	50 (4.7%)
Uncomplicated diabetes	78 (25.1%)	222 (21.6%)	132 (22.2%)	205 (19.1%)
Connective tissue disease	18 (5.8%)	16 (1.6%)	19 (3.2%)	41 (3.8%)
Renal disease	27 (8.7%)	127 (12.4%)	86 (14.5%)	139 (13.0%)
Complicated diabetes	21 (6.8%)	71 (6.9%)	43 (7.2%)	66 (6.2%)
Cancer	56 (18.0%)	172 (16.7%)	108 (18.2%)	201 (18.8%)
Moderate to severe liver disease	1 (0.3%)	4 (0.4%)	6 (1.0%)	11 (1.0%)
Metastatic carcinoma	9 (2.9%)	26 (2.5%)	20 (3.4%)	52 (4.9%)
HIV	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Hypertension	244 (78.5%)	769 (74.8%)	453 (76.1%)	751 (70.1%)
Previous stroke, TIA, or embolism	91 (29.3%)	289 (28.1%)	208 (35.0%)	291 (27.1%)

Appendix table 2b. (continued)

Baseline characteristics of intracranial haemorrhage cohort	NOAC (N=311)	Warfarin (N=1028)	Antiplatelet (N=595)	No treatment (N=1072)
Anaemia	64 (20.6%)	193 (18.8%)	165 (27.7%)	272 (25.4%)
Alcoholism	10 (3.2%)	37 (3.6%)	43 (7.2%)	95 (8.9%)
Prior bleed	47 (15.1%)	94 (9.1%)	105 (17.6%)	224 (20.9%)
Comedication, n (%)				
Concomitant antiplatelet*	5 (1.6%)	25 (2.4%)	12 (2.0%)	NA
Diuretic	129 (41.5%)	454 (44.2%)	293 (49.2%)	399 (37.2%)
Beta blocker	222 (71.4%)	712 (69.3%)	362 (60.8%)	631 (58.9%)
Ca channel blocker	81 (26.0%)	248 (24.1%)	128 (21.5%)	197 (18.4%)
RAAS inhibitor	165 (53.1%)	566 (55.1%)	268 (45.0%)	424 (39.6%)
Statin	110 (35.4%)	399 (38.8%)	200 (33.6%)	279 (26.0%)
Oral antidiabetic drug	34 (10.9%)	101 (9.8%)	45 (7.6%)	75 (7.0%)
Insulin	25 (8.0%)	94 (9.1%)	56 (9.4%)	71 (6.6%)
Antidepressant	69 (22.2%)	166 (16.1%)	149 (25.0%)	187 (17.4%)
Digoxin	48 (15.4%)	171 (16.6%)	80 (13.4%)	124 (11.6%)
Rhythm control drug	11 (3.5%)	34 (3.3%)	9 (1.5%)	25 (2.3%)
NSAID	20 (6.4%)	37 (3.6%)	34 (5.7%)	42 (3.9%)
Corticosteroid	26 (8.4%)	91 (8.9%)	50 (8.4%)	100 (9.3%)
PPI	90 (28.9%)	228 (22.2%)	178 (29.9%)	276 (25.7%)

** For the no treatment group, this is the mean number of years since a last prescription, only of patients that ever received any antithrombotic treatment.

Appendix table 2c. Complete baseline characteristics severe gastrointestinal bleed cohort

Baseline table of severe gastrointestinal bleed cohort	NOAC (N=652)	Warfarin (N=1293)	Antiplatelet (N=893)	No treatment (N=1453)
Female sex, n (%)	300 (46.0%)	526 (40.7%)	412 (46.1%)	607 (41.8%)
Low dose NOAC	254 (39.0%)	NA	NA	NA
Mean duration (years (SD))**	1.3 (1.2)	2.9 (2.1)	3.0 (2.0)	0.8 (1.0)
Age				
Mean (sd)	77.84 (9.36)	78.39 (9.60)	81.59 (10.40)	77.68 (11.43)
0-65	52 (8.0%)	103 (8.0%)	64 (7.2%)	185 (12.7%)
66-75	188 (28.8%)	331 (25.6%)	161 (18.0%)	360 (24.8%)
76-85	264 (40.5%)	510 (39.4%)	267 (29.9%)	474 (32.6%)
86-95	135 (20.7%)	331 (25.6%)	354 (39.6%)	396 (27.3%)
95+	13 (2.0%)	18 (1.4%)	47 (5.3%)	38 (2.6%)
Charlson Comorbidity Index				
Mean (sd)	5.77 (2.63)	6.09 (2.65)	6.61 (2.68)	6.29 (3.09)
0-2	42 (6.4%)	47 (3.6%)	29 (3.2%)	108 (7.4%)
3-4	192 (29.4%)	333 (25.8%)	167 (18.7%)	326 (22.4%)
4+	418 (64.1%)	913 (70.6%)	697 (78.1%)	1019 (70.1%)
CHADsVASc				
Mean (sd)	4.21 (1.81)	4.26 (1.65)	4.58 (1.74)	3.93 (1.86)
0-1	38 (5.8%)	40 (3.1%)	32 (3.6%)	147 (10.1%)
2-3	206 (31.6%)	385 (29.8%)	211 (23.6%)	448 (30.8%)

Appendix table 2c. (continued)

Baseline table of severe gastrointestinal bleed cohort	NOAC (N=652)	Warfarin (N=1293)	Antiplatelet (N=893)	No treatment (N=1453)
3+	408 (62.6%)	868 (67.1%)	650 (72.8%)	858 (59.1%)
HAS-BLED				
Mean (sd)	2.25 (0.93)	2.26 (0.92)	2.41 (1.02)	2.34 (1.17)
0-3	599 (91.9%)	1180 (91.3%)	768 (86.0%)	1233 (84.9%)
3+	53 (8.1%)	113 (8.7%)	125 (14.0%)	220 (15.1%)
Comorbidities underlying scores, n (%)				
Myocardial infarction	84 (12.9%)	220 (17.0%)	242 (27.1%)	202 (13.9%)
Heart failure	259 (39.7%)	623 (48.2%)	397 (44.5%)	567 (39.0%)
Peripheral vascular disease	72 (11.0%)	152 (11.8%)	149 (16.7%)	171 (11.8%)
Cerebral vascular disease	160 (24.5%)	244 (18.9%)	229 (25.6%)	314 (21.6%)
Dementia	29 (4.4%)	69 (5.3%)	124 (13.9%)	99 (6.8%)
COPD	129 (19.8%)	277 (21.4%)	191 (21.4%)	302 (20.8%)
Peptic ulcer	26 (4.0%)	79 (6.1%)	73 (8.2%)	144 (9.9%)
Rheumatoid arthritis	41 (6.3%)	119 (9.2%)	54 (6.0%)	107 (7.4%)
Mild liver disease	19 (2.9%)	39 (3.0%)	32 (3.6%)	91 (6.3%)
Uncomplicated diabetes	159 (24.4%)	339 (26.2%)	226 (25.3%)	328 (22.6%)
Connective tissue disease	29 (4.4%)	18 (1.4%)	16 (1.8%)	46 (3.2%)
Renal disease	62 (9.5%)	206 (15.9%)	157 (17.6%)	263 (18.1%)
Complicated diabetes	64 (9.8%)	106 (8.2%)	92 (10.3%)	131 (9.0%)
Cancer	131 (20.1%)	269 (20.8%)	203 (22.7%)	345 (23.7%)
Moderate to severe liver disease	6 (0.9%)	10 (0.8%)	11 (1.2%)	44 (3.0%)
Metastatic carcinoma	17 (2.6%)	46 (3.6%)	24 (2.7%)	83 (5.7%)
HIV	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Hypertension	499 (76.5%)	999 (77.3%)	664 (74.4%)	988 (68.0%)
Previous stroke, TIA, or embolism	158 (24.2%)	257 (19.9%)	228 (25.5%)	301 (20.7%)
Anaemia	179 (27.5%)	413 (31.9%)	339 (38.0%)	578 (39.8%)
Alcoholism	36 (5.5%)	40 (3.1%)	67 (7.5%)	139 (9.6%)
Prior bleed	76 (11.7%)	154 (11.9%)	146 (16.3%)	276 (19.0%)
Comedication, n (%)				
Concomitant antiplatelet*	41 (7.8%)	129 (8.1%)	54 (2.5%)	NA
Diuretic	289 (44.3%)	711 (55.0%)	479 (53.6%)	624 (42.9%)
Beta blocker	508 (77.9%)	928 (71.8%)	555 (62.2%)	819 (56.4%)
Ca channel blocker	167 (25.6%)	311 (24.1%)	206 (23.1%)	276 (19.0%)
RAAS inhibitor	358 (54.9%)	740 (57.2%)	433 (48.5%)	556 (38.3%)
Statin	238 (36.5%)	479 (37.0%)	322 (36.1%)	339 (23.3%)
Oral antidiabetic drug	71 (10.9%)	152 (11.8%)	61 (6.8%)	105 (7.2%)
Insulin	61 (9.4%)	127 (9.8%)	90 (10.1%)	138 (9.5%)
Antidepressant	123 (18.9%)	163 (12.6%)	159 (17.8%)	240 (16.5%)
Digoxin	88 (13.5%)	204 (15.8%)	87 (9.7%)	145 (10.0%)
Rhythm control drug	24 (3.7%)	57 (4.4%)	18 (2.0%)	33 (2.3%)
NSAID	51 (7.8%)	67 (5.2%)	84 (9.4%)	112 (7.7%)
Corticosteroid	71 (10.9%)	188 (14.5%)	95 (10.6%)	192 (13.2%)
PPI	234 (35.9%)	414 (32.0%)	361 (40.4%)	527 (36.3%)

** For the no treatment group, this is the mean number of years since a last prescription, only of patients that ever received any antithrombotic treatment.

Appendix table 3a. Baseline characteristics and standardized mean differences of the propensity score matched cohort after ischemic stroke.

	NOAC	Warf	SMD	NOAC	AP	SMD	NOAC	None	SMD
Age	79,75	80,13	-0,04	80,42	80,67	-0,03	79,26	79,53	-0,03
Female sex	52%	51%	0,02	53%	52%	0,03	52%	55%	-0,05
MI	13%	14%	-0,06	13%	15%	-0,05	12%	12%	0,01
CHF	36%	37%	-0,02	33%	36%	-0,05	34%	35%	-0,00
Peripheral vascular disease	12%	13%	-0,03	11%	12%	-0,01	12%	10%	0,08
Cerebral vascular disease	29%	28%	0,03	30%	32%	-0,05	30%	29%	0,02
Dementia	9%	7%	0,05	10%	10%	-0,01	9%	8%	0,02
COPD	15%	17%	-0,06	14%	15%	-0,01	15%	15%	-0,01
Peptic ulcer	3%	3%	-	4%	3%	0,01	4%	4%	0,01
Rheumatoid arthritis	6%	6%	-0,01	6%	5%	0,05	6%	6%	0,01
Mild liver disease	1%	0%	0,05	1%	1%	-0,03	1%	0%	0,05
Diabetes without complications	21%	23%	-0,04	22%	24%	-0,04	22%	22%	-0,01
Connective tissue damage	3%	2%	0,04	3%	3%	0,02	3%	3%	0,01
Renal disease	10%	9%	0,02	10%	9%	0,03	10%	10%	-0,03
Diabetes with complications	8%	9%	-0,03	9%	9%	-0,01	8%	9%	-0,02
Cancer	15%	14%	0,03	14%	13%	0,04	15%	14%	0,01
Metastatic carcinoma	2%	1%	0,02	2%	2%	-	2%	2%	-0,02
Hypertension	79%	80%	-0,02	80%	80%	-0,01	79%	78%	0,02
Stroke/TIA/Embolism	31%	30%	0,01	31%	33%	-0,04	31%	29%	0,04
Anaemia	18%	18%	0,01	19%	19%	-0,01	18%	19%	-0,01
Alcoholism	2%	2%	-	3%	3%	-	3%	2%	0,03
Prior bleed	11%	11%	0,01	12%	11%	0,02	12%	15%	-0,09
Diuretic	42%	44%	-0,04	41%	40%	0,02	41%	41%	-0,00
Beta blocker	77%	76%	0,01	75%	75%	0,01	76%	76%	0,02
Ca channel blocker	28%	31%	-0,05	29%	29%	-	29%	27%	0,04
RAAS inhibitor	53%	53%	0,00	52%	53%	-0,01	53%	49%	0,09
Statin	35%	38%	-0,05	34%	34%	-	34%	32%	0,06
Oral antidiabetic	10%	10%	-0,01	11%	11%	-0,01	10%	10%	0,01
Insulin	8%	8%	-0,03	8%	10%	-0,08	8%	9%	-0,04
Antidepressants	19%	19%	-	18%	19%	-0,02	19%	20%	-0,02
Digoxin	15%	15%	0,01	14%	14%	-	15%	15%	0,01
Rhythm control drugs	3%	3%	0,01	2%	2%	0,01	4%	3%	0,02
NSAIDs	5%	4%	0,01	5%	4%	0,07	5%	5%	0,01
Corticosteroids	9%	9%	0,01	9%	7%	0,07	9%	7%	0,06
PPI	28%	26%	0,06	28%	31%	-0,06	29%	27%	0,04
Year 2011	0%	0%	-	0%	1%	-0,11	0%	0%	-
Year 2012	2%	2%	-0,04	2%	2%	-0,02	2%	1%	0,05
Year 2013	4%	3%	0,04	4%	3%	0,05	4%	3%	0,06
Year 2014	11%	14%	-0,09	12%	13%	-0,03	10%	10%	-
Year 2015	18%	20%	-0,04	18%	22%	-0,11	17%	17%	0,02
Year 2016	27%	27%	-0,01	26%	28%	-0,03	26%	28%	-0,05
Year 2017	28%	26%	0,06	28%	24%	0,08	30%	32%	-0,05
Year 2018	9%	8%	0,05	10%	8%	0,08	11%	9%	0,06

Appendix table 3b. Baseline characteristics and standardized mean differences of the propensity score matched cohort after intracranial hemorrhage.

	NOAC	Warf	SMD	NOAC	AP	SMD	NOAC	None	SMD
Age	80,11	80,49	-0,04	81,53	81,76	-0,03	80,09	80,73	-0,07
Female sex	43%	42%	0,01	47%	47%	-	43%	41%	0,03
MI	11%	12%	-0,05	14%	13%	0,02	10%	8%	0,07
CHF	34%	34%	0,01	35%	32%	0,07	34%	34%	0,01
Peripheral vascular disease	9%	8%	0,02	10%	10%	-	9%	8%	0,03
Cerebral vascular disease	28%	28%	-0,01	35%	35%	0,01	30%	30%	-0,09
Dementia	12%	11%	0,03	15%	17%	-0,05	13%	11%	0,04
COPD	21%	19%	0,05	16%	14%	0,06	21%	18%	0,06
Peptic ulcer	2%	4%	-0,09	3%	3%	-0,03	3%	2%	0,04
Rheumatoid arthritis	6%	8%	-0,07	6%	7%	-0,02	7%	7%	-0,01
Mild liver disease	1%	2%	-0,06	2%	2%	-0,05	1%	1%	-
Diabetes without complications	25%	25%	-	25%	23%	0,04	24%	22%	0,05
Connective tissue damage	5%	4%	0,06	5%	5%	-	6%	4%	0,07
Renal disease	9%	10%	-0,03	10%	10%	-	9%	9%	-0,01
Diabetes with complications	7%	8%	-0,03	6%	8%	-0,09	7%	6%	0,05
Cancer	18%	18%	0,02	16%	15%	0,03	18%	19%	-0,03
Metastatic carcinoma	3%	3%	0,02	1%	1%	-	3%	3%	0,02
Hypertension	77%	76%	0,03	79%	77%	0,06	78%	80%	-0,04
Stroke/TIA/Embolism	28%	27%	0,03	35%	35%	-	30%	30%	-
Anaemia	20%	20%	0,01	23%	24%	-0,01	21%	20%	0,02
Alcoholism	4%	4%	-0,02	5%	5%	-	3%	2%	0,07
Prior bleed	11%	11%	0,01	15%	18%	-0,08	15%	14%	0,02
Diuretic	43%	43%	-	42%	42%	0,01	41%	41%	-
Beta blocker	70%	71%	-0,02	65%	65%	-	71%	69%	0,04
Ca channel blocker	26%	26%	-0,01	26%	22%	0,08	26%	29%	-0,07
RAAS inhibitor	54%	54%	-	47%	48%	-0,01	52%	50%	0,06
Statin	36%	33%	0,06	37%	39%	-0,05	35%	33%	0,05
Oral antidiabetic	11%	11%	-	10%	11%	-0,04	10%	10%	-
Insulin	8%	10%	-0,08	8%	9%	-0,04	8%	7%	0,02
Antidepressants	21%	20%	0,01	27%	23%	0,08	22%	20%	0,05
Digoxin	16%	16%	-	15%	15%	-	15%	13%	0,07
Rhythm control drugs	4%	4%	-0,02	2%	4%	-0,09	4%	3%	0,04
NSAIDs	6%	5%	0,03	6%	6%	0,02	6%	6%	-
Corticosteroids	9%	11%	-0,09	10%	9%	0,04	8%	8%	0,01
PPI	27%	27%	-	33%	31%	0,05	29%	29%	0,01
Year 2011	0%	0%	-	0%	1%	-	0%	0%	-
Year 2012	2%	1%	0,06	3%	3%	-0,05	2%	2%	-0,03
Year 2013	4%	5%	-0,10	6%	8%	-0,10	3%	3%	-
Year 2014	7%	7%	-	10%	12%	-0,05	6%	5%	0,05
Year 2015	20%	21%	-0,02	22%	24%	-0,05	19%	22%	-0,09
Year 2016	21%	20%	0,03	21%	22%	-0,01	20%	20%	0,02
Year 2017	30%	31%	-0,02	27%	23%	0,09	32%	33%	-0,01
Year 2018	16%	14%	0,05	10%	8%	0,08	18%	16%	0,06

Appendix table 3c. Baseline characteristics and standardized mean differences of the propensity score matched cohort after severe gastrointestinal bleed.

	NOAC	Warf	SMD	NOAC	AP	SMD	NOAC	None	SMD
Age	77,97	78,21	-0,03	79,18	79,88	-0,07	77,86	77,96	-0,01
Female sex	44%	42%	0,03	44%	47%	-0,05	46%	44%	0,03
MI	14%	15%	-0,03	18%	21%	-0,09	13%	14%	-0,02
CHF	45%	46%	-0,03	42%	43%	-0,02	40%	40%	0,01
Peripheral vascular disease	11%	12%	-0,01	15%	15%	-0,02	12%	11%	0,01
Cerebral vascular disease	23%	21%	0,05	26%	26%	-0,02	25%	23%	0,03
Dementia	5%	5%	-0,02	7%	9%	-0,09	6%	5%	0,01
COPD	20%	20%	-0,00	20%	21%	-0,03	20%	20%	-0,00
Peptic ulcer	5%	6%	-0,04	5%	5%	0,01	5%	5%	-0,02
Rheumatoid arthritis	6%	8%	-0,04	6%	6%	-0,02	7%	7%	-0,01
Mild liver disease	3%	3%	-0,04	4%	5%	-0,06	3%	2%	0,05
Diabetes without complications	26%	27%	-0,04	24%	23%	0,01	24%	23%	0,03
Connective tissue damage	4%	2%	0,08	4%	3%	0,06	5%	4%	0,02
Renal disease	12%	12%	-0,01	12%	14%	-0,09	11%	11%	-
Diabetes with complications	9%	10%	-0,01	9%	10%	-0,03	10%	9%	0,02
Cancer	22%	23%	-0,04	21%	21%	-0,01	21%	21%	0,01
Metastatic carcinoma	3%	4%	-0,06	3%	3%	-0,03	3%	3%	-
Hypertension	77%	79%	-0,05	76%	77%	-0,02	76%	75%	0,03
Stroke/TIA/Embolism	23%	22%	0,05	26%	26%	-0,02	25%	24%	0,03
Anaemia	30%	32%	-0,04	33%	35%	-0,05	32%	35%	-0,05
Alcoholism	4%	5%	-0,02	7%	7%	0,01	6%	7%	-0,06
Prior bleed	12%	14%	-0,04	15%	14%	0,02	13%	14%	-0,04
Diuretic	48%	50%	-0,04	48%	49%	-0,02	44%	44%	-
Beta blocker	78%	77%	0,01	73%	72%	0,04	76%	74%	0,05
Ca channel blocker	25%	25%	-0,02	25%	26%	-0,02	25%	23%	0,06
RAAS inhibitor	55%	56%	-0,01	54%	52%	0,04	53%	50%	0,06
Statin	36%	36%	0,01	40%	37%	0,06	36%	32%	0,08
Oral antidiabetic	11%	12%	-0,02	9%	8%	0,03	11%	10%	0,02
Insulin	9%	9%	-0,01	9%	10%	-0,05	9%	9%	0,01
Antidepressants	17%	16%	0,03	17%	18%	-0,05	19%	19%	0,02
Digoxin	14%	14%	0,01	11%	9%	0,07	13%	12%	0,02
Rhythm control drugs	4%	4%	-	3%	3%	-	4%	3%	0,03
NSAIDs	7%	7%	0,01	10%	9%	0,03	7%	8%	-0,02
Corticosteroids	11%	10%	0,01	10%	10%	-	11%	12%	-0,05
PPI	35%	35%	-0,00	38%	36%	0,03	37%	36%	0,02
Year 2011	0%	0%	-	0%	1%	-	0%	1%	-
Year 2012	3%	3%	-0,01	4%	4%	-0,04	2%	2%	0,02
Year 2013	4%	5%	-0,02	6%	6%	0,01	4%	3%	0,04
Year 2014	10%	11%	-0,03	13%	15%	-0,09	9%	11%	-0,06
Year 2015	22%	21%	0,03	23%	24%	-0,03	20%	20%	0,00
Year 2016	20%	24%	-0,10	22%	21%	0,03	20%	24%	-0,09
Year 2017	27%	26%	0,01	20%	19%	0,02	27%	25%	0,03
Year 2018	14%	11%	0,09	12%	9%	0,06	17%	14%	0,07

Appendix table 4. Array approach sensitivity analyses for unmeasured confounder.

Low HR	High HR	RR_{CD}	P_{C1}	P_{C0}	Low HR adjusted	High HR adjusted
1,36	1,57	1,0	0,50	0,1	1,36	1,57
1,36	1,57	1,5	0,50	0,1	1,14	1,32
1,36	1,57	2,0	0,50	0,1	1,00	1,15
1,36	1,57	2,5	0,50	0,1	0,89	1,03
1,36	1,57	3,0	0,50	0,1	0,82	0,94
1,36	1,57	3,5	0,50	0,1	0,76	0,87
1,36	1,57	4,0	0,50	0,1	0,71	0,82
1,36	1,57	4,5	0,50	0,1	0,67	0,77
1,36	1,57	5,0	0,50	0,1	0,63	0,73
1,36	1,57	1,0	0,40	0,1	1,36	1,57
1,36	1,57	1,5	0,40	0,1	1,19	1,37
1,36	1,57	2,0	0,40	0,1	1,07	1,23
1,36	1,57	2,5	0,40	0,1	0,98	1,13
1,36	1,57	3,0	0,40	0,1	0,91	1,05
1,36	1,57	3,5	0,40	0,1	0,85	0,98
1,36	1,57	4,0	0,40	0,1	0,80	0,93
1,36	1,57	4,5	0,40	0,1	0,77	0,88
1,36	1,57	5,0	0,40	0,1	0,73	0,85
1,36	1,57	1,0	0,30	0,1	1,36	1,57
1,36	1,57	1,5	0,30	0,1	1,24	1,43
1,36	1,57	2,0	0,30	0,1	1,15	1,33
1,36	1,57	2,5	0,30	0,1	1,08	1,25
1,36	1,57	3,0	0,30	0,1	1,02	1,18
1,36	1,57	3,5	0,30	0,1	0,97	1,12
1,36	1,57	4,0	0,30	0,1	0,93	1,07
1,36	1,57	4,5	0,30	0,1	0,90	1,03
1,36	1,57	5,0	0,30	0,1	0,87	1,00
1,36	1,57	1,0	0,20	0,1	1,36	1,57
1,36	1,57	1,5	0,20	0,1	1,30	1,50
1,36	1,57	2,0	0,20	0,1	1,25	1,44
1,36	1,57	2,5	0,20	0,1	1,20	1,39
1,36	1,57	3,0	0,20	0,1	1,17	1,35
1,36	1,57	3,5	0,20	0,1	1,13	1,31
1,36	1,57	4,0	0,20	0,1	1,11	1,28
1,36	1,57	4,5	0,20	0,1	1,1	1,25
1,36	1,57	5,0	0,20	0,1	1,1	1,22

Low HR: The weakest significant association found in the Cox regression. High HR: The strongest significant association found in the Cox regression. RRcd: The association of the confounder with mortality. E.g., if the RRcd is 3.0, it means a patient with this confounder is 3 times more likely to die. Pc1: The proportion of patients having the confounder in the comparator group. Pc0: The proportion of patients having the confounder in the NOAC group. Low HR adjusted: The HR of the weakest association if we take a confounder into account that has the properties of the columns on the left. High HR adjusted: The HR of the strongest association if we take a confounder into account that has the properties of the columns on the left.

Appendix table 5. Results from the sensitivity analyses when any prescription in the 180 days prior to inclusion was used to assess treatment at the event. Proportion of patients treated with different antithrombotic treatments and 90 day mortality rates.

	NOAC	Warfarin	Antiplatelet	No treatment
Ischaemic stroke				
n main analysis (%)	454 (7.5%)	1229 (20.4%)	2026 (33.7%)	2308 (38.4%)
n sensitivity (%)	577 (9.6%)	1717 (28.5%)	2290 (38.1%)	1433 (23.8%)
90 day mortality main analysis (%)	17.6%	17.6%	29.8%	26.3%
90 day mortality sensitivity (%)	18.2%	19.3%	30.7%	25.8%
Intracranial haemorrhage				
n main analysis (%)	311 (10.3%)	1028 (34.2%)	595 (19.8%)	1072 (35.7%)
n sensitivity (%)	370 (12.3%)	1377 (45.8%)	675 (22.5%)	584 (19.4%)
90 day mortality main analysis (%)	26.4%	32.4%	37.0%	29.4%
90 day mortality sensitivity (%)	25.1%	32.2%	36.7%	28.4%
Severe gastrointestinal bleed				
n main analysis (%)	652 (15.2%)	1293 (30.1%)	893 (20.8%)	1453 (33.9%)
n sensitivity (%)	765 (17.8%)	1680 (39.2%)	1014 (23.6%)	832 (19.4%)
90 day mortality main analysis (%)	10.9%	11.4%	21.7%	19.5%
90 day mortality sensitivity (%)	11.1%	11.5%	22.8%	22.5%

Appendix table 6. Results from the sensitivity analyses when including only primary diagnosis from inpatient care. The aHR are adjusted hazard ratios from the cox regression with the same covariates as the main analysis.

	NOAC	Warfarin	Antiplatelet	No treatment
Intracranial haemorrhage				
n main analysis (%)	311 (10.3%)	1028 (34.2%)	595 (19.8%)	1072 (35.7%)
n sensitivity (%)	225 (10.0%)	847 (37.8%)	428 (19.1%)	740 (33.0%)
90 day mortality main analysis (%)	26.4%	32.4%	37.0%	29.4%
90 day mortality sensitivity (%)	26.7%	32.7%	39.5%	31.5%
aHR sensitivity analysis	Reference	1.37 (1.00 – 1.88)	1.26 (0.87 – 1.84)	1.00 (0.73 – 1.39)
Severe gastrointestinal bleed				
n main analysis (%)	652 (15.2%)	1293 (30.1%)	893 (20.8%)	1453 (33.9%)
n sensitivity (%)	271 (12.5%)	681 (31.3%)	513 (23.6%)	709 (32.6%)
90 day mortality main analysis (%)	10.9%	11.4%	21.7%	19.5%
90 day mortality sensitivity (%)	12.5%	12.5%	24.6%	24.4%
aHR sensitivity analysis	Reference	1.03 (0.66 – 1.63)	1.82 (1.16 – 2.85)	1.93 (1.28 – 2.92)

Appendix table 7. Results from the sensitivity analyses where all patients receiving concomitant antiplatelet therapy (i.e., NOAC + antiplatelet, warfarin + antiplatelet or double antiplatelet therapy) were excluded.

	NOAC	Warfarin	Antiplatelet	No treatment
Ischemic stroke				
Original mortality	80 (17.6%)	216 (17.6%)	604 (29.8%)	608 (26.3%)
Mortality excluding double	74 (17.7%)	191 (17.0%)	590 (29.8%)	608 (26.3%)
Intracranial hemorrhage				
Original mortality	82 (26.4%)	333 (32.4%)	220 (37.0%)	315 (29.4%)
Mortality excluding double	77 (25.8%)	308 (32.1%)	208 (36.7%)	315 (29.4%)
Severe gastrointestinal bleed				
Original mortality	71 (10.9%)	147 (11.4%)	194 (21.7%)	284 (19.5%)
Mortality excluding double	68 (11.4%)	138 (12.0%)	191 (22.7%)	284 (19.5%)

4

THE GREEDY PROPENSITY SCORE MATCHING ALGORITHM

4.1

GREEDY CALIPER PROPENSITY SCORE MATCHING CAN YIELD VARIABLE ESTIMATES OF THE TREATMENT-OUTCOME ASSOCIATION - A SIMULATION STUDY

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ABSTRACT

Purpose

Greedy caliper propensity score (PS) matching is dependent on randomness, which can ultimately affect causal estimates. We sought to investigate the variation introduced by this randomness.

Methods

Based on a literature search to define the simulation parameters, we simulated 36 cohorts of different sizes, treatment prevalence, outcome prevalence, treatment-outcome-association. We performed 1:1 caliper and nearest neighbor (NN) caliper PS-matching and repeated this 1000 times in the same cohort, before calculating the treatment-outcome association.

Results

Repeating caliper and NN caliper matching in the same cohort yielded large variations in effect estimates, in all 36 scenarios, with both types of matching. The largest variation was found in smaller cohorts, where the odds ratio (OR) ranged from 0.53 to 10.00 (IQR of ORs: 1.11 – 1.67). The 95% confidence interval was not consistently overlapping a neutral association after repeating the matching with both algorithms. We confirmed these findings in a non-interventional example study.

Conclusion

Caliper PS-matching can yield highly variable estimates of the treatment-outcome association if the analysis is repeated.

BACKGROUND

In observational research, treatment allocation is not random, but allocated by the treating physician. Therefore, patient characteristics will likely influence the physician's decision to give a patient a certain treatment, or not [1]. Adjusting for these characteristics can decrease this bias, and the propensity score (PS) is often used for this purpose [2]. Besides using the PS for adjustment, weighting, or stratification [3], using the PS for matching is a popular way to achieve cohorts with comparable baseline characteristics [4, 5].

Greedy caliper matching is a popular method used in PS matching [6]. This method orders the treated subjects, and the first treated subject is randomly matched to an untreated (or alternatively treated) subject with a PS that is within a predefined caliper width. The initial ordering of subjects is often done randomly but may also be based on a subject's PS or other parameters. In addition to caliper matching, nearest neighbor (NN) caliper matching is often used, where the treated subject is matched to an untreated subject that has the closest propensity score within the caliper. Both methods do not consider that the untreated subject can potentially form a better pair with another treated subject that is further down the line; hence they are 'greedy' algorithms. Because of this, both methods are dependent on the random order in which the treated subjects are placed, if patients are not ordered based on their PS. In addition, caliper matching is also dependent on which untreated patient within the caliper is randomly matched.

Most statistical programs use a pseudo-random ordering, which can allow for the random ordering to be reproduced if the same random seed is used. However, how much the matching, and ultimately the estimated treatment effect, can differ with a different random seed, is unknown. We evaluated the extent to which observational studies analyzed using greedy caliper PS matching with random ordering and greedy NN caliper PS matching are susceptible to variable results due to the randomness in the matching.

METHODS

The study consisted of three parts. First, we conducted a review of matching procedures used in epidemiologic studies to identify realistic scenarios for a simulation study. Second, we repeatedly applied PS matching in several simulated cohorts. Third, we sought to replicate the findings in a real observational study of drug effectiveness.

Literature Search

We performed a literature search to find realistic parameters for our simulation. In PubMed, we searched for 'propensity score' AND (((match) OR matched) OR matching), filtering core clinical journals as defined by PubMed. The search was performed on August 22, 2019. We selected the 50 most recently published pharmacoepidemiology studies using PS matching, and 50 studies that were not pharmacoepidemiology, as defined by two independent reviewers (JK and AT). From these articles, we identified the matching algorithm that was used, which statistical program was used, the sample size, the treatment prevalence, the outcome prevalence, and the strength

of the association between treatment and outcome. These parameters were used to determine the parameters of the simulation study.

Data Simulation

We simulated a range of cohorts based on scenarios identified through our literature search. We simulated cohorts of different sizes (500, 2500, 10 000), different treatment prevalence (20%, 50%), different outcome prevalence (10%, 50%), and different associations between treatment and outcome (OR of 0.75, 1.0, 1.5), yielding 36 scenarios.

For the simulation of the cohorts, we used a 2-step process to define covariates. First, we created 8 variables (X_1 X_8): 6 binary variables (X_1 X_6) and 2 continuous variables (X_7, X_8). X_1 through X_6 were randomly drawn from a binomial distribution and had a prevalence of 0.2 and both X_7 and X_8 were drawn from a normal distribution and had a mean of 0 and a variance of 0.5 unit. All covariates were independent of each other. Based on these variables, we defined the probability of treatment *T* using a logistic model, and then simulated T from these probabilities:

$$1.\ p(T|X_1 \ldots X_8) = (1+\exp\ (-(\alpha_0 + \alpha_1 X_1 + \ldots + \alpha_8 X_8)))^{-1}$$

Finally, we simulated outcome *Y* based on the probability of *Y* given all 8 variables and the treatment *T*, using a logistic model:

$$2.\ p(Y|T,X_1 \ldots X_8) = (1+\exp\ (-(\beta_0 + \beta_1 X_1 + \ldots + \beta_8 X_8 + \beta_T T)))^{-1}$$

The range of values used in the models in different scenarios is presented in Table 1. The parameter values α_0 and β_0 were chosen to result in the desired prevalence for *T* of 0.2 and 0.5 and for *Y* of 0.1 and 0.5.

Propensity Score Matching

In all 36 generated cohorts, we applied greedy caliper matching, with and without using NN. First, in all 36 cohorts, we used logistic regression to calculate the probability for the treatment based on the simulated covariates, which was used as the PS. Then we used both matching methods in a 1:1 fashion without replacement and with a random ordering of treated patients, as was most used in the literature search and which is the default option in most statistical packages. We varied the caliper width using 0.2 and 0.01 of the standard deviation of the propensity score (SD_{ps}). In all 36 cohorts, we replicated both matching algorithms 1000 times with a different random seed for each repetition, to create a different order for each repetition. In all 1000 matched sets, we performed a conditional logistic regression for matched pairs, only including treatment and outcome, to calculate the association between treatment and outcome after matching. All statistical analyses were performed with statistical software R version 3.4.2 and RStudio Desktop

Table 1. Parameters for the Simulation Study and the Corresponding Values. Parameters were chosen based on the results from the literature review to create different scenarios with two levels of treatment prevalence, two levels of outcome prevalence, and three different treatment-outcome associations. a) Variable X_1 through X_6 are binary variables. Variable X_7 and X_8 are continuous variables.b) Prevalence for all binary variables (X_1 through X_2) and mean with variance for all continuous variables (X_7 and X_8).c) Odds ratio for the relation between parameter α and the treatment T, corresponding to formula 1.d) Odds ratio for the relation between parameter β and the outcome Y, corresponding to formula 2.e) Treatment prevalence of 20% and 50% in the whole population (approximate number).f) Outcome prevalence of 10% and 20% in the whole population (approximate number).

Variable[a]	Prevalence/mean(var)[b]	OR_T[c]	Parameter	OR_Y[d]	Parameter
X_1	0.2	2	α_1	1	β_1
X_2	0.2	1	α_2	2	β_2
X_3	0.2	0.5	α_3	0.5	β_3
X_4	0.2	2	α_4	0.5	β_4
X_5	0.2	1	α_5	1	β_5
X_6	0.2	0.5	α_6	2	β_6
X_7	0 (0.5)	1.5	α_7	0.5	β_7
X_8	0 (0.5)	0.5	α_8	1.5	β_8
T	0.2, 0.5[e]		α_0	0.75, 1.0, 1.5	β_9
Y	0.1, 0.2[f]				β_0

version 1.1.463. We used a modification of the 'MatchIt' package for the matching procedures [7]. That is, in the MatchIt package it is by default not possible to perform NN caliper matching, but only NN matching without calipers or caliper matching without NN. The modification allowed us to perform NN caliper matching.

We present the median, interquartile range (IQR), and full range of the 1000 ORs, coming from the corresponding 1000 matched sets. Second, we present the unadjusted OR in the full cohort. Third, we present the proportion of matched sets that yielded statistically significant results, both positive and negative (i.e. 95% confidence interval of the OR not containing 1). Fourth, we present the proportion of matched sets that were unsuccessfully matched (i.e., at least one of the covariates had a standardized mean difference (SMD) > 0.1 after PS matching). We performed a sensitivity analysis in which we excluded all unsuccessfully matched cohorts. Fifth, we present the mean number of matched subjects. We only present the results for the matching with a caliper width of 0.2 SD_{ps}. The results after matching with a caliper width of 0.01 SD_{ps} can be found in the appendix.

Real-life Dataset

We used the Stockholm Healthcare database for confirmation of our findings from the simulation dataset in a real-life setting. The database has been described elsewhere [8]. In short, the database contains demographic information for all Stockholm resident s (n=2.3 million), ATC-codes for dispensed drugs, and ICD-10 codes for inpatient and outpatient diagnoses from primary and secondary care.

From this database, we selected all patients prescribed with a vitamin K antagonist (VKA) or a non VKA oral anticoagulant (NOAC) with a prior diagnosis of atrial fibrillation (ICD-10: I48) and

no claim for any oral anticoagulant (OAC) in the year prior to inclusion. To vary the sample size of the cohort, we created the smallest cohort including patients initiated in the last quarter of 2013, a medium cohort including all patients initiated in 2013, and a large cohort of patients initiated in 2013 until 2015. The first prescription was defined as the index date and patients were followed for a maximum of one year. Patients were censored when they emigrated, died, or suffered from an outcome. The outcome of interest was a composite of an ischemic stroke, unspecified stroke or transient ischemic attack (TIA), registered as an ICD-10 code in a hospital setting and requiring acute care, as was done previously [9].

We used a PS matched intention-to-treat analysis to assess the association of NOACs versus VKA and the risk for the composite endpoint. The propensity score was the probability of receiving a NOAC compared to a VKA, calculated using logistic regression. In the logistic regression model, we used the components of the CHA_2Ds_2-VASC score (age, sex, heart failure, hypertension, prior stroke/TIA/embolism, vascular disease, and diabetes), registered in the 5 years prior to index date [10].

We used both 1:1 caliper matching and 1:1 NN caliper matching with a caliper width of 0.2 SD_{ps} or 0.01 SD_{ps} without replacement. We replicated the matching procedure 1000 times with a different random seed for each repetition. In each matched set, we used a stratified Cox proportional hazards model for matched pairs to assess the association of NOAC versus VKA with the risk for the composite outcome.

RESULTS

Literature search

We assessed 100 articles. Of the 72 articles mentioning the kind of matching algorithm used, 51 used nearest neighbor matching (32 with a caliper), 17 used caliper matching, two used 5:1-digit matching, one used optimal matching, and one used kernel matching. SAS was mentioned in 32 articles, R in 25, SPSS in 17, and STATA in 14. The MatchIt package in R was the most frequently mentioned package (n =13) but most often no package, macro, or program was mentioned at all (n = 79).

Simulation Study

Repeating the PS matching 1000 times with a different random seed yielded wide variation in the OR for the association of treatment and outcome, especially in caliper matching and less in NN caliper matching (see Figure 1 and Tables 2a-c, appendix Table 1a-c). The variation was largest with caliper matching in a sample size of 500, where the smallest OR was 0.53 (CI: 0.23 – 1.26) and the largest was 10.00 (CI: 1.28 – 78.1) with an IQR from 1.11 to 1.67.

Originating from the same cohort, some matched sets yielded a 95% confidence interval that overlapped 1, while other matched sets did not, both after applying caliper matching as in NN caliper matching. For example, in a cohort with a simulated OR of 1.5 (n = 2500), in 37.9% of the cases after caliper matching and in 38.2% of the cases after NN caliper matching, the 95% confidence interval did not overlap 1, while in the other cases it did.

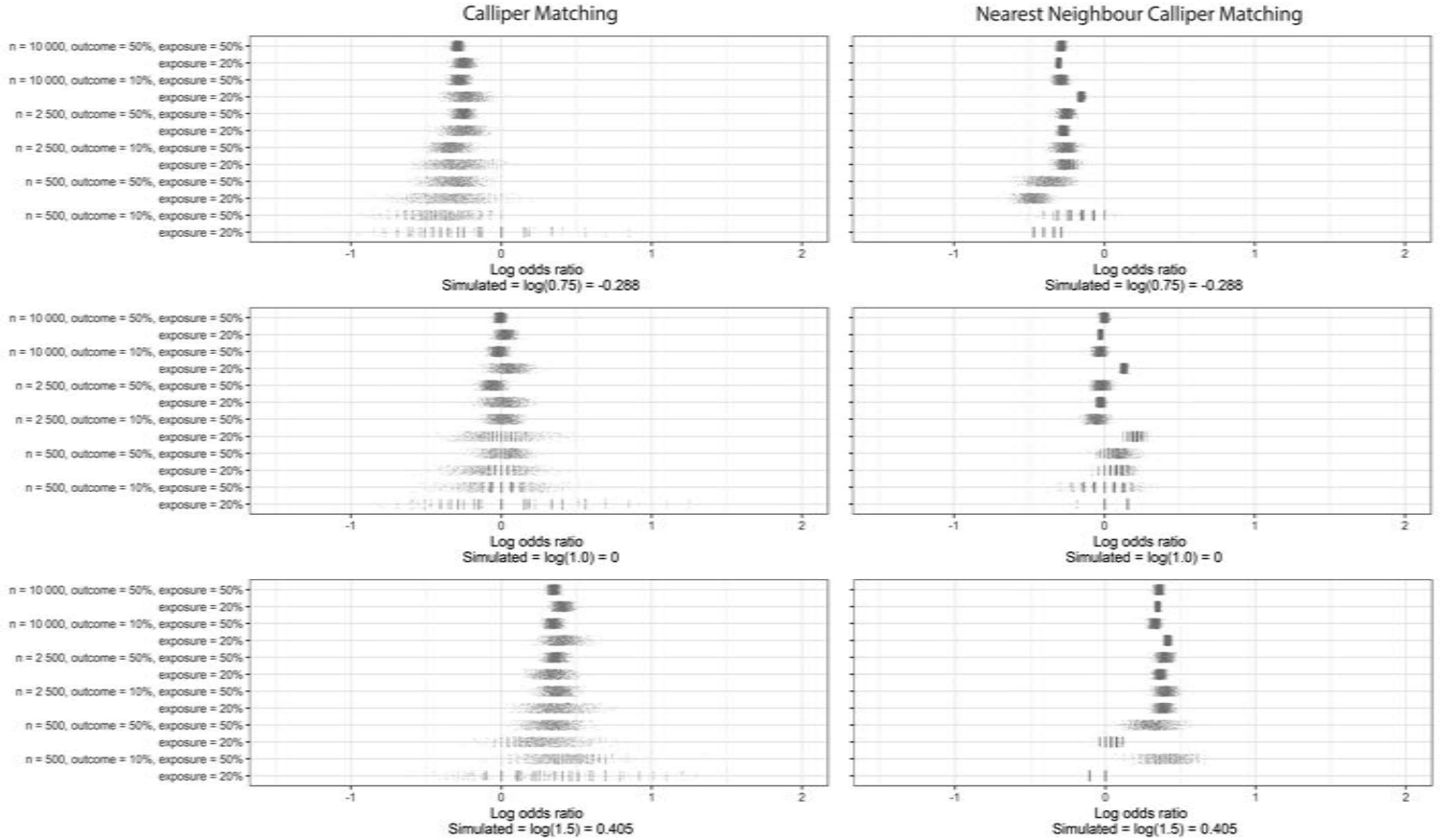

Figure 1. Scatterplot of the distribution of odds ratios in the 1000 matched sets after caliper matching and after nearest neighbor caliper matching in the different simulation scenarios.

Table 2a. Results from the 1000 Matched Sets in Different Scenarios with a Simulated Odds Ratio of 0.75 and a caliper width of 0.2 SD_{ps}.OR = odds ratio; T 50% = treatment prevalence 50%; O 50% = outcome prevalence 50%; % sign low/high risk = percentage of the 1000 matched sets with a significantly increased or decreased risk.

		Median OR	Interquartile range OR	Full range OR	Unadjusted OR	% sign low risk	% sign high risk	Mean n matches	% unsuccessful matches
N = 10.000									
Caliper Matching	T 50%, O 50%	0,75	(0,74-0,76)	(0,69-0,81)	0,59	100,0%	0,0%	7266	0,0%
	T 20%, O 50%	0,78	(0,76-0,80)	(0,70-0,89)	0,58	99,9%	0,0%	3902	0,0%
	T 50%, O 10%	0,76	(0,74-0,78)	(0,67-0,84)	0,56	100,0%	0,0%	7049	0,0%
	T 20%, O 10%	0,79	(0,76-0,83)	(0,66-1,03)	0,54	45,4%	0,0%	3902	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,75	(0,74-0,76)	(0,71-0,79)	0,59	100,0%	0,0%	7162	0,0%
	T 20%, O 50%	0,74	(0,73-0,74)	(0,72-0,76)	0,58	100,0%	0,0%	3898	0,0%
	T 50%, O 10%	0,75	(0,74-0,76)	(0,70-0,80)	0,56	100,0%	0,0%	6935	0,0%
	T 20%, O 10%	0,86	(0,85-0,86)	(0,83-0,89)	0,54	0,0%	0,0%	3898	0,0%
N = 2500									
Caliper Matching	T 50%, O 50%	0,78	(0,76-0,79)	(0,69-0,86)	0,62	97,6%	0,0%	1883	0,0%
	T 20%, O 50%	0,78	(0,74-0,82)	(0,61-1,02)	0,59	49,4%	0,0%	1048	3,1%
	T 50%, O 10%	0,72	(0,69-0,75)	(0,56-0,90)	0,52	48,2%	0,0%	1883	0,0%
	T 20%, O 10%	0,74	(0,69-0,81)	(0,55-1,13)	0,65	10,9%	0,0%	1038	3,6%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,78	(0,76-0,79)	(0,70-0,84)	0,62	99,6%	0,0%	1865	0,0%
	T 20%, O 50%	0,76	(0,75-0,77)	(0,72-0,82)	0,59	91,6%	0,0%	1046	0,0%
	T 50%, O 10%	0,77	(0,75-0,79)	(0,67-0,88)	0,52	3,0%	0,0%	1865	0,0%
	T 20%, O 10%	0,78	(0,76-0,80)	(0,69-0,88)	0,65	0,0%	0,0%	1031	0,0%

Table 2a. (continued)

		Median OR	Interquartile range OR	Full range OR	Unadjusted OR	% sign low risk	% sign high risk	Mean n matches	% unsuccessful matches
N = 500									
Caliper Matching	T 50%, O 50%	0,73	(0,68-0,78)	(0,51-1,00)	0,53	10,5%	0,0%	339	37,4%
	T 20%, O 50%	0,71	(0,64-0,79)	(0,39-1,22)	0,54	6,9%	0,0%	210	71,9%
	T 50%, O 10%	0,67	(0,61-0,75)	(0,33-1,18)	0,55	1,5%	0,0%	353	25,4%
	T 20%, O 10%	0,78	(0,67-1,00)	(0,31-3,50)	0,60	0,2%	0,0%	202	76,2%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,69	(0,65-0,73)	(0,53-0,91)	0,53	19,6%	0,0%	335	41,2%
	T 20%, O 50%	0,63	(0,60-0,65)	(0,52-0,73)	0,54	8,0%	0,0%	207	94,6%
	T 50%, O 10%	0,86	(0,79-0,92)	(0,57-1,08)	0,55	0,0%	0,0%	347	24,9%
	T 20%, O 10%	0,71	(0,67-0,71)	(0,63-0,75)	0,60	0,0%	0,0%	202	20,7%

Table 2b. Results from the 1000 Matched Sets in Different Scenarios with a Simulated Odds Ratio of 1.0 and a caliper width of 0.2 SD_{ps}.OR = odds ratio; T 50% = treatment prevalence 50%; O 50% = outcome prevalence 50%; % sign low/high risk = percentage of the 1000 matched sets with a significantly increased or decreased risk.

		Median OR	Interquartile range OR	Full range OR	Unadjusted OR	% sign low risk	% sign high risk	Mean n matches	% unsuccessful matches
N = 10.000									
Caliper Matching	T 50%, O 50%	0,99	(0,98-1,01)	(0,91-1,04)	0,77	0,0%	0,0%	7266	0,0%
	T 20%, O 50%	1,02	(1,00-1,05)	(0,92-1,17)	0,76	0,0%	0,2%	3902	0,0%
	T 50%, O 10%	0,98	(0,96-1,00)	(0,90-1,07)	0,74	0,0%	0,0%	7049	0,0%
	T 20%, O 10%	1,05	(1,01-1,10)	(0,87-1,37)	0,72	0,0%	0,5%	3902	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,00	(0,99-1,01)	(0,96-1,05)	0,77	0,0%	0,0%	7162	0,0%
	T 20%, O 50%	0,97	(0,97-0,98)	(0,95-1,00)	0,76	0,0%	0,0%	3898	0,0%
	T 50%, O 10%	0,97	(0,96-0,99)	(0,91-1,04)	0,74	0,0%	0,0%	6935	0,0%
	T 20%, O 10%	1,14	(1,13-1,15)	(1,09-1,18)	0,72	0,0%	0,0%	3898	0,0%
N = 2500									
Caliper Matching	T 50%, O 50%	0,94	(0,92-0,97)	(0,79-1,10)	0,77	0,2%	0,0%	1731	0,0%
	T 20%, O 50%	1,02	(0,96-1,07)	(0,77-1,30)	0,68	0,0%	0,0%	954	4,3%
	T 50%, O 10%	1,01	(0,98-1,05)	(0,85-1,17)	0,77	0,0%	0,0%	1823	0,0%
	T 20%, O 10%	1,00	(0,89-1,10)	(0,65-1,72)	0,63	0,0%	0,0%	911	8,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,98	(0,96-1,00)	(0,90-1,08)	0,77	0,0%	0,0%	1701	0,0%
	T 20%, O 50%	0,97	(0,96-0,98)	(0,91-1,03)	0,68	0,0%	0,0%	949	0,0%
	T 50%, O 10%	0,95	(0,92-0,98)	(0,82-1,07)	0,77	0,0%	0,0%	1809	0,0%
	T 20%, O 10%	1,24	(1,21-1,25)	(1,13-1,36)	0,63	0,0%	0,0%	907	0,0%

Table 2b. (continued)

		Median OR	Interquartile range OR	Full range OR	Unadjusted OR	% sign low risk	% sign high risk	Mean n matches	% unsuccessful matches
N = 500									
Caliper Matching	T 50%, O 50%	1,02	(0,96-1,08)	(0,73-1,35)	0,70	0,0%	0,0%	357	23,4%
	T 20%, O 50%	0,96	(0,87-1,09)	(0,54-1,59)	0,74	0,0%	0,0%	190	83,6%
	T 50%, O 10%	1,00	(0,88-1,13)	(0,53-2,57)	0,78	0,0%	0,1%	349	19,6%
	T 20%, O 10%	1,00	(0,78-1,20)	(0,33-7,00)	0,60	0,0%	0,0%	190	83,6%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,08	(1,03-1,13)	(0,89-1,34)	0,70	0,0%	0,0%	356	53,1%
	T 20%, O 50%	1,08	(1,04-1,13)	(0,92-1,30)	0,74	0,0%	0,0%	190	81,9%
	T 50%, O 10%	1,00	(0,93-1,07)	(0,67-1,43)	0,78	0,0%	0,0%	346	9,0%
	T 20%, O 10%	1,17	(1,00-1,17)	(0,83-1,17)	0,60	0,0%	0,0%	190	81,9%

Table 2c. Results from the 1000 Matched Sets in Different Scenarios with a Simulated Odds Ratio of 1.5 and a caliper width of 0.2 SD_{ps}.OR = odds ratio; T 50% = treatment prevalence 50%; O 50% = outcome prevalence 50%; % sign low/high risk = percentage of the 1000 matched sets with a significantly increased or decreased risk.

		Median OR	Interquartile range OR	Full range OR	Unadjusted OR	% sign low risk	% sign high risk	Mean n matches	% unsuccessful matches
N = 10.000									
Caliper Matching	T 50%, O 50%	1,42	(1,40-1,44)	(1,33-1,51)	1,11	0,0%	100,0%	7266	0,0%
	T 20%, O 50%	1,50	(1,46-1,54)	(1,34-1,69)	1,08	0,0%	100,0%	3902	0,0%
	T 50%, O 10%	1,41	(1,38-1,44)	(1,29-1,55)	1,05	0,0%	100,0%	7049	0,0%
	T 20%, O 10%	1,49	(1,43-1,57)	(1,21-1,95)	1,05	0,0%	99,8%	3820	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,43	(1,41-1,44)	(1,35-1,50)	1,11	0,0%	100,0%	7162	0,0%
	T 20%, O 50%	1,42	(1,41-1,42)	(1,38-1,46)	1,08	0,0%	100,0%	3898	0,0%
	T 50%, O 10%	1,39	(1,37-1,41)	(1,29-1,48)	1,05	0,0%	100,0%	6935	0,0%
	T 20%, O 10%	1,51	(1,50-1,53)	(1,46-1,57)	1,05	0,0%	100,0%	3807	0,0%
N = 2500									
Caliper Matching	T 50%, O 50%	1,43	(1,40-1,47)	(1,26-1,62)	1,04	0,0%	100,0%	1823	0,0%
	T 20%, O 50%	1,40	(1,34-1,47)	(1,13-1,79)	1,09	0,0%	89,4%	1038	3,6%
	T 50%, O 10%	1,45	(1,39-1,51)	(1,15-1,73)	1,01	0,0%	92,0%	1731	0,0%
	T 20%, O 10%	1,44	(1,33-1,56)	(1,04-2,29)	1,25	0,0%	37,9%	1038	3,6%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,48	(1,46-1,51)	(1,35-1,61)	1,04	0,0%	100,0%	1809	0,0%
	T 20%, O 50%	1,44	(1,42-1,46)	(1,34-1,55)	1,09	0,0%	100,0%	1031	0,0%
	T 50%, O 10%	1,49	(1,45-1,53)	(1,29-1,69)	1,01	0,0%	99,8%	1701	0,0%
	T 20%, O 10%	1,47	(1,44-1,50)	(1,33-1,64)	1,25	0,0%	38,2%	1031	0,0%

Table 2c.(continued)

		Median OR	Interquartile range OR	Full range OR	Unadjusted OR	% sign low risk	% sign high risk	Mean n matches	% unsuccessful matches
N = 500									
Caliper Matching	T 50%, O 50%	1,41	(1,31-1,50)	(1,00-2,04)	1,09	0,0%	13,4%	326	27,0%
	T 20%, O 50%	1,30	(1,17-1,47)	(0,76-2,50)	1,05	0,0%	2,7%	187	82,6%
	T 50%, O 10%	1,50	(1,35-1,69)	(0,90-3,86)	1,17	0,0%	4,0%	349	19,6%
	T 20%, O 10%	1,29	(1,11-1,67)	(0,53-10,00)	0,96	0,0%	0,4%	185	87,7%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,37	(1,29-1,45)	(1,03-1,85)	1,09	0,0%	4,0%	322	32,6%
	T 20%, O 50%	1,04	(1,00-1,07)	(0,92-1,14)	1,05	0,0%	0,0%	187	87,6%
	T 50%, O 10%	1,50	(1,40-1,60)	(1,07-2,08)	1,17	0,0%	0,4%	346	9,0%
	T 20%, O 10%	1,00	(0,90-1,00)	(0,90-1,00)	0,96	0,0%	0,0%	183	100,0%

When only including successfully matched sets, i.e., only sets with all covariates having a SMD ≤ 0.1 after matching, the variation was smaller for both caliper matching as nearest neighbor caliper matching (see Appendix Tables 2a-c and Appendix Tables 3a-c). After removing all unsuccessful matched sets, there were still sets yielding a 95% confidence interval that overlapped 1, while other sets did not, both with caliper matching as NN caliper matching.

Real life dataset

In line with the simulations, the largest variation was visible in the smallest cohort (n = 1594) after caliper matching with a median HR of 0.94 (IQR: 0.82 – 1.06), ranging from 0.52 (CI: 0.27 – 1.01) to 2.43 (CI: 1.01 – 5.86). The variation was smaller in the large cohort and after NN caliper matching (see Figure 2 and Table 3). Again, the 95% confidence was non consistently overlapping 1 after repeating the matches.

DISCUSSION

We used simulations and an empirical example to illustrate that there can be large variation in point estimates when repeatedly applying the greedy caliper PS matching algorithm, in which patients are randomly ordered, on the same cohort. This variability was, to a lesser extent, also visible when applying greedy NN caliper PS matching. With increasing sample sizes, the variation decreased, but whether a value of 1 was within the estimated confidence intervals after matching was inconsistent after replication. In simulated cohorts with low outcome prevalence, the variability was largest, while in these situations, propensity score methods (and thus matching) are frequently used. Using a real-life dataset comparing NOACs to VKAs and the risk for stroke, we confirmed these findings.

From our literature search, we found that the NN matching algorithm was the most commonly used matching method, followed by caliper matching. We found that the MatchIt package was the most frequently used software package for matching (and the only package mentioned when using R), and in this package it is not possible to perform NN caliper matching, but only caliper matching without NN or NN matching without caliper. Interestingly, nine papers specifically mentioned they used the MatchIt package for NN caliper matching, and it could be those papers actually performed caliper matching without NN, with the risk of high variability. As the statistical package is not mentioned in most articles (n = 79), it is not possible to determine how the matching procedure took place. We recommend better reporting of matching procedures used, including which statistical software, as this can ultimately affect the results of a study, and is necessary for study replication.

In addition, we found that approximately 50% of the studies were conducted in a cohort with a sample size of 2 500 or less. In our simulation study, we showed that in these sample sizes the treatment effects are largely influenced by the selected random seed, which in practice is not often specified or reported. In addition, whether the 95% CI overlapped 1 was inconsistent with different random seeds. However, this can also be a result of too little power in the limited sample sizes. But still, results of studies using caliper PS matching in datasets with these sample sizes should

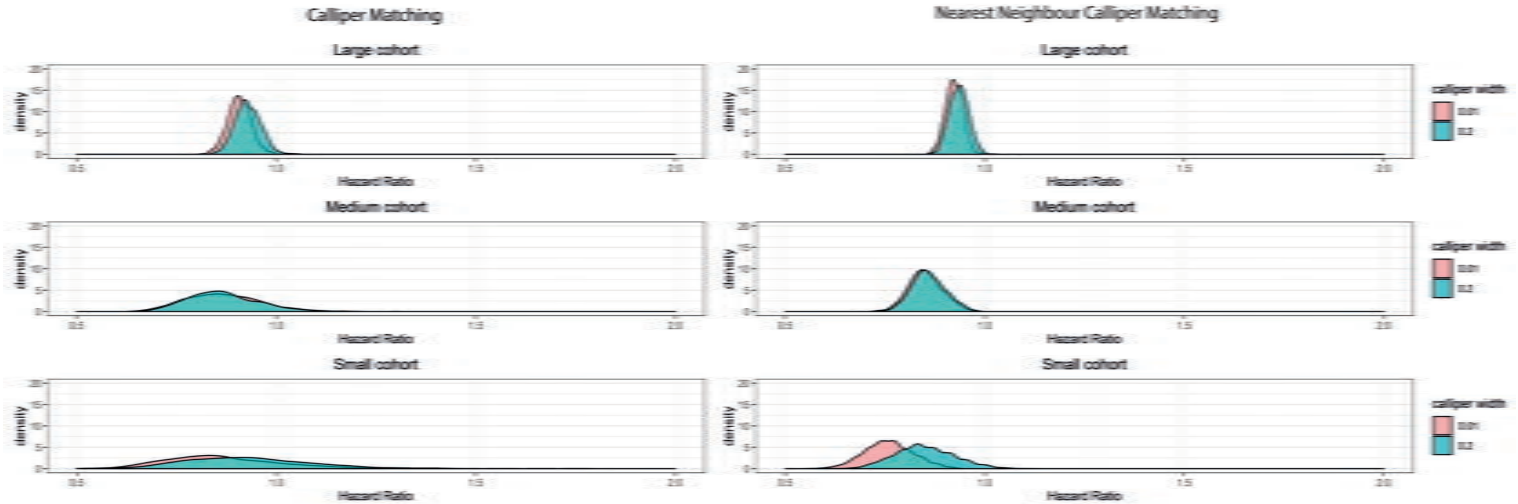

Figure 2. Density plots of the distribution of the hazard ratio of the 1000 matched sets from the three Stockholm atrial fibrillation cohorts after caliper matching and after nearest neighbor caliper matching.

Table 3. Results real life observational study Results from the 1000 matched sets in the three sizes of the Stockholm AF cohort. HR =hazard ratio; % sign low/high risk = percentage of the 1000 matched sets with a significantly increased or decreased risk

	Median HR	Interquartile range HR	Full range HR	% sign low risk	% sign high risk
Large cohort (n = 18 203)					
Caliper Matching	0,91	0,04 (0,89-0,93)	0,19 (0,81-0,99)	4,7%	0,0%
Nearest Neighbor Caliper Matching	0,92	0,03 (0,91-0,94)	0,14 (0,86-1,00)	0,0%	0,0%
Medium cohort (n = 5 696)					
Caliper Matching	0,86	0,13 (0,80-0,93)	0,67 (0,65-1,32)	2,7%	0,0%
Nearest Neighbor Caliper Matching	0,85	0,06 (0,82-0,88)	0,25 (0,72-0,97)	0,1%	0,0%
Small cohort (n = 1 594)					
Caliper Matching	0,94	0,24 (0,82-1,06)	1,91 (0,52-2,43)	0,0%	0,1%
Nearest Neighbor Caliper Matching	0,76	0,09 (0,71-0,81)	0,35 (0,57-0,92)	0,0%	0,0%

be interpreted with caution, as the choice of starting seed for the matching algorithm could be manipulated to yield a significant test statistic.

One way researchers often show whether matching was successful or not, is by showing the SMD for all covariates [11]. It is common practice to consider matching successful when the SMD for all covariates is below 0.1 [12]. In our simulation study, we showed that the SMDs are also dependent on the random seed that is used, in particular in datasets with small sample sizes. Removing matched sets with unsuccessful matching only slightly decreased the variation of the point estimates. Therefore, repeating the matching until all SMDs are below 0.1 will not solve the issue of variability.

With caliper matching, we found that the median OR of the 1 000 repetitions was close to the simulated parameter, while in NN caliper matching in some instances the median OR was not as expected, indicating this approach might introduce some bias. Potentially, a future direction could be to apply repeated caliper PS matching and use the mean or median for the point estimate, as this is independent of the random ordering. Approaches have been made in using bagged one-to-one matching, which overcomes the variability introduced by the matching through bagging (i.e., use bootstrapping to resample a cohort and propensity score match and analyze all resamples) [13, 14], but it remains unknown how this approach would compare to repeated caliper PS matching.

To avoid the proposed problem, we suggest that researchers stop using greedy caliper matching with random ordering. In addition, the use of NN caliper matching should be reconsidered, as there are alternative propensity score matching methods that are not affected by random variability, such as optimal matching [15]. The NN matching procedure can also yield findings independent of random ordering. For example, if treated patients are not ordered at random prior to matching, if the algorithm is performed without calipers and with replacement, or if the best match is selected at first. However, it is not within the scope of the current research to make statements on which approach is preferred.

In conclusion, replication of greedy caliper PS matching in the same cohort can yield highly variable estimates of the treatment-outcome association, already in moderately sized cohorts of

2500 patients. To avoid the problem of random variability in point estimates, researchers should refrain from using versions of greedy matching that are dependent on random ordering and/or random within caliper matching. If a greedy matching algorithm is used, nearest neighbor within caliper matching combined with non-random ordering (e.g., best first, ascending, descending) would be preferred.

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APPENDICES

Appendix table 1a. Results of repeated calliper and nearest neighbour calliper propensity score matching in cohorts with a simulated odds ratio of 0.75. The calliper was set at 0.01 of the standard deviation of the propensity score. The % sign low and sign high risk state in how many of the successfully matched cohorts the treatment-outcome associations was statistically different from 1. The % unsuccessful matches is in how many instances there was at least one of the SMDs above 0.1. OR: odds ratio.

		Median OR	Interquartile range OR	Full range OR	% sign low risk	% sign high risk	Mean n matches	% unsuccessful matches
N = 10.000								
Caliper Matching	T 50%, O 50%	0,77	(0,76-0,78)	(0,72-0,82)	100,0%	0,0%	7069	0,0%
	T 20%, O 50%	0,77	(0,75-0,78)	(0,67-0,85)	100,0%	0,0%	3752	0,0%
	T 50%, O 10%	0,78	(0,76-0,80)	(0,69-0,90)	99,5%	0,0%	6836	0,0%
	T 20%, O 10%	0,79	(0,76-0,83)	(0,59-1,01)	43,8%	0,0%	3752	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,76	(0,75-0,77)	(0,72-0,79)	100,0%	0,0%	7041	0,0%
	T 20%, O 50%	0,73	(0,72-0,73)	(0,71-0,75)	100,0%	0,0%	3747	0,0%
	T 50%, O 10%	0,77	(0,76-0,78)	(0,70-0,84)	100,0%	0,0%	6811	0,0%
	T 20%, O 10%	0,84	(0,84-0,85)	(0,81-0,88)	0,0%	0,0%	3747	0,0%
N = 2500								
Caliper Matching	T 50%, O 50%	0,77	(0,74-0,79)	(0,68-0,86)	96,4%	0,0%	1722	0,0%
	T 20%, O 50%	0,82	(0,78-0,86)	(0,62-1,04)	21,5%	0,0%	948	8,7%
	T 50%, O 10%	0,73	(0,70-0,77)	(0,58-0,88)	30,2%	0,0%	1722	0,0%
	T 20%, O 10%	0,77	(0,70-0,83)	(0,51-1,14)	5,4%	0,0%	931	3,3%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,76	(0,75-0,78)	(0,70-0,85)	99,5%	0,0%	1701	0,0%
	T 20%, O 50%	0,78	(0,76-0,79)	(0,72-0,83)	37,9%	0,0%	942	0,0%
	T 50%, O 10%	0,84	(0,82-0,87)	(0,73-0,97)	0,0%	0,0%	1701	0,0%
	T 20%, O 10%	0,82	(0,79-0,84)	(0,74-0,94)	0,0%	0,0%	930	0,0%

Appendix table 1a. (continued)

		Median OR	Interquartile range OR	Full range OR	% sign low risk	% sign high risk	Mean n matches	% unsuccessful matches
N = 500								
Caliper Matching	T 50%, O 50%	0,76	(0,71-0,80)	(0,58-1,00)	0,9%	0,0%	252	84,9%
	T 20%, O 50%	0,50	(0,46-0,56)	(0,27-0,89)	55,6%	0,0%	152	87,0%
	T 50%, O 10%	0,80	(0,71-0,91)	(0,47-1,22)	0,0%	0,0%	244	100,0%
	T 20%, O 10%	0,75	(0,67-0,86)	(0,38-1,50)	0,1%	0,0%	143	100,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,73	(0,69-0,76)	(0,58-0,97)	0,2%	0,0%	249	77,4%
	T 20%, O 50%	0,46	(0,43-0,48)	(0,38-0,52)	100,0%	0,0%	152	100,0%
	T 50%, O 10%	0,92	(0,83-0,92)	(0,75-1,00)	0,0%	0,0%	242	100,0%
	T 20%, O 10%	0,83	(0,71-0,83)	(0,71-0,83)	0,0%	0,0%	142	100,0%

Appendix table 1b. Results of repeated calliper and nearest neighbour calliper propensity score matching in cohorts with a simulated odds ratio of 1.0. The calliper was set at 0.01 of the standard deviation of the propensity score. The % sign low and sign high risk state in how many of the successfully matched cohorts the treatment-outcome associations was statistically different from 1. The % unsuccessful matches is in how many instances there was at least one of the SMDs above 0.1. OR: odds ratio.

		Median OR	Interquartile range OR	Full range OR	% sign low risk	% sign high risk	Mean n matches	% unsuccessful matches
N = 10.000								
Caliper Matching	T 50%, O 50%	1,02	(1,00-1,03)	(0,95-1,09)	0,0%	0,0%	7069	0,0%
	T 20%, O 50%	1,01	(0,99-1,03)	(0,90-1,13)	0,0%	0,0%	3752	0,0%
	T 50%, O 10%	1,01	(0,98-1,03)	(0,88-1,17)	0,0%	0,1%	6836	0,0%
	T 20%, O 10%	1,06	(1,01-1,11)	(0,81-1,33)	0,0%	1,0%	3752	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,01	(1,00-1,02)	(0,97-1,06)	0,0%	0,0%	7041	0,0%
	T 20%, O 50%	0,96	(0,96-0,97)	(0,93-1,00)	0,0%	0,0%	3747	0,0%
	T 50%, O 10%	1,00	(0,98-1,01)	(0,93-1,07)	0,0%	0,0%	6811	0,0%
	T 20%, O 10%	1,13	(1,12-1,14)	(1,08-1,18)	0,0%	0,0%	3747	0,0%
N = 2500								
Caliper Matching	T 50%, O 50%	1,00	(0,97-1,03)	(0,86-1,15)	0,0%	0,0%	1621	0,0%
	T 20%, O 50%	1,08	(1,03-1,14)	(0,87-1,38)	0,0%	0,5%	871	12,8%
	T 50%, O 10%	1,05	(1,01-1,10)	(0,83-1,34)	0,0%	0,0%	1672	0,1%
	T 20%, O 10%	1,12	(1,03-1,26)	(0,71-1,89)	0,0%	0,5%	838	7,9%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,02	(0,99-1,04)	(0,93-1,12)	0,0%	0,0%	1605	0,0%
	T 20%, O 50%	1,01	(1,00-1,02)	(0,95-1,08)	0,0%	0,0%	869	0,3%
	T 50%, O 10%	1,04	(1,00-1,07)	(0,88-1,21)	0,0%	0,0%	1651	0,0%
	T 20%, O 10%	1,33	(1,30-1,35)	(1,25-1,38)	0,0%	0,0%	840	0,0%

Appendix table 1b. (continued)

		Median OR	Interquartile range OR	Full range OR	% sign low risk	% sign high risk	Mean n matches	% unsuccessful matches
N = 500								
Caliper Matching	T 50%, O 50%	0,93	(0,87-0,97)	(0,65-1,22)	0,0%	0,0%	245	99,0%
	T 20%, O 50%	0,78	(0,70-0,85)	(0,50-1,29)	0,1%	0,0%	135	99,3%
	T 50%, O 10%	1,00	(0,90-1,11)	(0,50-1,83)	0,0%	0,0%	239	57,3%
	T 20%, O 10%	1,25	(1,00-1,25)	(0,56-2,50)	0,0%	0,0%	135	99,3%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,93	(0,88-1,00)	(0,68-1,26)	0,0%	0,0%	241	100,0%
	T 20%, O 50%	0,89	(0,85-0,90)	(0,81-0,95)	0,0%	0,0%	136	100,0%
	T 50%, O 10%	1,00	(1,00-1,10)	(0,73-1,40)	0,0%	0,0%	240	54,7%
	T 20%, O 10%	1,25	(1,25-1,25)	(1,25-1,25)	0,0%	0,0%	136	100,0%

Appendix table 1c. Results of repeated calliper and nearest neighbour calliper propensity score matching in cohorts with a simulated odds ratio of 1.5. The calliper was set at 0.01 of the standard deviation of the propensity score. The % sign low and sign high risk state in how many of the successfully matched cohorts the treatment-outcome associations was statistically different from 1. The % unsuccessful matches is in how many instances there was at least one of the SMDs above 0.1. OR: odds ratio.

		Median OR	Interquartile range OR	Full range OR	% sign low risk	% sign high risk	Mean n matches	% unsuccessful matches
N = 10.000								
Caliper Matching	T 50%, O 50%	1,46	(1,43-1,48)	(1,36-1,58)	0,0%	100,0%	7069	0,0%
	T 20%, O 50%	1,47	(1,44-1,51)	(1,30-1,63)	0,0%	100,0%	3752	0,0%
	T 50%, O 10%	1,44	(1,41-1,47)	(1,27-1,62)	0,0%	100,0%	6836	0,0%
	T 20%, O 10%	1,54	(1,46-1,60)	(1,24-1,94)	0,0%	100,0%	3700	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,45	(1,43-1,46)	(1,37-1,51)	0,0%	100,0%	7041	0,0%
	T 20%, O 50%	1,40	(1,39-1,41)	(1,35-1,44)	0,0%	100,0%	3747	0,0%
	T 50%, O 10%	1,42	(1,40-1,45)	(1,33-1,51)	0,0%	100,0%	6811	0,0%
	T 20%, O 10%	1,54	(1,53-1,56)	(1,48-1,60)	0,0%	100,0%	3689	0,0%
N = 2500								
Caliper Matching	T 50%, O 50%	1,45	(1,40-1,49)	(1,27-1,74)	0,0%	100,0%	1672	0,1%
	T 20%, O 50%	1,39	(1,33-1,47)	(1,12-1,75)	0,0%	83,0%	931	3,3%
	T 50%, O 10%	1,41	(1,35-1,48)	(1,11-1,73)	0,0%	77,2%	1621	0,0%
	T 20%, O 10%	1,49	(1,36-1,61)	(0,98-2,24)	0,0%	41,0%	931	3,3%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,49	(1,45-1,52)	(1,35-1,63)	0,0%	100,0%	1651	0,0%
	T 20%, O 50%	1,45	(1,43-1,47)	(1,34-1,57)	0,0%	100,0%	930	0,0%
	T 50%, O 10%	1,48	(1,44-1,52)	(1,30-1,65)	0,0%	99,1%	1605	0,0%
	T 20%, O 10%	1,57	(1,53-1,62)	(1,42-1,81)	0,0%	80,9%	930	0,0%

Appendix table 1c. (continued)

		Median OR	Interquartile range OR	Full range OR	% sign low risk	% sign high risk	Mean n matches	% unsuccessful matches
N = 500								
Caliper Matching	T 50%, O 50%	1,48	(1,38-1,60)	(1,04-2,00)	0,0%	9,0%	240	70,4%
	T 20%, O 50%	1,37	(1,26-1,50)	(0,89-2,09)	0,0%	0,5%	134	98,3%
	T 50%, O 10%	1,56	(1,40-1,78)	(0,91-3,40)	0,0%	1,6%	239	57,3%
	T 20%, O 10%	1,14	(1,00-1,33)	(0,62-3,00)	0,0%	0,0%	126	98,4%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,58	(1,50-1,70)	(1,21-2,13)	0,0%	13,6%	239	82,2%
	T 20%, O 50%	1,24	(1,18-1,27)	(1,06-1,43)	0,0%	0,0%	132	100,0%
	T 50%, O 10%	1,60	(1,50-1,70)	(1,09-2,11)	0,0%	0,0%	240	54,7%
	T 20%, O 10%	1,14	(1,14-1,14)	(1,14-1,14)	0,0%	0,0%	125	100,0%

Appendix table 2a. Results of repeated calliper and nearest neighbour calliper propensity score matching in cohorts with a simulated odds ratio of 0.75 where the SMD for all covariates was ≤ 0.1 after matching. The calliper was set at 0.2 of the standard deviation of the propensity score. The % sign low and sign high risk state in how many of the successfully matched cohorts the treatment-outcome associations was statistically different from 1. OR: odds ratio.

		Median OR	Interquartile range OR	Full range OR	% sign low risk	% sign high risk
N = 10.000						
Caliper Matching	T 50%, O 50%	0,75	(0,74-0,76)	(0,69-0,81)	100,0%	0,0%
	T 20%, O 50%	0,78	(0,76-0,80)	(0,70-0,89)	99,9%	0,0%
	T 50%, O 10%	0,76	(0,74-0,78)	(0,67-0,84)	100,0%	0,0%
	T 20%, O 10%	0,79	(0,76-0,83)	(0,66-1,03)	45,4%	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,75	(0,74-0,76)	(0,71-0,79)	100,0%	0,0%
	T 20%, O 50%	0,74	(0,73-0,74)	(0,72-0,76)	100,0%	0,0%
	T 50%, O 10%	0,75	(0,74-0,76)	(0,70-0,80)	100,0%	0,0%
	T 20%, O 10%	0,86	(0,85-0,86)	(0,83-0,89)	0,0%	0,0%
N = 2500						
Caliper Matching	T 50%, O 50%	0,78	(0,76-0,79)	(0,69-0,86)	97,6%	0,0%
	T 20%, O 50%	0,78	(0,74-0,82)	(0,61-1,02)	48,1%	0,0%
	T 50%, O 10%	0,72	(0,69-0,75)	(0,56-0,90)	48,2%	0,0%
	T 20%, O 10%	0,74	(0,69-0,81)	(0,55-1,13)	10,4%	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,78	(0,76-0,79)	(0,70-0,84)	99,6%	0,0%
	T 20%, O 50%	0,76	(0,75-0,77)	(0,72-0,82)	91,6%	0,0%
	T 50%, O 10%	0,77	(0,75-0,79)	(0,67-0,88)	3,0%	0,0%
	T 20%, O 10%	0,78	(0,76-0,80)	(0,69-0,88)	0,0%	0,0%
N = 500						
Caliper Matching	T 50%, O 50%	0,73	(0,68-0,78)	(0,51-1,00)	6,9%	0,0%
	T 20%, O 50%	0,73	(0,64-0,80)	(0,49-1,13)	2,0%	0,0%
	T 50%, O 10%	0,68	(0,61-0,75)	(0,33-1,07)	0,6%	0,0%
	T 20%, O 10%	0,78	(0,67-1,00)	(0,43-2,33)	0,0%	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,69	(0,65-0,74)	(0,53-0,91)	10,1%	0,0%
	T 20%, O 50%	0,66	(0,63-0,67)	(0,58-0,71)	0,1%	0,0%
	T 50%, O 10%	0,86	(0,80-0,93)	(0,57-1,08)	0,0%	0,0%
	T 20%, O 10%	0,71	(0,67-0,71)	(0,63-0,75)	0,0%	0,0%

Appendix table 2b. Results of repeated calliper and nearest neighbour calliper propensity score matching in cohorts with a simulated odds ratio of 1.0 where the SMD for all covariates was ≤ 0.1 after matching. The calliper was set at 0.2 of the standard deviation of the propensity score. The % sign low and sign high risk state in how many of the successfully matched cohorts the treatment-outcome associations was statistically different from 1. OR: odds ratio.

		Median OR	Interquartile range OR	Full range OR	% sign low risk	% sign high risk
N = 10.000						
Caliper Matching	T 50%, O 50%	0,99	(0,98-1,01)	(0,91-1,04)	0,0%	0,0%
	T 20%, O 50%	1,02	(1,00-1,05)	(0,92-1,17)	0,0%	0,2%
	T 50%, O 10%	0,98	(0,96-1,00)	(0,90-1,07)	0,0%	0,0%
	T 20%, O 10%	1,05	(1,01-1,10)	(0,87-1,37)	0,0%	0,5%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,00	(0,99-1,01)	(0,96-1,05)	0,0%	0,0%
	T 20%, O 50%	0,97	(0,97-0,98)	(0,95-1,00)	0,0%	0,0%
	T 50%, O 10%	0,97	(0,96-0,99)	(0,91-1,04)	0,0%	0,0%
	T 20%, O 10%	1,14	(1,13-1,15)	(1,09-1,18)	0,0%	0,0%
N = 2500						
Caliper Matching	T 50%, O 50%	0,94	(0,92-0,97)	(0,79-1,10)	0,2%	0,0%
	T 20%, O 50%	1,02	(0,96-1,07)	(0,77-1,30)	0,0%	0,0%
	T 50%, O 10%	1,01	(0,98-1,05)	(0,85-1,17)	0,0%	0,0%
	T 20%, O 10%	1,00	(0,89-1,10)	(0,65-1,72)	0,0%	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,98	(0,96-1,00)	(0,90-1,08)	0,0%	0,0%
	T 20%, O 50%	0,97	(0,96-0,98)	(0,91-1,03)	0,0%	0,0%
	T 50%, O 10%	0,95	(0,92-0,98)	(0,82-1,07)	0,0%	0,0%
	T 20%, O 10%	1,24	(1,21-1,25)	(1,13-1,36)	0,0%	0,0%
N = 500						
Caliper Matching	T 50%, O 50%	1,02	(0,97-1,09)	(0,73-1,35)	0,0%	0,0%
	T 20%, O 50%	0,96	(0,86-1,09)	(0,61-1,35)	0,0%	0,0%
	T 50%, O 10%	1,00	(0,88-1,13)	(0,53-2,57)	0,0%	0,1%
	T 20%, O 10%	1,00	(0,83-1,20)	(0,40-3,50)	0,0%	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,08	(1,03-1,13)	(0,89-1,34)	0,0%	0,0%
	T 20%, O 50%	1,08	(1,04-1,12)	(0,92-1,23)	0,0%	0,0%
	T 50%, O 10%	1,00	(0,93-1,07)	(0,67-1,43)	0,0%	0,0%
	T 20%, O 10%	1,00	(1,00-1,00)	(0,83-1,00)	0,0%	0,0%

Appendix table 2c. Results of repeated calliper and nearest neighbour calliper propensity score matching in cohorts with a simulated odds ratio of 1.5 where the SMD for all covariates was ≤ 0.1 after matching. The calliper was set at 0.2 of the standard deviation of the propensity score. The % sign low and sign high risk state in how many of the successfully matched cohorts the treatment-outcome associations was statistically different from 1. OR: odds ratio.

		Median OR	Interquartile range OR	Full range OR	% sign low risk	% sign high risk
N = 10.000						
Caliper Matching	T 50%, O 50%	1,42	(1,40-1,44)	(1,33-1,51)	0,0%	100,0%
	T 20%, O 50%	1,50	(1,46-1,54)	(1,34-1,69)	0,0%	100,0%
	T 50%, O 10%	1,41	(1,38-1,44)	(1,29-1,55)	0,0%	100,0%
	T 20%, O 10%	1,49	(1,43-1,57)	(1,21-1,95)	0,0%	99,8%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,43	(1,41-1,44)	(1,35-1,50)	0,0%	100,0%
	T 20%, O 50%	1,42	(1,41-1,42)	(1,38-1,46)	0,0%	100,0%
	T 50%, O 10%	1,39	(1,37-1,41)	(1,29-1,48)	0,0%	100,0%
	T 20%, O 10%	1,51	(1,50-1,53)	(1,46-1,57)	0,0%	100,0%
N = 2500						
Caliper Matching	T 50%, O 50%	1,43	(1,40-1,47)	(1,26-1,62)	0,0%	100,0%
	T 20%, O 50%	1,40	(1,34-1,47)	(1,13-1,79)	0,0%	86,1%
	T 50%, O 10%	1,45	(1,39-1,51)	(1,15-1,73)	0,0%	92,0%
	T 20%, O 10%	1,44	(1,33-1,56)	(1,04-2,29)	0,0%	36,5%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,48	(1,46-1,51)	(1,35-1,61)	0,0%	100,0%
	T 20%, O 50%	1,44	(1,42-1,46)	(1,34-1,55)	0,0%	100,0%
	T 50%, O 10%	1,49	(1,45-1,53)	(1,29-1,69)	0,0%	99,8%
	T 20%, O 10%	1,47	(1,44-1,50)	(1,33-1,64)	0,0%	38,2%
N = 500						
Caliper Matching	T 50%, O 50%	1,41	(1,31-1,50)	(1,02-2,04)	0,0%	9,8%
	T 20%, O 50%	1,29	(1,18-1,44)	(0,91-1,85)	0,0%	0,1%
	T 50%, O 10%	1,50	(1,35-1,69)	(0,90-3,86)	0,0%	3,3%
	T 20%, O 10%	1,25	(1,11-1,67)	(0,64-3,00)	0,0%	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,37	(1,29-1,45)	(1,03-1,85)	0,0%	2,8%
	T 20%, O 50%	1,04	(1,00-1,04)	(0,93-1,12)	0,0%	0,0%
	T 50%, O 10%	1,50	(1,40-1,60)	(1,07-2,00)	0,0%	0,2%
	T 20%, O 10%	#N/A	#N/A	#N/A	0,0%	0,0%

Appendix table 3a. Results of repeated calliper and nearest neighbour calliper propensity score matching in cohorts with a simulated odds ratio of 0.75 where the SMD for all covariates was ≤ 0.1 after matching. The calliper was set at 0.01 of the standard deviation of the propensity score. The % sign low and sign high risk state in how many of the successfully matched cohorts the treatment-outcome associations was statistically different from 1. OR: odds ratio.

		Median OR	Interquartile range OR	Full range OR	% sign low risk	% sign high risk
N = 10.000						
Caliper Matching	T 50%, O 50%	0,77	(0,76-0,78)	(0,72-0,82)	100,0%	0,0%
	T 20%, O 50%	0,77	(0,75-0,78)	(0,67-0,85)	100,0%	0,0%
	T 50%, O 10%	0,78	(0,76-0,80)	(0,69-0,90)	99,5%	0,0%
	T 20%, O 10%	0,79	(0,76-0,83)	(0,59-1,01)	43,8%	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,76	(0,75-0,77)	(0,72-0,79)	100,0%	0,0%
	T 20%, O 50%	0,73	(0,72-0,73)	(0,71-0,75)	100,0%	0,0%
	T 50%, O 10%	0,77	(0,76-0,78)	(0,70-0,84)	100,0%	0,0%
	T 20%, O 10%	0,84	(0,84-0,85)	(0,81-0,88)	0,0%	0,0%
N = 2500						
Caliper Matching	T 50%, O 50%	0,77	(0,74-0,79)	(0,68-0,86)	96,4%	0,0%
	T 20%, O 50%	0,82	(0,78-0,85)	(0,62-1,04)	19,9%	0,0%
	T 50%, O 10%	0,73	(0,70-0,77)	(0,58-0,88)	30,2%	0,0%
	T 20%, O 10%	0,77	(0,70-0,83)	(0,51-1,14)	5,3%	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,76	(0,75-0,78)	(0,70-0,85)	99,5%	0,0%
	T 20%, O 50%	0,78	(0,76-0,79)	(0,72-0,83)	37,9%	0,0%
	T 50%, O 10%	0,84	(0,82-0,87)	(0,73-0,97)	0,0%	0,0%
	T 20%, O 10%	0,82	(0,79-0,84)	(0,74-0,94)	0,0%	0,0%
N = 500						
Caliper Matching	T 50%, O 50%	0,76	(0,72-0,81)	(0,58-0,94)	0,1%	0,0%
	T 20%, O 50%	0,50	(0,46-0,57)	(0,31-0,70)	7,0%	0,0%
	T 50%, O 10%	#N/A	#N/A	#N/A	0,0%	0,0%
	T 20%, O 10%	#N/A	#N/A	#N/A	0,0%	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	0,73	(0,69-0,76)	(0,60-0,89)	0,1%	0,0%
	T 20%, O 50%	#N/A	#N/A	#N/A	0,0%	0,0%
	T 50%, O 10%	#N/A	#N/A	#N/A	0,0%	0,0%
	T 20%, O 10%	#N/A	#N/A	#N/A	0,0%	0,0%

Appendix table 3b. Results of repeated calliper and nearest neighbour calliper propensity score matching in cohorts with a simulated odds ratio of 1.0 where the SMD for all covariates was ≤ 0.1 after matching. The calliper was set at 0.01 of the standard deviation of the propensity score. The % sign low and sign high risk state in how many of the successfully matched cohorts the treatment-outcome associations was statistically different from 1. OR: odds ratio.

		Median OR	Interquartile range OR	Full range OR	% sign low risk	% sign high risk
N = 10.000						
Caliper Matching	T 50%, O 50%	1,02	(1,00-1,03)	(0,95-1,09)	0,0%	0,0%
	T 20%, O 50%	1,01	(0,99-1,03)	(0,90-1,13)	0,0%	0,0%
	T 50%, O 10%	1,01	(0,98-1,03)	(0,88-1,17)	0,0%	0,1%
	T 20%, O 10%	1,06	(1,01-1,11)	(0,81-1,33)	0,0%	1,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,01	(1,00-1,02)	(0,97-1,06)	0,0%	0,0%
	T 20%, O 50%	0,96	(0,96-0,97)	(0,93-1,00)	0,0%	0,0%
	T 50%, O 10%	1,00	(0,98-1,01)	(0,93-1,07)	0,0%	0,0%
	T 20%, O 10%	1,13	(1,12-1,14)	(1,08-1,18)	0,0%	0,0%
N = 2500						
Caliper Matching	T 50%, O 50%	1,00	(0,97-1,03)	(0,86-1,15)	0,0%	0,0%
	T 20%, O 50%	1,08	(1,02-1,14)	(0,87-1,38)	0,0%	0,5%
	T 50%, O 10%	1,05	(1,01-1,10)	(0,83-1,34)	0,0%	0,0%
	T 20%, O 10%	1,11	(1,03-1,24)	(0,71-1,89)	0,0%	0,5%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,02	(0,99-1,04)	(0,93-1,12)	0,0%	0,0%
	T 20%, O 50%	1,01	(1,00-1,02)	(0,95-1,08)	0,0%	0,0%
	T 50%, O 10%	1,04	(1,00-1,07)	(0,88-1,21)	0,0%	0,0%
	T 20%, O 10%	1,33	(1,30-1,35)	(1,25-1,38)	0,0%	0,0%
N = 500						
Caliper Matching	T 50%, O 50%	0,90	(0,85-0,93)	(0,71-1,10)	0,0%	0,0%
	T 20%, O 50%	0,78	(0,74-0,80)	(0,73-0,85)	0,0%	0,0%
	T 50%, O 10%	1,00	(0,90-1,13)	(0,54-1,83)	0,0%	0,0%
	T 20%, O 10%	1,25	(1,13-1,88)	(0,83-2,50)	0,0%	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	#N/A	#N/A	#N/A	0,0%	0,0%
	T 20%, O 50%	#N/A	#N/A	#N/A	0,0%	0,0%
	T 50%, O 10%	1,00	(1,00-1,10)	(0,73-1,40)	0,0%	0,0%
	T 20%, O 10%	#N/A	#N/A	#N/A	0,0%	0,0%

Appendix table 3c. Results of repeated calliper and nearest neighbour calliper propensity score matching in cohorts with a simulated odds ratio of 1.5 where the SMD for all covariates was ≤ 0.1 after matching. The calliper was set at 0.01 of the standard deviation of the propensity score. The % sign low and sign high risk state in how many of the successfully matched cohorts the treatment-outcome associations was statistically different from 1. OR: odds ratio.

		Median OR	Interquartile range OR	Full range OR	% sign low risk	% sign high risk
N = 10.000						
Caliper Matching	T 50%, O 50%	1,46	(1,43-1,48)	(1,36-1,58)	0,0%	100,0%
	T 20%, O 50%	1,47	(1,44-1,51)	(1,30-1,63)	0,0%	100,0%
	T 50%, O 10%	1,44	(1,41-1,47)	(1,27-1,62)	0,0%	100,0%
	T 20%, O 10%	1,54	(1,46-1,60)	(1,24-1,94)	0,0%	100,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,45	(1,43-1,46)	(1,37-1,51)	0,0%	100,0%
	T 20%, O 50%	1,40	(1,39-1,41)	(1,35-1,44)	0,0%	100,0%
	T 50%, O 10%	1,42	(1,40-1,45)	(1,33-1,51)	0,0%	100,0%
	T 20%, O 10%	1,54	(1,53-1,56)	(1,48-1,60)	0,0%	100,0%
N = 2500						
Caliper Matching	T 50%, O 50%	1,45	(1,40-1,49)	(1,27-1,72)	0,0%	99,9%
	T 20%, O 50%	1,39	(1,32-1,47)	(1,12-1,75)	0,0%	79,9%
	T 50%, O 10%	1,41	(1,35-1,48)	(1,11-1,73)	0,0%	77,2%
	T 20%, O 10%	1,48	(1,36-1,62)	(0,98-2,24)	0,0%	39,4%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,49	(1,45-1,52)	(1,35-1,63)	0,0%	100,0%
	T 20%, O 50%	1,45	(1,43-1,47)	(1,34-1,57)	0,0%	100,0%
	T 50%, O 10%	1,48	(1,44-1,52)	(1,30-1,65)	0,0%	99,1%
	T 20%, O 10%	1,57	(1,53-1,62)	(1,42-1,81)	0,0%	80,9%
N = 500						
Caliper Matching	T 50%, O 50%	1,46	(1,36-1,57)	(1,12-2,00)	0,0%	2,1%
	T 20%, O 50%	1,37	(1,24-1,41)	(0,95-1,60)	0,0%	0,0%
	T 50%, O 10%	1,60	(1,40-1,78)	(1,00-3,40)	0,0%	0,7%
	T 20%, O 10%	1,29	(1,00-1,50)	(0,89-2,25)	0,0%	0,0%
Nearest Neighbor Caliper Matching	T 50%, O 50%	1,57	(1,50-1,67)	(1,27-2,06)	0,0%	2,7%
	T 20%, O 50%	#N/A	#N/A	#N/A	0,0%	0,0%
	T 50%, O 10%	1,60	(1,45-1,70)	(1,09-2,11)	0,0%	0,0%
	T 20%, O 10%	#N/A	#N/A	#N/A	0,0%	0,0%

4.2

REPEATING GREEDY CALLIPER MATCHING INCREASES PRECISION AND REDUCES VARIABILITY: A MONTE-CARLO SIMULATION STUDY

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Manuscript ready for submission

ABSTRACT

Background

Propensity score matching is frequently used to reduce confounding bias in observational studies. The greedy matching algorithm is a popular matching algorithm used in medical literature. We propose a new matching procedure that repeatedly applies the greedy matching algorithm.

Methods

We performed 1000 Monte-Carlo simulation in several scenarios at different levels of exposure and calculated the variance, bias, and mean squared error (MSE) of different methods. We compared the proposed method to caliper matching, nearest neighbor caliper matching, and pair-wise nearest neighbor matching. For the proposed method, we repeated caliper matching up to 1000 times and used different caliper widths to find the optimal approach.

Results

Increasing the number of matching repetitions decreased the MSE, without increasing the bias, up to repeating the procedure 100 times, after which it only marginally improved. At all different levels of exposure prevalence, the repeated matching with a calliper width of 0.01*SD of the logit of the propensity score performed best in terms of the lowest MSE. The repeated matching yielded a variance of approximately two times lower compared to all other methods, without increasing the bias, resulting in twice as low MSEs.

Conclusion

Using Monte-Carlo simulation we have shown that repeating the matching with caliper of 0.01*SD performs better in terms of MSE than the other matching procedures considered in this study.

BACKGROUND

Propensity score (PS) matching is a frequently used method to overcome confounding in observational studies [1]. The PS is informally defined as the probability of being exposed or not, based on known covariates. Matching on the PS removes confounding by balancing covariates across exposure groups [2].

Previous work has shown that greedy calliper PS matching is the most frequently used PS method in the medical literature [3]. However, this method is dependent on random variability since it orders unexposed units in a random order prior to matching [4]. The exposed units can be ordered in several ways but are also often ordered in a random order. The greedy algorithm then matches the highest exposed unit on the list to a randomly selected unexposed unit. When using nearest neighbour greedy matching, the unexposed unit with the closest PS is matched. A maximum allowable distance between the exposed and unexposed unit in terms of the PS can be defined by the calliper. In all the different methods, the created matched cohort is dependent on the random ordering prior to matching.

This random ordering can largely affect the exposure-outcome association after matching, especially in studies with small sample sizes (i.e., ≤ 2500). Repeated greedy PS matching could potentially be a promising approach as a new PS matching method. Through repeating the matching procedure, this randomness will be removed, which, theoretically, increases the precision of the matching method.

The aim of this study was to compare the performance of the proposed repeated greedy calliper matching with a range of other PS matching methods through a Monte-Carlo simulation.

METHODS

Monte Carlo simulation

We based our Monte Carlo data simulation on a previous study by Austin et al. that examined the performance of different calliper widths in greedy nearest neighbour calliper matching [5]. In short, we generated cohorts of 1000 subjects. First, we assigned exposure randomly, then we generated ten covariates based on this exposure, and finally we generated the outcome based on the covariates and exposure.

The exposure was randomly allocated based on a Bernoulli distribution. The subject-specific probability of exposure was set at 0.1, 0.2, 0.3, 0.4, or 0.5, to generate cohorts with an exposure prevalence of 10% - 50%, respectively.

We created ten different covariates: five dichotomous and five continuous. The five dichotomous covariates, B1, B2, B3, B4, and B5, were created so that the prevalence of the covariates in the unexposed subjects was 0.1, 0.2, 0.3, 0.4, and 0.5. The prevalence of these covariates in the exposed subjects was 0.168, 0.331, 0.492, 0.642, and 0.776. This was done to achieve a standardize difference of the values between the exposed and unexposed group of 0.2, 0.3, 0.4, 0.5, and 0.6.

We used the following distribution to generate the continuous covariates with a given standardized difference, *d:*

$$C_i \sim N(E_i \times d, 1)$$

E_i equals the exposure status of a given subject; 1 for exposed, 0 for unexposed. This yields a distribution of the covariate of $N(0,1)$ for an exposed subjects, and $N(d,1)$ for an exposed subject. We varied the standardized difference d with d = 0.2, 0.3, 0.4, 0.5, and 0.6, which are referred to as C1 through C5.

Finally, we created a continuous outcome variable according to the following formula:

4.2

$$Y_i = -2.8 + 1.5C_{1i} + 2C_{3i} + 4C_{4i} + 5B + 5B_{1i} + 4B_{2i} + 3B_{3i} + 2B_{4i} + 1.5B_{5i} + E_i + \varepsilon_i$$

where the error term $\varepsilon_i \sim N(0, \sigma = 2)$, and E_i is the exposure status of the *i*-th subject. Therefore, being exposed increases the outcome by 1 unit.

Propensity score matching

In each dataset, we calculated the PS using logistic regression including all covariates, with exposure status as the dependent variable. We then compared several matching methods, including the newly proposed repeated matching.

First, we used greedy calliper matching. This matching procedure randomly orders both the exposed and unexposed subjects. The first untreated subject that is within a predefined calliper is then matched to the treated subject that is on top of the list. We varied the callipers with values of 0.2, 0.02, and 0.01, and values that were a fraction of the standard deviation of the logit of the propensity score (SD_{ps}); again 0.2, 0.02, and 0.01.

Second, we used greedy nearest neighbour calliper matching. This procedure is similar to the previous method. However, in this method, the match is not randomly made, but the untreated subject that is closest to the treated subject, and within the predefined calliper, is matched to the treated subject on top of the list. We used the same values of the callipers for this procedure.

Third, we used an approach in which the distance between each pair of patients is minimized, so called pair-wise nearest-neighbour calliper matching [6]. In each step, this algorithm looks for the pair that forms the closest match, instead of only looking at the first subject in the list. Even though the algorithm does not guarantee that the overall distance between exposed and unexposed is optimal, in practice it does approach this. In addition, this method is far less computationally extensive and since this method is not only taking the first treated subject into consideration, it is not dependent on randomness as with the other methods.

Fourth, we used the newly proposed approach using repeated matching. As mentioned, greedy calliper matching is dependent on random ordering. Previous work has shown that repeating this matching procedure yields an average exposure-outcome estimate that is close to the simulated

estimate. Therefore, we repeated the greedy calliper matching (i.e., randomly match treated to untreated within calliper) up to 2,500 times.

After all matching procedures, we calculated the exposure-outcome association by subtracting the mean outcome in the exposed group from the mean outcome in the unexposed group. We report the relative bias and the mean squared error for the different matching procedures. First, we compared the repeated matching procedure, by increasing the repetitions from 5 to 10, 25, 50, 100, 250, 500, 750, and 1000 with different calliper widths. Then we compared the best performing calliper for repeated matching with the above-mentioned single matching procedures.

RESULTS

Increasing the number of matching repetitions decreased the MSE, without increasing the bias (table 1 for exposure level 0.3, appendix table 1A-D for exposure levels 0.1, 0.2, 0.4, and 0.5). This decrease in MSE was especially present up to 100 repetitions, after which there was little improvement in the MSE. At all different levels of exposure prevalence, the repeated matching with a calliper width of 0.01*SD of the logit of the propensity score performed best in terms of the lowest MSE. In practice, the 0.01*SD calliper width is also the lowest calliper. Given that a lower calliper width might even decrease the MSE further, we performed some post-hoc analyses with even smaller calliper widths of $0.005*SD_{ps}$ and $0.001*SD_{ps}$, which did not further decrease the MSE (Appendix Table 2)

When comparing repeated matching to different single matching procedures, the results were consistent. In all scenarios, the repeated PS matching yielded a variance of approximately two times lower compared to all other methods. The bias with the repeated matching was comparable to the other methods, although the bias was approximately 5% in the cohort with a treatment prevalence of 0.1, which was slightly higher. However, this increased bias was substantially lower than the decrease in variance, yielding an MSE which was approximately twice as low for repeated matching compared to any method, in any scenario.

DISCUSSION

Using Monte-Carlo simulation we have shown that repeating the matching with calliper of 0.01*SD performs better in terms of MSE than the other matching procedures considered in this study. This improvement was already present after repeating the matching procedure only five times and improved even further up to repeating the procedure 100 times, after which it only marginally improved.

One advantage of repeated matching is that it is not dependent on random ordering, as it uses the random ordering to find precise estimates. Previous work has shown that this random variability can largely affect study results when repeating the matching procedure. Another advantage of the method is the limited computing time required, as the greedy calliper matching algorithm is computationally scalable even with multiple repetitions of the algorithm. This in contrast to optimal matching or bagged one-to-one matching, which are more computationally intensive, especially with large datasets [7].

Table 1. The bias, variance, and mean squared error with increasing number of matching repetitions at different calliper widths at an exposure level of 0.3. The results of the other exposure levels are in Appendix table 1A-D.

	0.01*SD			0.02*SD			0.01			0.02		
Reps	**Bias**	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**
5	0.1%	0.0582	0.0581	4.5%	0.0511	0.0530	0.1%	0.0896	0.0895	1.4%	0.0659	0.0660
10	0.2%	0.0535	0.0535	4.5%	0.0464	0.0484	0.3%	0.0848	0.0847	1.3%	0.0616	0.0618
25	0.3%	0.0513	0.0513	4.5%	0.0448	0.0467	0.3%	0.0816	0.0816	1.2%	0.0580	0.0581
50	0.2%	0.0497	0.0496	4.5%	0.0439	0.0459	0.2%	0.0807	0.0806	1.1%	0.0571	0.0572
100	0.2%	0.0494	0.0494	4.5%	0.0434	0.0453	0.2%	0.0798	0.0797	1.2%	0.0566	0.0567
250	0.2%	0.0491	0.0491	4.5%	0.0430	0.0450	0.2%	0.0798	0.0797	1.3%	0.0562	0.0563
500	0.2%	0.0490	0.0490	4.5%	0.0428	0.0448	0.2%	0.0796	0.0795	1.3%	0.0563	0.0564
750	0.2%	0.0489	0.0489	4.5%	0.0428	0.0448	0.2%	0.0795	0.0794	1.3%	0.0564	0.0565
1000	0.3%	0.0489	0.0488	4.5%	0.0428	0.0447	0.2%	0.0795	0.0794	1.3%	0.0563	0.0564

Table 2. The bias, variance, and mean squared error for the different matching procedures at different exposure levels. MSE: mean squared error. SD: standard deviation. Rep: repetitions

	0.1			0.2			0.3		
	Bias	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**
Unmatched	948.3%	0.8059	90.7414	944.9%	0.4908	89.7798	941.6%	0.3256	88.9786
Caliper 0.01	6.2%	0.2794	0.2830	-0.9%	0.1375	0.1375	0.9%	0.0968	0.0968
Caliper 0.02	15.6%	0.2773	0.3015	6.2%	0.1181	0.1218	3.8%	0.0866	0.0880
Caliper 0.2*SD	24.2%	0.2756	0.3342	23.2%	0.1278	0.1815	24.5%	0.0943	0.1543
NN caliper 0.01	1.3%	0.2677	0.2677	0.2%	0.1279	0.1277	1.2%	0.1025	0.1025
NN caliper 0.02	-0.5%	0.2516	0.2514	0.8%	0.1140	0.1139	0.4%	0.0900	0.0899
NN caliper 0.2*SD	-1.2%	0.2499	0.2498	3.0%	0.1211	0.1219	5.3%	0.0884	0.0911
Balanced NN	0.2%	0.2552	0.2549	0.2%	0.1167	0.1166	0.0%	0.0908	0.0907
5 rep 0.01*SD	4.7%	0.1297	0.1317	1.2%	0.0762	0.0763	0.1%	0.0582	0.0581
100 rep 0.01*SD	4.9%	0.0946	0.0969	1.1%	0.0612	0.0613	0.2%	0.0494	0.0494
1000 rep 0.01*SD	4.9%	0.0938	0.0962	1.1%	0.0604	0.0605	0.3%	0.0489	0.0488

	0.4			0.5		
	Bias	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**
Unmatched	944.1%	0.2981	89.4268	944.2%	0.2702	89.4231
Caliper 0.01	0.7%	0.0781	0.0780	0.8%	0.0731	0.0731
Caliper 0.02	1.9%	0.0720	0.0723	4.1%	0.0705	0.0721
Caliper 0.2*SD	27.8%	0.0794	0.1564	35.8%	0.0761	0.2043
NN caliper 0.01	-0.5%	0.0783	0.0782	0.2%	0.0756	0.0755
NN caliper 0.02	1.1%	0.0717	0.0717	1.4%	0.0742	0.0744
NN caliper 0.2*SD	9.5%	0.0785	0.0875	14.4%	0.0677	0.0885
Balanced NN	-0.1%	0.0771	0.0771	-0.4%	0.0733	0.0732
5 rep 0.01*SD	0.2%	0.0517	0.0517	1.1%	0.0535	0.0536
100 rep 0.01*SD	0.0%	0.0464	0.0463	1.1%	0.0495	0.0496
1000 rep 0.01*SD	0.0%	0.0463	0.0462	1.0%	0.0493	0.0493

Future research should focus on the practicalities of the method. First, it should be determined how baseline covariates should be presented, which is not as straightforward as with single greedy matching. Second, it should be determined how statistical inference can be drawn from the repeated matching.

Our study has some limitations. We have only compared our procedure to the most frequently used PS matching methods in the medical literature. Improvements have been made with stratification, optimal matching, doubly robust methods, etc., to which this method should also be compared. Second, we have used a rather simple data generation process, without including, for example, interaction terms, which are often present in real life data. However, this method focusses on the matching procedure which occurs after the PS is already calculated. As complexities in the data are dealt with in calculating the PS, we believe that increasing complexities in the data will not alter our results. Second, we only used a rather limited sample size of 1000 subject. In practice,

datasets can be larger or smaller. However, a previous literature search has shown that PS matching is often used in datasets of approximately 1000 subjects.

In conclusion, we have shown that repeating greedy calliper matching performs better than frequently used matching procedures in terms of a lower MSE. Especially with low exposure prevalence, repeated matching yielded an MSE twice as low as other matching methods.

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APPENDICES

Appendix table 1A. bias and mean squared error (MSE) at different numbers of repeated propensity score matching in a simulated dataset with an exposure prevalence of 0.1

	0.01*SD			0.02*SD			0.01			0.02		
	Bias	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**
5	4,7%	0,1297	0,1317	16,0%	0,1303	0,1558	0,4%	0,2927	0,2924	-1,2%	0,2168	0,2167
10	5,0%	0,1116	0,1139	16,3%	0,1085	0,1349	0,1%	0,2698	0,2695	-1,0%	0,1971	0,1970
25	4,7%	0,0995	0,1016	16,3%	0,0946	0,1211	0,3%	0,2624	0,2621	-0,8%	0,1814	0,1813
50	5,0%	0,0962	0,0986	16,2%	0,0933	0,1195	0,4%	0,2584	0,2582	-0,7%	0,1759	0,1758
100	4,9%	0,0946	0,0969	16,1%	0,0922	0,1181	0,4%	0,2589	0,2586	-0,9%	0,1752	0,1751
250	5,0%	0,0938	0,0961	16,3%	0,0919	0,1182	0,4%	0,2589	0,2586	-0,9%	0,1751	0,1750
500	5,0%	0,0936	0,0960	16,3%	0,0924	0,1187	0,3%	0,2586	0,2583	-0,8%	0,1749	0,1748
750	4,9%	0,0938	0,0962	16,3%	0,0927	0,1192	0,3%	0,2585	0,2582	-0,8%	0,1751	0,1750
1000	4,9%	0,0938	0,0962	16,3%	0,0922	0,1187	0,3%	0,2583	0,2580	-0,8%	0,1751	0,1750

Appendix table 1B. bias and mean squared error (MSE) at different numbers of repeated propensity score matching in a simulated dataset with an exposure prevalence of 0.2

	0.01*SD			0.02*SD			0.01			0.02		
	Bias	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**
5	1,2%	0,0762	0,0763	6,9%	0,0666	0,0713	0,1%	0,1255	0,1254	0,8%	0,0899	0,0899
10	0,8%	0,0687	0,0687	6,9%	0,0597	0,0643	0,4%	0,1157	0,1156	1,2%	0,0855	0,0856
25	0,7%	0,0623	0,0623	6,9%	0,0559	0,0605	0,4%	0,1119	0,1118	1,0%	0,0811	0,0811
50	0,8%	0,0617	0,0617	6,7%	0,0527	0,0572	0,4%	0,1105	0,1105	1,2%	0,0793	0,0794
100	1,1%	0,0612	0,0613	6,7%	0,0526	0,0571	0,2%	0,1094	0,1093	1,1%	0,0781	0,0782
250	1,0%	0,0609	0,0609	6,7%	0,0523	0,0568	0,2%	0,1084	0,1083	1,1%	0,0772	0,0773
500	1,0%	0,0608	0,0608	6,7%	0,0523	0,0568	0,2%	0,1085	0,1084	1,1%	0,0772	0,0773
750	1,0%	0,0605	0,0605	6,7%	0,0523	0,0567	0,2%	0,1085	0,1084	1,1%	0,0773	0,0774
1000	1,1%	0,0604	0,0605	6,7%	0,0523	0,0567	0,2%	0,1087	0,1086	1,1%	0,0774	0,0774

Appendix table 1C. bias and mean squared error (MSE) at different numbers of repeated propensity score matching in a simulated dataset with an exposure prevalence of 0.4

	0.01*SD			0.02*SD			0.01			0.02		
	Bias	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**
5	0,2%	0,0517	0,0517	2,6%	0,0476	0,0483	-1,0%	0,0782	0,0782	-1,3%	0,0559	0,0560
10	0,0%	0,0486	0,0486	2,6%	0,0437	0,0444	-0,6%	0,0748	0,0748	-1,2%	0,0522	0,0523
25	-0,1%	0,0476	0,0475	2,8%	0,0424	0,0431	-0,6%	0,0728	0,0728	-1,2%	0,0497	0,0498
50	0,1%	0,0474	0,0473	2,7%	0,0420	0,0427	-0,5%	0,0725	0,0724	-1,3%	0,0499	0,0500
100	0,0%	0,0464	0,0463	2,7%	0,0420	0,0427	-0,5%	0,0719	0,0719	-1,2%	0,0491	0,0492
250	0,0%	0,0464	0,0463	2,7%	0,0417	0,0424	-0,5%	0,0712	0,0712	-1,2%	0,0489	0,0490
500	0,0%	0,0461	0,0461	2,7%	0,0416	0,0423	-0,5%	0,0711	0,0710	-1,2%	0,0491	0,0491
750	0,0%	0,0462	0,0462	2,7%	0,0416	0,0422	-0,6%	0,0710	0,0710	-1,2%	0,0490	0,0491
1000	0,0%	0,0463	0,0462	2,7%	0,0416	0,0423	-0,6%	0,0711	0,0711	-1,1%	0,0490	0,0491

Appendix table 1D. bias and mean squared error (MSE) at different numbers of repeated propensity score matching in a simulated dataset with an exposure prevalence of 0.5

	0.01*SD			0.02*SD			0.01			0.02		
	Bias	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**
5	1,1%	0,0535	0,0536	3,1%	0,0505	0,0514	-0,4%	0,0733	0,0732	-0,8%	0,0540	0,0540
10	1,0%	0,0516	0,0516	3,0%	0,0485	0,0494	-0,7%	0,0697	0,0697	-0,8%	0,0515	0,0515
25	1,0%	0,0509	0,0509	3,0%	0,0466	0,0475	-0,6%	0,0685	0,0684	-0,7%	0,0499	0,0499
50	1,0%	0,0498	0,0499	3,0%	0,0463	0,0472	-0,7%	0,0681	0,0681	-0,6%	0,0492	0,0492
100	1,1%	0,0495	0,0496	3,0%	0,0461	0,0469	-0,6%	0,0682	0,0682	-0,6%	0,0486	0,0486
250	1,0%	0,0493	0,0494	3,1%	0,0460	0,0469	-0,7%	0,0681	0,0680	-0,6%	0,0484	0,0484
500	1,1%	0,0492	0,0492	3,0%	0,0461	0,0470	-0,7%	0,0680	0,0680	-0,6%	0,0483	0,0482
750	1,0%	0,0492	0,0493	3,1%	0,0461	0,0470	-0,7%	0,0680	0,0680	-0,6%	0,0482	0,0482
1000	1,0%	0,0493	0,0493	3,1%	0,0460	0,0469	-0,7%	0,0681	0,0681	-0,6%	0,0482	0,0482

Appendix table 2. Bias and mean squared error (MSE) for the post-hoc analyses with callipers of 0.005*SD_{ps} and 0.001*SD_{ps} in a simulated dataset with an exposure prevalence of 0.3.

	0.005*SD			0.001*SD		
	Bias	**Variance**	**MSE**	**Bias**	**Variance**	**MSE**
5	0,6%	0,2839	0,2836	5,4%	1,3850	1,3865
10	0,6%	0,2792	0,2789	5,7%	1,3686	1,3704
25	0,8%	0,2773	0,2770	5,7%	1,3693	1,3712
50	0,8%	0,2751	0,2749	5,7%	1,3697	1,3715
100	0,8%	0,2752	0,2749	5,7%	1,3678	1,3697
250	0,7%	0,2750	0,2748	5,8%	1,3659	1,3679
500	0,7%	0,2748	0,2746	5,8%	1,3679	1,3699
750	0,7%	0,2746	0,2744	5,8%	1,3674	1,3694
1000	0,6%	0,2746	0,2743	5,8%	1,3675	1,3694

5

GENERAL DISCUSSION

INTRODUCTION

As mentioned in the general introduction, usually, a new drug can receive market approval after a randomized controlled trial (RCT) has shown the efficacy and safety of the drug compared to an active comparator or to a placebo. However, as there are several limitations to an RCT, there are remaining unanswered questions when a new drug is used in clinical practice. Some of these limitations of an RCT include a limited sample size, a short duration of follow-up, and a selected patient population. This will pose unanswered questions regarding rare adverse side-effects, long-term effectiveness and safety, and the generalizability of the effects of the RCT to groups of patients not included in the RCTs. In addition, there can also be remaining questions about the utilization patterns of newly introduced drugs, for example regarding persistence and adherence to a treatment.

Non-vitamin K antagonist oral anticoagulants (NOACs) are a recently introduced new group of oral anticoagulants (OAC). RCTs showed that NOAC treatment was just as efficacious and safe as vitamin K antagonist (VKA) treatment for stroke prevention in patients with atrial fibrillation (AF). These results were confirmed in clinical practice by several observational studies. The main aim of this thesis was to assess utilization patterns, safety, and effectiveness of NOAC treatment for stroke prevention in patients with AF, using advanced pharmacoepidemiologic methods.

THE INTRODUCTION OF NOAC TREATMENT IN CLINICAL PRACTICE

After the RE-LY trial showed that dabigatran was just as efficacious and safe as warfarin for stroke prevention in patients with AF, it was the first NOAC to receive market approval in April 2011 [1]. Dabigatran was followed by rivaroxaban, apixaban, and edoxaban [2–4]. After a drug receives market approval, there are several factors that can affect the uptake of a drug in clinical practice, such as reimbursement decisions and clinical guidelines [5]. In chapter 2.1, we showed that reimbursement decisions and the European Society for Cardiology (ESC) guidelines were both associated with the initial increase in NOAC use in the Stockholm healthcare region. However, the regional Drug and Therapeutics Committee recommendation of apixaban as the first line NOAC was associated with the largest change in choice for NOAC prescriptions; in the months before this recommendation, all NOACs were used in equal amounts, while three months after the recommendation, apixaban was used four times more often compared to dabigatran and rivaroxaban combined (edoxaban was not yet on the market at that time). The increase in NOAC use after the publication of clinical guidelines was also found in Denmark and Ontario, Canada [6,7]. The overall uptake of NOAC treatment during the same period varied between countries, and was fastest in the United States and slowest in the United Kingdom [8–11].

In chapter 2.2 we showed that between March 2015 and February 2016, when NOACs were widely used in the Stockholm healthcare region, patients with high stroke and bleeding risks were more often prescribed low-dose aspirin or VKA treatment, instead of NOAC treatment, which is problematic given that aspirin treatment is less effective for stroke prevention [12]. Amongst patients receiving NOAC treatment, apixaban was the favoured NOAC treatment among elderly and

high-risk patients, while dabigatran was used in low-risk patients. The finding that NOAC treatment was channelled towards low-risk patients and VKA treatment towards high-risk patients was similar to other studies from the United States and Canada [9,13–15].

Chapters 2.3 and 2.4 consist of similar studies, however performed in different settings. First, chapter 2.3 showed that after the NOAC introduction in Stockholm more patients received an OAC and fewer patients received low-dose aspirin. This yielded a lower risk for stroke after the NOAC introduction, while the bleeding risk remained the same. In chapter 2.4 we replicated this study in three other countries (Denmark, Scotland, and Norway) and found that OAC treatment increased in all countries while aspirin treatment decreased, just as in Stockholm. However, the reduction in stroke rate was only present in Stockholm, Denmark, and Norway, while in Scotland the stroke rate was unchanged after the NOAC introduction. The stroke rate was already the lowest in Scotland before NOAC introduction, which may explain why it did not decrease any further. Similarly, the bleeding rate was unchanged in Stockholm, Denmark, and Norway, while it was increased in Scotland.

Chapters 2.5 and 2.6 focus on the persistence and adherence with NOAC treatment, which are both essential for a drug therapy's effectiveness. Persistence refers to whether a patient continues treatment after initiation, while adherence refers to whether a patient takes the treatment as prescribed [16]. In chapter 2.5, we studied this in the Stockholm healthcare database and found that in patients with AF newly initiated with NOAC treatment, 70% of the patients were persistent after five years of follow-up, and 85% of the patients were on treatment during follow-up, when including restarters. The medication possession rate (MPR), a commonly used adherence measure [17], was approximately 90% in persistent patients. In addition, we showed that non-persistence and sub-optimal adherence (MPR ≤ 90%) to NOAC therapy were associated with an approximately two-fold increased risk for stroke. This was in line with a recent study from Korea which also showed that stroke prevention was optimal at an MPR above 90%, indicating that caregivers should try to achieve this goal in patients for optimal stroke prevention with NOAC treatment [18]. In chapter 2.6 we found that persistence and adherence to NOAC treatment was high in five Western European healthcare settings (Stockholm, Denmark, Norway, Scotland, and Germany). However, 20% of the patients did not have an MPR above 90%, implying sub-optimal stroke prevention in one out of five patients. In addition, both persistence and adherence were lower with dabigatran compared to rivaroxaban and apixaban in all countries, indicating a need for additional monitoring and efforts to remain on treatment in patients initiated on dabigatran.

IMPROVING THE SAFETY AND EFFECTIVENESS OF NOAC TREATMENT IN CLINICAL PRACTICE

After market introduction of new drugs, there will be remaining unanswered clinical questions. In this thesis, we have provided answers to four clinical questions. First, in chapter 3.1 we showed that in patients with AF and a moderate stroke risk (i.e., CHA_2DS_2-VASc of 1 for male patients and 2 for female patients), NOAC treatment was safer and more effective than VKA treatment or no treatment. This was mainly driven by the fact that NOAC treatment did not increase the risk for

intracranial haemorrhage (ICH) but reduced the risk for stroke compared to no treatment. VKA treatment also reduced the risk for a stroke, but increased the risk for ICH, and therefore there was no net clinical benefit for VKA treatment compared to no treatment in this patient category. This was the first study to compare NOAC treatment to no treatment in these patients. There have been prior studies comparing VKA treatment to no treatment in those patients but results from these studies were inconclusive regarding whether VKA treatment had a positive effect or not, yielding guidelines recommendations that OAC therapy could be considered, instead of clear recommendations for treatment or not [19–22]. The results in chapter 3.1 indicate that NOAC treatment may be the preferred treatment in patients with AF and a moderate stroke risk.

In chapters 3.2 and 3.3 we investigated the concomitant use of two different drug classes with NOAC or VKA treatment, namely antidepressants and proton pump inhibitors (PPI). Antidepressants are known to increase the risk for bleeding and have also been associated with an increased risk for stroke [23–25], while PPI co-treatment can reduce the risk for gastrointestinal bleeds. In 3.2 we showed that concomitant antidepressant use in patients with AF and either NOAC or VKA treatment was significantly associated with an increased bleeding risk (hazard ratio (HR): 1.42; 95% confidence interval (CI): 1.12 - 1.80), but not significantly associated with an increased stroke risk (HR: 1.23; 95%CI: 0.93 - 1.62). This indicated the need for a critical evaluation whether antidepressant therapy is required in these patients. In chapter 3.3 we showed that PPI use was associated with a reduced risk for upper GIB in patients with AF treated with a NOAC (incidence rate ratio (IRR): 0.75; 95%CI: 0.59 - 0.95). These results are in line with previous observational work from the United States and Hong-Kong, which also showed a protective effect on GIB, indicating that PPI therapy may be considered in patients with AF treated with a NOAC [26,27].

In chapter 3.4 we showed high 90-day mortality rates after an ischemic stroke (25.1%), ICH (31.6%), and GIB (16.2%). Patients receiving VKA treatment at the time of the ICH had a higher risk of dying compared to patients receiving NOAC treatment (HR: 1.36; 95%CI: 1.04 - 1.78). This adds evidence to the current guidelines that NOAC treatment should be preferred over VKA treatment [22]; NOAC treatment is not only safer than VKA treatment in terms of less ICH risk, but ICH during NOAC treatment appears to be less severe than during VKA treatment. Previous studies found a similarly lowered risk of mortality after an ICH or an ischemic stroke during NOAC treatment compared to VKA treatment [28,29].

PROPENSITY SCORE MATCHING IN PHARMACOEPIDEMIOLOGY

Greedy matching is one of the most frequently used algorithms for propensity score matching [30]. In chapter 4.1 we performed a systematic literature search, showing that greedy matching was used in 71% of the selected studies. With the greedy matching algorithm, treated and untreated patients are by default both randomly sorted. After this, the algorithm matches the first treated patient to the first untreated patient. Often this is done within a predefined caliper; in that case the algorithm matches the first untreated patient that has a propensity score within a maximum difference from the propensity score of the treated patient. Another frequently used option is to use nearest neighbor greedy matching; in that case, the algorithm finds an untreated patient

that has a propensity score that is closest to the treated patient. All these greedy methods have in common that they only look at the first treated patient and match an untreated patient based on which specific method is defined.

In chapter 4.1, we created several simulated cohorts and repeated the greedy matching algorithm 1000 times in each cohort. This yielded a high variation in the treatment-outcome association after the matching procedure was repeated. Especially in smaller cohorts the odds ratio in the 1000 matched sets could range from 0.53 to 10.0, with an interquartile range of the 1000 odds ratios of 1.11 to 1.67. This finding warrants careful interpretation of studies using this matching algorithm, especially in smaller cohorts (i.e., smaller than 2500 patients), as the variation was largest in these cohorts. In chapter 4.2 we used this random variability to propose a new matching procedure, in which greedy matching is repeated and the mean of the repeated matches is used as the final treatment-outcome association. We used a Monte-Carlo simulation to show that this method outperformed any standard propensity score matching procedure we compared it with by markedly increasing precision without increasing bias.

OBSERVATIONAL RESEARCH AND RCTS

As described in the introduction, RCTs are the gold standard to establish the efficacy and safety of a new drug, since randomization removes confounding bias [31]. There are no equally valid alternatives to randomization to achieve unconfounded estimates of the efficacy and safety of a treatment. Although there are scenarios in which randomization does not produce fully unconfounded results, such as selective loss to follow-up or unsuccessful randomization, a well conducted RCT provides results which are not biased by confounding. In several examples it has been demonstrated that when observational research is properly performed it can produce estimates that are almost identical to estimates from an RCT. Dickerman *et al*. have shown this using the example of statins and diabetes type 2 [32]. They performed an observational study using the Clinical Practice Research Databank (CPRD), a database commonly used in pharmacoepidemiologic studies, and studied the association between statin use and diabetes type 2. From meta-analyses of RCTs, it is known that the odds ratio for diabetes type 2 with statin use is 1.09; 95%CI: 1.02 - 1.17 [33]. Using the observational database and applying the same inclusion criteria, they found a hazard ratio of 1.11; 95%CI: 0.98 - 1.25, almost identical to the association in the meta-analysis and thus showing that residual confounding was hardly present in this example. However, when using a flawed design, which introduced immortal time bias in the study, they found a large protective effect of statins against diabetes, with a hazard ratio of 0.19 95%CI: 0.18-0.20.

The point Dickerman *et al*. want to make is that confounding is often *not* the largest pitfall in observational research. The larger issue, they state, has to do with flaws in the study design, mainly driven by immortal-time bias [34]. There can be additional important flaws in an observational study designs, for example when comparing prevalent users to incident users or when choosing the wrong comparator which can introduce confounding by indication [35]. However, the largest bias is often due to immortal time bias, which has been the cause of very implausible research findings, for example statins reducing the risk for colorectal cancer by 50% [36], a diagnosis of skin cancer reducing the risk

of dying by 48% [37], or that having malignant melanoma reduces the risk of dying by 11% compared to not having this life-threatening form of cancer [37].

Immortal time bias occurs when exposure status is defined after the start of follow-up and unexposed person-time before the exposure is incorrectly classified as exposed person-time or excluded. Thus, exposed patients will per definition survive until they become exposed. Patients that have died before becoming exposed are always considered unexposed, yielding a big protective effect in exposed patients. Chapters 3.1, 3.2, and 3.3 were also prone to immortal time bias. In chapter 3.1 patients were included at the time of a first AF diagnosis, but could claim a VKA or NOAC prescription after this moment. In chapters 3.2 and 3.3, patients could claim an antidepressant or PPI prescription after being included based on a VKA or NOAC prescription. In each of these studies, we have considered the time prior to claiming the exposure of interest as unexposed person-time, and thus avoided immortal-time bias.

CONFOUNDING

In observational studies, there are two ways to minimize the risk for confounding, namely through the design of a study and through the statistical adjustment. As described above, using the right study design is essential for getting unconfounded study results. When using a flawed study design, it is impossible to still get unconfounded study results through statistical adjustment. Statistical adjustment is only useful when added to a well-designed observational study to adjust for any remaining inequal distributions of risk factors in two treatment arms, as was the case in some chapters from this thesis. In chapter 3.1, untreated patients were slightly younger, which decreases the risk for a stroke or a bleed. In chapter 3.2, patients treated with concomitant antidepressants were older and had more comorbidities, just as patients treated with a PPI in chapter 3.3, meaning these patients were at an increased risk for a stroke or a bleed to begin with. And finally, in chapter 3.4, patients on antiplatelet treatment during a stroke, ICH, or GIB were older, and therefore had an increased risk for mortality.

We used different analytical approaches in the different chapters to account for potential confounding bias. In chapter 3.1, we used an inverse probability of treatment weighted (IPTW) Cox regression, in chapters 3.2 and 3.4 we used a multivariable adjusted Cox regression, and in 3.3 a time varying IPTW Poisson regression. The approach when deciding on which analytical method was preferred, was always to use the least complicated approach that would be adequate to adjust for confounding. That is, to use a multivariable adjusted Cox regression when possible, as was done in chapters 3.2 and 3.4. When the numbers of events per covariate are too low, multivariable regression yields biased results since the model cannot converge anymore, which would be the case in chapters 3.1 and 3.4. In those chapters, we chose to use the propensity score, as the number of covariates to adjust for is then not limited by the number of outcomes. In 3.1 we used the propensity score for an IPTW Cox regression, as we were only interested in adjusting for baseline characteristics. In chapter 3.3, however, we also wanted to adjust for covariates that could change over time and may have affected both the risk for exposure (i.e., a PPI prescription) and the outcome (i.e., an upper GIB). In a time-varying Cox regression that makes use of the propensity score, a marginal structural model

is the preferred approach to take this into account. In a marginal structural model, the IPTWs are multiplied at each study time-point. In chapter 3.3, patients could switch from PPI status back and forth yielding many study time-points, which would create extremely large weights at time-points near the end of the study. Therefore, we chose a time varying IPTW Poisson regression, in which weights are not multiplied over time, and thus we avoided the issue of these large weights.

In most chapters, we performed additional sensitivity analyses with a different analytical approach than used in the main statistical analysis to assess if this would yield different results. In chapters 3.2 and 3.4 we performed an additional propensity score matched analysis, and in chapter 3.3 we performed an additional analysis where we kept all covariates fixed at baseline, which created a standard, non-time varying IPTW Poisson regression. None of the sensitivity analyses yielded noteworthy differences in any of the examples; there were slight differences in point estimates, but all results would still be interpreted the same way if the alternative methods were to be used. This adds to the robustness of the findings in general and is in line with the conclusions of Dickerman *et al*. that confounding bias and adjusting for this in the analysis phase is seldom so influential that it completely changes the outcome of a study.

In this thesis, we also observed that the method of controlling for confounding in the analysis phase was not the largest issue in our studies, as in none of our studies did we find different results when using a different approach to adjust for confounding bias. . Also, previous work by Sanni Ali *et al*. showed that there were hardly any differences when using a marginal structural model, a time-varying Cox regression, and different propensity score methods to test the association between antidepressants and hip fracture, again indicating that differences in statistical methods to adjust for confounding do not importantly affect study results [38]. On the other hand, Lalmohamed *et al*. have shown that there can be large differences in study results when using different, and flawed, study designs when studying the association between statins and the risk of lower limb revision surgery [39]. These findings provide further evidence to the hypothesis that the way statistical adjustment is done in the analytical phase plays only a small role in handling confounding bias when a study has a valid design.

There are, however, some instances in which we did find unexplainable results that may have been due to uncontrolled residual confounding. In chapter 3.1, we found that untreated patients with AF at moderate stroke-risk had a much higher mortality-risk compared to treated patients, as the mortality rate was approximately three times higher. From randomized trial evidence, it is known that treatment with oral anticoagulants reduces the mortality risk by approximately 26% [12], which is far less than in our study. This is probably caused by the fact that treatment is withheld from patients near the end of life, which is a clearly a large confounder that is badly captured in databases and thus cannot be adjusted for [40]. On the other hand, one could also argue this is more of a design flaw, given that the wrong comparator was chosen for this outcome.

In conclusion, this thesis adds to the call for more focus and attention to using an appropriate study design. Pharmacoepidemiology has come a long way to account for confounding, and many commonly applied methods work, in most of the cases, sufficiently to handle confounding. With a focus shift towards avoiding flaws in the study design, while showing that confounding can be handled sufficiently, the pharmacoepidemiologic society has the possibility to convince even non-

believers in the usefulness of observational research [41]. With adequate study designs, observational research can minimize the production of unbelievable results as has happened in the past, and this ultimately increases the trust in observational research by the medical and scientific society. In the end, this can improve clinical practice and patient outcomes, as data from RCTs and observational research complement each other, by filling knowledge-gaps that both forms of research will inevitably leave behind [42].

STUDY DESIGN

Dickerman *et al*. state that observational studies should try to mimic the design of an RCT, ideally by using an intention-to-treat (ITT) approach. In an RCT, an ITT analysis is required to maintain the randomization [31]. However, in an observational study there is no randomization, and thus an ITT analysis is not required. Some even say that using an ITT approach for observational studies is the worst of both worlds, as it combines a major limitation of observational studies, namely the lack of randomization, with a common limitation of an RCT, namely imperfect adherence to the assigned treatment [43].

In chapters 3.2 and 3.3 we sought to investigate concomitant use of NOACs with antidepressants and PPI therapy, and ran into issues of not being able to use an ITT analysis. In these studies, an ITT approach is not feasible, as concomitant use of a treatment is often intermittent, and thus an ITT approach will not represent the actual use of the drug by the patient. Therefore, we used a study design in which patients could switch from being exposed to being unexposed. In addition, in chapter 3.1 we used a range of study designs, including an ITT approach, but also an as-treated approach. These different approaches yielded comparable results, indicating that an ITT approach is not per se a requirement to get reliable results in observational studies. The recommendation by Dickerman *et al*. to mimic an RCT and use an ITT analysis in which eligibility and exposure are defined at baseline, is made so researchers do not fall into the immortal-time bias pitfall. However, if an observational study uses time-varying exposure, it also avoids immortal-time bias and can give a better representation of the actual use of the drug in clinical practice.

Explaining complicated study designs in writing is challenging. However, given the importance of a study design for interpretation and understanding of its results, even more so when trying to replicate a study, in several chapters of this thesis we used the graphical depictions from the REPEAT initiative to present the full study design in one illustration [44]. The goal of these illustrations is to make all design decisions as transparent and understandable as possible to a broad audience.

In chapters 2.1, 2.3, and 2.4 we used study designs that were less prone to confounding bias compared to study designs used in chapter 3. It must be said that these chapters were not comparing two different treatment regimens and were not looking for associations with a certain outcome. The chapters, however, contained methods that compared different periods in time. In chapter 2.1 we used an interrupted time series analysis, which is a quasi-experimental study design and is considered one of the strongest study designs to study the effect of an intervention [45]. This design uses the trend before an intervention and assesses deviations from this trend after the intervention. In chapter 2.3 and 2.4 we looked at the antithrombotic treatment in patients with AF and the rates

of strokes and bleeds in 2012 and 2017, of which 2012 was considered prior to the NOAC introduction and 2017 after the NOAC introduction. With this analysis we were able to create a full picture of how the introduction of the NOACs, a new treatment option, impacted clinical practice and how this affected patient outcomes. Given that these study designs compare periods in time, instead of patients, there can only be confounding bias that is caused by factors that have changed over time. In chapter 2.3 and 2.4 it could have been that, for example, there were lower blood-pressure levels and healthier lifestyles over time [46]. In chapter 2.1 we studied very clear interventions, each occurring at one specific point in time. In chapter 2.3 and 2.4 we studied a less clear intervention that did not occur at one specific point in time, since the introduction of a new drug takes time, and therefore we chose to compare two years in time, instead of using an interrupted time series design for these studies as well.

SENSITIVITY ANALYSES

Besides performing sensitivity analyses in which the analytical approaches were changed, this thesis contains a range of other sensitivity analyses that were conducted to test the robustness of the findings to residual confounding. In chapters 2.5, 3.1, 3.2, and 3.3 we used falsification endpoints [47], in chapter 3.2 we analysed former user periods, in chapter 3.3 we calculated E-values [48], and in chapter 3.4 we performed an asymmetric trimmed propensity score matched analysis and an array approach for unmeasured confounding [49,50].

Falsification endpoints are outcomes that are not supposed to be associated with the treatment of interest, but with potential unmeasured confounders. If a falsification endpoint is analysed in the same way as the actual outcomes are analysed, and have the same confounders in common [51], the falsification endpoints are supposed to yield a neutral association with the treatment. However, if the falsification endpoint shows a significant association with any of the treatments, in the same direction, it indicates that that the found association of interest is probably (partly) explained by this residual confounding. In none of the chapters 2.5, 3.1, 3.2, and 3.3 did we find a significant association with the falsification endpoints, indicating no signs for residual confounding. We have used several different falsification endpoints throughout this thesis. The requirement for the right falsification endpoint was that it should not be associated with the exposure of interest. Especially in chapter 3.2 this was challenging, as antidepressant use has been associated with many diseases throughout history.

Besides falsification endpoints, we also analysed former-user periods in chapter 3.2. A former-user period consists of person-time after a patient was exposed to the exposure of interest. In chapter 3.2, this was when a patient received antidepressant treatment for a period but stopped taking this treatment; the former-user period is the person time at which the patient had stopped taking the treatment. During this former-user person-time, the risk for the outcome is supposed to be similar to the risk in person-time of patients that were never exposed to antidepressant treatment, and this was the case in chapter 3.2, indicating no signs for residual confounding.

In chapter 3.3 we performed an array approach for unmeasured confounding and in chapter 3.4 we calculated E-values [48,50]. Both approaches are similar in presenting how large an unmeasured

confounder, or group of confounders, would have to be to explain the found association. The array approach yields a full overview of different values for the confounders in terms of the strength of the association, the prevalence of the confounder, and the association of the confounder with the treatment. The E-value consists of one number that embodies these variables into one value. The strength of the E-value lies in the possibility to compare E-values across studies. The strength of the array approach is that one gets a better impression of what the characteristics of a confounder should be to explain the association and can then compare this to the values of confounders that were found in the study.

In chapter 3.4 we performed a sensitivity analysis which used asymmetrically trimmed propensity score matching [49]. Patients that have a propensity score that is amongst the highest and lowest scores, are often the patients with the highest risk for unmeasured confounders. By removing those patients and repeating the analysis, one can see if the results are different because unmeasured confounding is supposed to be removed in this approach. We found similar results with the trimmed analysis, indicating that the results were not likely explained by residual confounding.

In this thesis we have only used a small selection of all different sensitivity analyses that are possible. The goal of this thesis was not to identify which method is best. However, we were able to show that the applied sensitivity analyses are very feasible, even in cross-national comparisons. Those analyses add to the robustness of observational research findings and should be part of each observational study to improve the credibility of the findings. Especially given the large focus people are giving to confounding and specifically unmeasured confounding, applying a range of sensitivity analyses to an observational study can remove some of the concerns related to this phenomenon.

MULTI-DATABASE STUDIES

Observational studies are often performed as single center studies. This can be in one hospital, one healthcare system, one country, etc. One of the often-mentioned advantages of observational research is that it is not hampered by a limited sample size as often as in an RCT and can therefore be used to study rare adverse events [52]. However, in the meta-analysis by Ntaios *et al.* reviewing observational studies comparing NOAC to VKA treatment, in 21 of the 28 included studies the NOAC group was smaller than the apixaban group in the ARISTOTLE trial, the NOAC trial with the largest NOAC treatment arm [3,53]. This shows that in practice, at least in NOAC research, many observational studies are in fact not larger than an RCT, even though most of the studies in the meta-analysis were performed in what are considered large databases, for example several national databases. Therefore, multi-database studies are needed to provide observational research with large enough sample sizes to study rare outcomes, rare exposures, or subgroups. In addition, performing multi-database studies can add to the credibility of research findings as studies are in essence simultaneously replicated in different databases.

The studies in chapters 2.4, 2.6, 3.1, and 3.3 were conducted in different countries, and the results in chapters 3.1 and 3.3 were meta-analyzed to pool the study results. By combining data from different countries and databases, these studies became large enough to find meaningful results in very specific populations. Especially in chapters 3.1 and 3.3, the associations were not statistically

significant in the databases separately, but only when the results were pooled using a meta-analysis. In addition, in chapter 2.6 we were able to make valid comparisons of persistence and adherence in different countries, which is otherwise difficult to do as the ways persistence and adherence are measured often varies between studies. Through our common data model and common protocol, we were able to make valid comparisons of persistence and adherence in multiple countries, as they were both measured in the exact same way with the same definitions.

We combined the data from the different databases using a common data model, on which we locally ran the same analytical script [54]. The common protocol implies that we used the same study design and analysis in each database. To realize this, we used the same analytical R script in all databases. Through this, we were certain that each analysis was conducted identically in each database. The common data model was used to create datasets on which the analytical script would fit.

In this thesis, we combined data from databases with similar content to begin with; all databases contain diagnostic data from secondary care and prescription claims data. In addition, all databases had diagnostic data coded in the ICD-10 coding system and prescription claims data in ATC coding. Therefore, creating the common data model was rather straightforward, as this only required renaming and restructuring of variables, but no re-mapping of variables or other more complicated procedures. In Stockholm, we had additional data available from primary care as well. We used this data to perform sensitivity analyses by in- and excluding data from primary care to see if and how this affected our results, but neither in chapter 3.1, 3.2, or 3.4 did this yield any difference in results.

To further improve these multi-database studies, cross-database validation studies are required. In this thesis, we used the common local knowledge from all centers to create code lists for comedication and comorbidities for each study. In most databases, prior validation studies have shown that certain codes generate a high specificity and sensitivity. However, for these cross-national studies, we could not use these specific code lists from each database since we created a common protocol and thus had to combine these validated code lists. In practice, most of the code lists per database overlapped with the code lists from other databases. Besides different code lists, there are also underlying differences per country, such as different reimbursement systems, guidelines, and prescriber preferences, which also merit further research to assess the role they play in multi-database studies.

We have shown that the common data model and common protocol approach used in this thesis is suited for many purposes. The approach was useful for descriptive multi-database studies such as in chapters 2.4 and 2.6, but also for more advanced association studies such as in chapters 3.1 and 3.3. In addition, the approach was shown to be flexible, as we could use the same approach for different countries and selection of countries. In all cross-national studies we used data from Stockholm and Denmark, but in 2.4 and 3.1 we added data from Norway and Scotland, in 2.6 from Norway, Scotland, and Germany, and in 3.3 additional data from the Dutch PHARMO database, all using the same common data model and common protocol approach.

Reasons why studies on NOACs have been a good use-case for this approach include the way NOACs are prescribed and the outcomes associated with NOAC treatment. First, the use of NOACs is well described in guidelines and there are clear dose recommendations in terms of the number of tablets per day [22]. Second, the outcomes of interest in most studies, strokes and bleeds, are

captured in a hospital setting and are hardly subject to local interpretation, which makes them easy to compare between countries and enables pooling of the results from different countries. Using the same approach for more complicated outcomes, such as psychological outcomes, or for drugs with more complicated dosing regimens, such as oncological drugs, will be more challenging.

CLINICAL RELEVANCE

All studies in this thesis, but especially those in chapter 3, have been based on collaboration between clinicians and pharmacoepidemiology experts. Therefore, the studies in this thesis aimed to study relevant research questions, that would provide answers for clinically relevant issues. We were amongst the first to test the association between antidepressants and bleeding and stroke risk in patients with AF treated with a NOAC, to test the protective effect of PPIs in patients with AF treated with a NOAC, and to compare NOAC, VKA, and no treatment in moderate stroke-risk patients. These studies provided answers that could immediately impact clinical practice.

Sometimes, researchers focus too much on using the perfect methods in their study and tend to forget the clinical importance of their work, and vice versa there may also be too much focus on the clinical aspect while the methodological part is neglected. This stresses the importance of collaboration between methodological and clinical experts when performing any kind of research, but especially observational research. It goes without saying that addressing clinically relevant questions with poor research methods is useless. Using advanced studies for irrelevant research questions, however, might be just as redundant, especially in the era of big data with the emergence of many available databases. If more and more observational research is performed without a biological rationale, occasionally, an unexplainable study result will come out, and potentially be published, purely based on chance [55]. The medical and scientific societies might subsequently lose confidence in observational medical research, given the risk of such false positive research findings. Ultimately, this will harm the credibility of observational research and it should therefore be encouraged to study clinically relevant research questions. One approach to reduce the chances of "cherry-picking" from a database is through registering a protocol prior to conducting a study, for example in the ENCePP register of study protocols, which is already mandatory for all regulatory imposed studies.

Besides finding clinically relevant research questions, the collaboration between medical and methodological experts is also needed when interpreting study results. Along the line of increasing data availability, databases also tend to increase in size. Through this, results from studies in these databases will have narrow confidence intervals given the large sample sizes, which ultimately leads to more studies reporting statistically significant results which may not bear clinical meaning. Therefore, the collaboration between the methodological and clinical experts is increasingly important be able to find the optimum between statistical significance and clinical relevance.

There are some exceptions when it can be useful to perform research without a biological rationale, i.e. when hypotheses-generating studies are performed. This has been done, for example, when screening for potential associations between prescribed drugs and cancer [56]. But, these results should be considered as hypotheses, and these hypotheses should be confirmed in well-designed hypothesis-testing studies or preferably randomized controlled trials if feasible [57].

COMBINING RANDOMIZATION AND REGISTRY DATA

There are several promising developments that could lift observational research to another level [58]. One approach combines the strength of a randomized trial with the usefulness of observational data; patients are randomized to a certain treatment and then followed in a registry [59]. Strictly speaking this is no longer an observational study as patients are randomized, but it uses the infrastructure of the same databases used in observational studies. One example for this was the DANNOAC-trial [60]. The idea of this trial was to randomize hospitals in Denmark and each hospital would only prescribe one specific NOAC for six months to patients that were newly initiated on NOAC treatment. After six months hospitals would switch to initiating treatment in new patients with another NOAC and after two years each NOAC would have come by. The randomization would decide the order in which the NOACs were given. After this, patients would be followed in the Danish National Registries until an outcome of interest was registered or the end of follow-up.

This approach has the best of both observational research and an RCT. It has the advantage of an RCT since treatment is allocated at random, thus there will be no confounding bias. In addition, the study will be performed in a broad patient population, although only those initiated on treatment in secondary care. There would be no need for any additional monitoring of these patients besides standard care, which would make the trial far less expensive compared to a standard RCT. Unfortunately, the DANNOAC-trial was never conducted due to ethical reasons, but a Swedish study using a similar approach for a different research question has successfully been conducted [61].

PROPENSITY SCORE MATCHING

In chapters 4.1 and 4.2 we performed two studies to evaluate greedy propensity score matching and to suggest and test a new approach for matching. As explained in the introduction, greedy matching only looks at the first treated patient and then matches an untreated patient to this treated patient [30]. Therefore, this method is dependent on which treated patient is on top of the list of treated patients and in many cases this list is ordered randomly. This randomness can introduce variability in the matched pairs and through this ultimately in the treatment-outcome association in a study, as we showed in chapter 4.1.

In chapter 4.2 we used this randomness to propose a new method for greedy matching, namely, to repeat the matching procedure which reduces the variability. Using a Monte-Carlo simulation, we showed that our proposed method indeed markedly increased the precision, without increasing the bias when comparing this method to commonly used propensity score methods. This method was superior to those methods in terms of the mean squared error, a measure which includes both variance and bias.

Since greedy matching is by far the most frequently used matching procedure, as was seen in the literature review from chapter 4.1, the proposed method should be easy to use for most researchers, as it only repeats the standard greedy matching procedure. In addition, the procedure does not require that much computational power compared to, for example, optimal matching or bagged one to one matching [30,62]. Therefore, this method could be proposed as the future method

for propensity score matching, as it performs better than current methods without requiring much additional computational power.

However, there are some developments that are needed for this method to be used in practice. First, it needs to be determined how baseline characteristics after matching can be presented [63]. Potentially, this can be done by using the mean values for these characteristics of the, e.g., 100 matched sets. Second, it needs to be determined how statistical inference can be drawn from the repeated matching.

LIMITATIONS AND FUTURE RESEARCH

There are several limitations to the studies in this thesis. The first limitation has to do with data validity, especially of outcomes but also for comorbidities. In the multi-database studies, we noticed that the crude event rates differed between the different countries. For example, in chapter 3.3 we found the crude rate for an upper gastro-intestinal bleed to be 0.29/100 person-years in Denmark, 0.23/100 person-years in Stockholm, and 0.11/100 person-years in PHARMO. Although there might be slight differences in the actual rates of events between countries, this is more likely due to a data validity issue. This could be due to better/worse registrations of the outcomes, but also due to potentially different patient populations. Eventually, the point estimates for the association in the study from the different countries were consistent, therefore we do not believe this has been an issue for the validity of the results. However, future research should focus on performing cross-national validation studies to further improve the rigidity of multi-database studies.

The second limitation of this thesis that merits further investigation has to do with the differences in underlying healthcare systems and reimbursement systems. In the multi-database studies from this thesis, we had access to data from countries that were rather similar and therefore we did not investigate these issues any further. However, one can imagine that different reimbursement systems can ultimately lead to a different patient population receiving a certain drug in a country, especially in the case of very specialized or expensive medicines. Future studies should investigate how and if this can affect the patient population of a study and potentially also how this ultimately affects the association of interest of a study.

KEY MESSAGES

The work in this thesis can be summarized in a few key messages as stated below:

1. It is feasible to conduct high quality multi-database observational research
   In this thesis, we have shown that it is possible to perform high-quality observational research in different countries, using a common data model, common protocol approach. Through this, sample sizes can be drastically increased, creating the opportunity to perform observational research on rare outcomes or in specific patient populations. In addition, combining results from different countries yields study results that can be generalizable towards other countries and patients. This thesis provides an example of a framework to systematically perform post-marketing observational studies in a European multi-database

setting. This framework was proven to be useful for descriptive as well as association studies and was flexible enough to include a range of countries.

2. In observational research, more focus is needed on study the design, while maintaining optimal control for confounding.

   In this thesis, numerous sensitivity analyses were performed to test to what extent our study results would have been affected by using a different analytical approach. In none of these studies there were different findings when using an alternative analytical approach, indicating that choosing the right analytical approach is not that influential in the final study results. However, much attention in observational research is spent on controlling for confounding in the analysis phase, while in this thesis we demonstrated that this can be dealt with quite successfully when using any appropriate analytical approach, if the right study design is used. On the other hand, the past has shown that biased study designs can be the cause of much larger problems in observational research. Therefore, more focus on using unbiased study designs is needed, as this can influence study results to a much larger extent.

3. Repeated greedy propensity score matching has the potential to become the preferred way of propensity score matching.

   Greedy propensity score matching can be highly variable due to the randomness that comes with the algorithm. Especially in small cohorts, greedy caliper matching yielded highly variable results, which ultimately affect the implications of an observational study. The proposed method of repeated greedy propensity score matching resulted in increased precision without changing the bias compared to several commonly used matching methods. Although there are some practicalities left before the method can be used in practice, it has shown promising results without demanding too much computational power.

4. Antithrombotic treatment in patients with AF can be improved with the following findings:

   a. *PPI treatment can be considered in patients with AF treated with a NOAC.*

      Concomitant use of PPI therapy in patients with AF treated with a NOAC was associated with a reduced the risk for an upper GIB. This association was strongest in the elderly and high-risk patients.

   b. *In patients with AF treated with an oral anticoagulant, the need for antidepressant therapy should be critically reconsidered.*

      Concomitant use of antidepressant therapy in patients with AF and either VKA or NOAC treatment was associated with an increased bleeding risk. In addition, there were signs of an increased stroke risk. These findings should encourage physicians to carefully reconsider the need for an antidepressant to these patients, and if this therapy is clearly indicated, these patients require additional attention.

   c. *In patients with AF treated with a NOAC, the goal for adherence should be an MPR of at least 90%.*

      Patients that had an MPR of 90% or higher were optimally protected from a stroke. In patients with an MPR below 90%, there was a meaningfully increased stroke risk compared to patients with adherence levels above this threshold.

d. *In patients with AF at moderate risk for a stroke, NOAC therapy should be considered.* NOAC treatment had a positive net clinical benefit compared to VKA treatment or no treatment in patients with AF at moderate risk for a stroke, i.e., a CHA_2DS_2-VASc score of one for male patients, and two for female patients. Compared to no treatment, NOAC treatment was associated with a reduced risk for stroke without increasing the risk for intracranial hemorrhage. Compared to VKA treatment, NOAC treatment was associated with comparable risk for stroke, but a reduced risk for intracranial hemorrhage. Compared to no treatment, VKA treatment was associated with a reduced stroke risk but an increased risk for intracranial hemorrhage, yielding a neutral net clinical benefit.

CONCLUSION

In conclusion, the studies in this thesis have added to the knowledge on the utilization, safety, and effectiveness of NOAC treatment in patients with AF. Almost a decade after the introduction of NOACs to the market, they are now widely being used in daily clinical practice throughout Europe and in most countries, this has contributed to an overall better stroke prevention. The studies in this thesis have contributed to the further improvement of the clinical knowledge on the safety and effectiveness of NOAC treatment in patients with AF. While doing so, this thesis provides an example of how post-marketing observational studies could, and potentially should, be conducted. The studies contained advanced methods and were performed in a multi-database setting, to provide answers to clinically relevant questions. The studies used a wide range of methods to handle confounding, accompanied by sensitivity analyses to test the robustness of these findings; these approaches and sensitivity analyses provide a framework for how to assess the use, safety, and effectiveness of new drugs in clinical practice on an international level.

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6

APPENDICES

6.1

ENGLISH SUMMARY

INTRODUCTION

In a randomized controlled trial (RCT), randomization determines which patient receives which treatment. Therefore, there is no correlation between patient characteristics and the treatment decision, and thus no confounding bias. In observational research, the treating physician decides for a treatment. In that case, patient characteristics do, rightfully so, play a large role in which treatment a patient receives, which can lead to confounding bias. Therefore, RCTs are the golden standard to estimate the efficacy and safety of a drug and are predominantly required before a drug receives market approval.

Non-vitamin K antagonist oral anticoagulants (NOACs) are a group of recently introduced drugs on the market that have gone through the phases of RCTs to receive market approval, after which several studies have confirmed the safety and effectiveness in clinical practice. NOACs are an alternative to vitamin K antagonists (VKAs) for stroke prevention in patients with atrial fibrillation (AF). Both drugs share their mechanism of action by inhibiting the coagulation cascade, through which they also have the same adverse events, namely bleeds.

Results from RCTs need to be confirmed in daily clinical practice and remaining clinical questions can and need to be answered using observational studies. The main aim of this thesis was therefore to assess utilization patterns, safety, and effectiveness of NOAC treatment for stroke prevention in patients with AF, using advanced pharmacoepidemiologic methods.

THE INTRODUCTION OF NOAC TREATMENT IN CLINICAL PRACTICE

After a drug receives market approval, several factors affect how the drug is implemented in clinical practice. In the Stockholm healthcare region, the regional clinical recommendations of having apixaban as the preferred NOAC, had a large influence on the prescribing of NOACs (chapter 2.1). Before the recommendation, all NOACs were used equally, while three months after the recommendation, apixaban was used four times more often compared to dabigatran and rivaroxaban combined. We used an interrupted time series analysis to quantify the increase and found that five months after the recommendations, apixaban use was increased with 19.5%; 95% confidence interval (CI): 13.3 – 22.7. In patients initiated on antithrombotic therapy between March 2015 and February 2016, when NOACs were widely used in the Stockholm healthcare region, patients with high stroke and bleeding risks were more often prescribed low-dose aspirin or VKA treatment, instead of NOAC treatment, which is problematic given that aspirin treatment is less effective for stroke prevention (chapter 2.2).

The introduction of NOACs was accompanied by an overall better antithrombotic treatment in the Stockholm Healthcare region (chapter 2.3). Comparing a cohort of patients with AF from 2012 from the Stockholm Healthcare region, which was considered prior to the NOAC introduction, with a cohort from 2017, which was considered after the NOAC introduction, we found that treatment with oral anticoagulants increased from 51.6% to 73.8% of all patients with AF. This was accompanied by a stroke reduction of 42% without an increased bleeding risk. We found similar changes in treatment when repeating this study simultaneously in Stockholm, Denmark, Scotland, and Norway (chapter 2.4). However, the reduction in stroke rate was only present in Stockholm,

Denmark, and Norway, while in Scotland the stroke rate was higher after the NOAC introduction. Similarly, the bleeding rate was unchanged in Stockholm, Denmark, and Norway, while it was increased in Scotland.

Before a drug receives market approval, it is unknown how persistence and adherence to a treatment will be in clinical practice, especially not the long-term persistence and adherence. In the Stockholm Healthcare region, in patients with AF newly initiated with NOAC treatment, 70% was persistent after five years of follow-up, and 85% were on treatment during follow-up when including restarters (chapter 2.5). The medication possession rate (MPR) was approximately 90% in persistent patients. In addition, we used a case-control design to show that non-persistence and sub-optimal adherence (MPR ≤ 90%) to NOAC therapy were associated with an approximately two-fold increased risk for stroke. We used bone fractures and respiratory infections as falsification endpoints, to disentangle a potential "healthy-adherer" effect and found no significant association with any of these outcomes. Persistence and adherence were also high in five Western European healthcare settings (Stockholm, Denmark, Norway, Scotland, and Germany) (chapter 2.6). However, 20% of the patients did not have an MPR above 90%, implying sub-optimal stroke prevention in one out of five patients. In addition, both first year persistence and adherence were lower with dabigatran (persistence: 77%, adherence: 65%) compared to apixaban (86% and 75%) and rivaroxaban (83% and 75%) and were statistically lower after adjusting for patient characteristics. Adherence and persistence with dabigatran remained lower throughout follow-up.

IMPROVING THE SAFETY AND EFFECTIVENESS OF NOAC TREATMENT IN CLINICAL PRACTICE

In patients with AF at a moderate stroke risk (i.e., CHA_2DS_2-VASc of 1 for male patients and 2 for female patients), there are no clear recommendations whether to treat a patient with an oral anticoagulant or not. We found that NOAC treatment had a positive net clinical benefit compared to VKA treatment and no treatment in these patients from Stockholm, Denmark, Norway, and Scotland (chapter 3.1). This was mainly driven by the fact that NOAC treatment did not increase the risk for intracranial haemorrhage (ICH) (HR: 0.84; CI: 0.54-1.40) but reduced the risk for stroke compared to no treatment (HR: 0.72; CI: 0.56-0.94). VKA treatment also tended to reduce the risk for a stroke (HR: 0.81; CI: 0.59-1.09) but increased the risk for ICH (HR: 1.41; CI: 0.88-2.14), and therefore there was no net clinical benefit for VKA treatment compared to no treatment in this patient category. We used a modified intention to treat approach to capture a potential delay in starting treatment after a first AF diagnosis. We tested the robustness of this approach by using a classical intention to treat analysis and an on-treatment analysis, of which neither showed different results. In addition, several comorbidities of the CHA_2DS_2-VASc are potentially only captured in primary care and we did not have access to primary care data in Denmark, Norway, and Scotland. Therefore, we tested several algorithms in the Stockholm database, which did have access primary care data, to find additional diagnoses based on prescription data, in order to have as little misclassification as possible. In addition, we tested how results would differ in the Stockholm data by excluding data from primary care and found no different results.

Treatment with antidepressants is associated with an increased bleeding risk, as well as an increased stroke risk. In patients with AF from Stockholm, treated with either a VKA or a NOAC, there was a significantly increased bleeding risk in patients using concomitant antidepressant therapy (HR: 1.42; CI: 1.12-1.80), but not a significantly increased stroke risk (HR: 1.23; CI: 0.93-1.62) compared to patients without concomitant antidepressant use (chapter 3.2). Besides the main analysis using an adjusted Cox regression, we also performed a sensitivity analysis using a propensity score matched analysis and found similar results. To test for the potential of unmeasured confounding, we used falsification endpoints and former-user periods, both showing no signs for unmeasured confounding.

Treatment with a proton pump inhibitor (PPI) can reduce the risk for GIB while NOAC therapy is known to increase the risk of GIB. In patients with AF receiving NOAC therapy from Stockholm, Denmark, and the Netherlands, there was a reduced risk for upper GIB when using concomitant PPI therapy (incidence rate ratio (IRR): 0.75; CI: 0.59-0.95) (chapter 3.3). As PPI therapy may be intermittent, we used time-varying inverse-probability-weighted (IPW) Poisson regression to adjust for confounding. We accompanied this with a time-fixed IPW Poisson regression to account for potential reversed-causality and found no different results. We used falsification endpoints and calculated E-values to quantify potential unmeasured confounding and found no signs for unmeasured confounding.

Suffering from a stroke, an intracranial haemorrhage (ICH), or a GIB can be life-threatening. In patients with AF, the 90-day mortality after these were high in the Stockholm Healthcare region; 25.1% after an ischemic stroke, 31.6% after an ICH and 16.2% after a GIB (16.2%) (chapter 3.4). Patients receiving VKA treatment at the time of the ICH had a higher risk of dying compared to patients receiving NOAC treatment (HR: 1.36; CI: 1.04-1.78), which adds to the evidence that NOAC treatment is preferred over VKA treatment in stroke prevention in AF. We used an adjusted Cox regression model to adjust for differences in baseline comorbidities. We accompanied the main analysis with a propensity score matched analysis. In addition, we performed an array approach to quantify how large a residual confounder needed to be to cause the association and performed an asymmetrically trimmed propensity score matched analysis, which showed similar results and thus no signs of residual confounding.

PROPENSITY SCORE MATCHING IN PHARMACOEPIDEMIOLOGY

Greedy matching is one of the most frequently used algorithms for propensity score (PS) matching. In the systematic literature search, greedy matching was used in 71% of the selected studies (chapter 4.1). Most variations of the greedy matching algorithm are dependent on the random order in which subjects are sorter prior to matching. This random process introduces a variability when repeating the PS matching procedure. In small cohorts (500 subjects) the odds ratio after repeating the PS matching procedure 1000 times in the same cohort could range from 0.53 to 10.0, with an interquartile range of the 1000 odds ratios of 1.11 to 1.67 (chapter 4.1). However, this random variability appeared to be useful in a newly proposed matching procedure, in which greedy matching is repeated and the mean of the repeated matches is used as the final treatment-outcome

association. A Monte-Carlo simulation showed this method performed better than any standard propensity score matching procedure to which it was compared with by markedly increasing precision without increasing bias (chapter 4.2).

DISCUSSION

In observational studies, there are two ways to minimize the risk for confounding, namely through the design of a study and through the statistical adjustment, of which the former is the most important. In this thesis, numerous sensitivity analyses were performed to test to what extent our study results would have been affected by using a different statistical approach. In none of these analyses there were different findings when using an alternative statistical approach, indicating that choosing the right analytical approach is not that influential in the final study results if the right study design is used. On the other hand, the past has shown that biased study-designs can be the cause of much larger problems in observational research. Therefore, more focus on using unbiased study designs is needed, as this can influence study results to a much larger extent.

In this thesis, we have shown that it is possible to perform high-quality observational research in different countries, using a common data model and common protocol approach. Through this, sample sizes can be drastically increased, creating the opportunity to perform observational research on rare outcomes or in specific patient populations. In addition, combining results from different countries yields study results that can be generalizable towards other countries and patients. This thesis provides an example of a framework to systematically perform post-marketing observational studies in a European multi-database setting. This framework was proven to be useful for descriptive as well as association studies and was flexible enough to include a range of countries.

CONCLUSION

In conclusion, the studies in this thesis have added to the knowledge on the utilization, safety, and effectiveness of NOAC treatment in patients with AF. Almost a decade after the introduction of NOACs to the market, they are now widely being used in daily clinical practice throughout Europe and in most countries, this has contributed to an overall better stroke prevention. The studies in this thesis have contributed to the further improvement of the clinical knowledge on the safety and effectiveness of NOAC treatment in patients with AF. While doing so, this thesis provides an example of how post-marketing observational studies could, and potentially should, be conducted. The studies contained advanced methods and were performed in a multi-database setting, to provide answers to clinically relevant questions. The studies used a wide range of methods to handle confounding, accompanied by sensitivity analyses to test the robustness of these findings; these approaches and sensitivity analyses provide a framework for how to assess the use, safety, and effectiveness of new drugs in clinical practice on an international level.

6.2

NEDERLANDSE SAMENVATTING

INTRODUCTIE

In een gerandomiseerde gecontroleerde trial (RCT) bepaalt randomisatie welke patiënt welke behandeling krijgt. Daardoor is er geen verband tussen patiëntkarakteristieken en de keuze voor een behandeling en dus geen confounding bias. In observationeel onderzoek maakt de behandelend arts de keuze welke patiënt welke behandeling krijgt. Hierbij spelen patiëntkarakteristieken, terecht, juist wel een rol. Als de patiëntkarakteristieken die een rol spelen in de keuze voor een behandeling ook invloed hebben op het risico voor een uitkomst, is er sprake van confounding bias. Omdat RCTs door middel van randomisatie confounding bias voorkomen, zijn deze de gouden standaard om de effectiviteit en de veiligheid van een nieuw geneesmiddel te bepalen. Daarom zijn RCTs normaliter vereist voor een geneesmiddel wordt toegelaten op de markt.

Non-vitamine K-antagonisten orale anticoagulantia (NOACs) is een groep geneesmiddelen die recent het traject tot markttoelating op basis van RCTs hebben doorlopen. Hierna hebben verschillende observationele studies de effectiviteit en veiligheid in de klinische praktijk bevestigd. NOACs zijn een alternatief voor vitamine K-antagonisten (VKAs) in het voorkomen van beroertes bij patiënten met atriumfibrilleren (AF). Beide geneesmiddelgroepen werken door de stollingscascade te remmen wat heta\ risico op een beroerte verkleint, maar tegelijkertijd het bloedingsrisico vergroot.

Los van het feit dat resultaten van een RCT in de klinische praktijk door middel van observationeel onderzoek bevestigd dienen te worden, blijven er na een RCT nog onbeantwoorde vragen over. Ook die moeten door middel van observationeel onderzoek beantwoord worden. Het doel van dit proefschrift was daarom om het gebruik, de effectiviteit en de veiligheid van NOAC-behandeling in beroertepreventie bij patiënten met AF te bestuderen, gebruikmakend van geavanceerde farmaco-epidemiologische methoden.

DE INTRODUCTIE VAN NOAC-BEHANDELING IN DE KLINISCHE PRAKTIJK

Nadat een geneesmiddel op de markt is gekomen, spelen verschillende factoren een rol in de opname van het geneesmiddel in de klinische praktijk. In de provincie Stockholm had de publicatie van de lokale richtlijnen, die de voorkeur aan apixaban gaven, de grootste invloed op het voorschrijven van NOACs (hoofdstuk 2.1). Voordat deze richtlijnen gepubliceerd waren, werden alle drie de NOACs ongeveer in gelijke mate voorgeschreven. Drie maanden na publicatie werd apixaban echter vier keer zoveel voorgeschreven als beide andere NOACs samen. We hebben een *interrupted time series* analyse gebruikt om deze toename te kwantificeren en zagen dat vijf maanden na de publicatie van de richlijnen, apixabangebruik met 19,5% was toegenomen op een absolute schaal (95% betrouwbaarheidsinterval (BI): 13,3-22,7). Patiënten met een hoog beroerte- en bloedingsrisico die gestart waren met antistollingstherapie tussen maart 2015 en februari 2016, toen NOACs ruim onderdeel waren van klinische praktijk, kregen vaker aspirine of een VKA voorgeschreven dan een NOAC (hoofdstuk 2.2). Dit resultaat was zorgelijk, aangezien aspirine minder effectief is in het voorkomen van beroertes dan NOAC- of VKA-therapie.

De introductie van NOACs ging gepaard met een verbetering van de antistollingstherapie bij patiënten met AF in Stockholm (hoofdstuk 2.3). Bij vergelijking van een cohort van patiënten met AF uit 2012, beschouwd als een kalenderjaar vóór de NOAC introductie, met een cohort uit 2017, een kalenderjaar na NOAC introductie, zagen we een toename van de behandeling met orale anticoagulantia bij patiënten met AF van 51,6% naar 73,8%. Dit ging gepaard met een afname van beroertes van 42% zonder een toename in bloedingen. Bij herhaling van deze studie in Stockholm, Denemarken, Schotland en Noorwegen zagen we ook in deze landen een vergelijkbare verbetering in de antistollingstherapie (hoofdstuk 2.4). Echter, de afname van het aantal beroertes was alleen zichtbaar in Stockholm, Denemarken en Noorwegen, terwijl in Schotland het aantal beroertes hoger was na de NOAC-introductie. Iets vergelijkbaars was zichtbaar bij het aantal bloedingen; deze was onveranderd in Stockholm, Denemarken en Noorwegen, terwijl deze was toegenomen in Schotland.

Voordat een geneesmiddel toegang tot de markt krijgt, is het onbekend hoe de therapietrouw voor een geneesmiddel in de dagelijkse praktijk zal zijn. Therapietrouw kan opgesplitst worden in *adherence* en *persistence*. *Adherence* geeft aan in hoeverre een patiënt zich houdt aan de voorgeschreven dosering en *persistence* in hoeverre een patiënt doorgaat met het gebruiken van een geneesmiddel. Van de patiënten met AF uit de Stockholm regio die waren gestart met een NOAC, gebruikte 70% na vijf jaar onafgebroken een NOAC (de persistente gebruikers) en gebruikte 85% van de patiënten nog een NOAC als herstarters ook meegeteld werden (hoofdstuk 2.5). De *medication possession rate* (MPR), een maat om *adherence* te duiden, was ongeveer 90% onder patiënten die persistent waren met hun NOAC-therapie. Daarnaast vonden we in dezelfde studie, door middel van een patiënt-controle analyse, dat patiënten met slechte therapietrouw ongeveer twee keer zoveel risico hadden op het krijgen van een beroerte. De therapietrouw bleek ook hoog in vijf West-Europese landen bij herhaling van deze studie (Stockholm, Denemarken, Noorwegen, Schotland en Duitsland, hoofdstuk 2.6). Echter, 20% van de patiënten had een suboptimale therapietrouw, wat betekent dat één op de vijf patiënten geen optimale bescherming voor beroertes had. Zowel *persistence* als *adherence* was in het eerste jaar van behandeling lager onder patiënten die startten met dabigatran (*persistence:* 77%, *adherence:* 65%) ten opzichte van starters met apixaban (86% en 75%) en rivaroxaban (83% en 75%). Deze verschillen waren statistisch significant na het corrigeren voor verschillen in patiëntkarakteristieken. Zowel *persistence* als *adherence* met dabigatran bleef daarna ook lager gedurende de rest van de studie.

VERBETEREN VAN DE VEILIGHEID EN EFFECTIVITEIT VAN NOAC THERAPIE IN DE KLINISCHE PRAKTIJK

Voor patiënten met AF en een gematigd beroerterisico (dat wil zeggen een CHA_2DS_2-VASc-score van 1 voor mannelijke en 2 voor vrouwelijke patiënten) is er geen duidelijke aanbeveling in de richtlijnen over behandeling met orale anticoagulantia. Wij vonden dat behandeling met een NOAC een positief netto klinisch effect opleverde in vergelijking met behandeling met een VKA in deze patiëntengroep uit Stockholm, Denemarken, Noorwegen en Schotland (hoofdstuk 3.1). Dit kwam vooral doordat een NOAC-behandeling geen verhoogd risico gaf op intracraniale bloedingen

(*hazard ratio* (HR): 0,84; BI: 0,54-1,40), maar wel een verlaagd risico gaf op een beroerte (HR: 0,72; BI: 0,56-0,94) ten opzichte van geen behandeling. Behandeling met een VKA leek ook enigszins het beroerterisico te verlagen (HR: 0,81; BI: 0,59-1,09), maar verhoogde wel het risico op een intracaniale bloeding (HR: 1,41; BI: 0,88-2,14). Daardoor was er geen positief netto klinisch effect voor een VKA-behandeling ten opzichte van geen behandeling in deze patiëntengroep.

Behandeling met antidepressiva kan zowel het risico op bloedingen als beroertes verhogen. Patiënten met AF uit Stockholm die werden behandeld met een VKA of een NOAC hadden een significant verhoogd risico op het krijgen van een bloeding als deze patiënten gelijktijdig antidepressiva gebruikten (HR: 1,42; BI: 1,12-1,80), maar niet een significant verhoogd beroerterisico (HR: 1,23; BI: 0,93-1,62) (hoofdstuk 3.2). Extra waakzaamheid wordt daarom aangeraden bij patiënten die de combinatie van deze twee geneesmiddelen voorgeschreven krijgen.

Behandeling met een protonpompremmer, een zogenaamde PPI, kan het risico op een gastrointestinale bloeding (GIB) verkleinen, terwijl behandeling met een NOAC juist het risico op een GIB vergroot. Patiënten met AF uit Stockholm, Denemarken en Nederland die een NOAC gebruikten, hadden een lager risico op een GIB als deze patiënten gelijktijdig een PPI gebruikten (*incidence rate ratio* (IRR): 0,75; BI: 0,59-0,95) (hoofdstuk 3.3). De resultaten van deze studie laten zien dat het aan te bevelen kan zijn om een PPI voor te schrijven aan patiënten die een NOAC krijgen om het risico op een GIB te verkleinen.

PROPENSITY SCORE MATCHING IN FARMACO-EPIDEMIOLOGIE

Greedy matching is een van de meestgebruikte algoritmes voor *propensity score* (PS) matchen. In ons systematische literatuuronderzoek vonden we dat *greedy* matchen gebruikt werd in 71% van de geselecteerde studies (hoofdstuk 4.1). De meeste vormen van het *greedy matching* algoritme zijn afhankelijk van de willekeurige volgorde waarop eenheden worden gesorteerd voordat het matchen plaatsvindt. Deze willekeurige stap zorgt ervoor dat er variabiliteit in de resultaten kan komen wanneer de PS matchingsprocedure herhaald wordt. Wanneer de PS matchingsprocedure 1000 keer herhaald werd in hetzelfde cohort van 500 eenheden, was er een spreiding in de *odds ratios* van 0,53 tot 10,0, met een interkwartielafstand van 1,11 tot 1,67. Echter, deze spreiding bleek bruikbaar in een voorstel voor een nieuwe manier van matchen, waarbij *greedy* matchen herhaald wordt en de gemiddelde uitkomst na de herhaalde matches als uiteindelijke uitkomst wordt gebruikt. Met een Monte-Carlo simulatie hebben we laten zien dat deze nieuwe methode beter presteert dan elke standaard matchingmethode waarmee we het vergeleken hebben, met preciezere resultaten zonder de bias te vergroten (hoofdstuk 4.2).

DISCUSSIE

In observationale studies zijn er twee manieren om het risico op confounding zo klein mogelijk te maken, namelijk via de opzet van de studie en door statistische correctie, waarvan de eerstgenoemde de meest belangrijke is. In dit proefschrift hebben we een heel scala aan sensitiviteitsanalayses uitgevoerd om te testen in hoeverre onze studieresultaten anders waren geweest wanneer we een andere statistische analyse hadden gedaan. In geen van deze analyses

zagen we noemenswaardige verschillen, wat laat zien dat het kiezen van de juiste statistische analyse niet zo belangrijk is wanneer er al een juiste studie-opzet is gebruikt. Aan de andere kant zijn er vanuit het verleden talrijke voorbeelden die hebben laten zien dat een onjuiste studie-opzet kan leiden tot grote problemen in observationeel onderzoek. Daarom zou er veel meer focus moeten zijn op het kiezen van de juiste studie-opzet, aangezien dit veel grotere invloed heeft op de uiteindelijke studieresultaten.

In dit proefschrift hebben we laten zien dat het mogelijk is om observationeel onderzoek van hoge kwaliteit uit te voeren in verschillende landen, door gebruik te maken van een gemeenschappelijk datamodel en een gemeenschappelijk protocol. Hierdoor is het mogelijk om de patiëntaantallen in studies drastisch te vergroten, wat de mogelijkheid geeft om onderzoek te doen naar zeldzame uitkomsten of in specifieke populaties. Daarnaast zorgt het combineren van resultaten uit verschillende landen ervoor dat studieresultaten generaliseerbaar zijn naar andere landen en patiënten. Dit proefschrift geeft een voorbeeld hoe systematisch post-marketing observationeel onderzoek gedaan kan worden in een Europese multi-database setting. Deze aanpak is bruikbaar gebleken voor zowel beschrijvende observationele studies als geavanceerde associatiestudies en was flexibel genoeg om met data uit verschillende landen te werken.

6.2

CONCLUSIE

Concluderend hebben de studies in dit proefschrift bijgedragen aan de kennis over het gebruik, de veiligheid en de effectiviteit van NOAC-behandeling van patiënten met AF. Bijna een decenium na de introductie van NOACs op de markt, worden NOACs nu volop gebruikt in de klinische praktijk in Europa. In de meeste landen heeft dit geleid tot een betere beroertepreventie. Dit proefschrift kan als voorbeeld dienen hoe post-marketing observationeel onderzoek zou kunnen, en potentieel zou moeten, worden uitgevoerd. In de studies werden geavanceerde methodes toegepast in een multi-database setting om antwoord te geven op klinisch relevante vragen. De studies bevatten een breed scala aan methodes om met confounding bias om te gaan, samen met verschillende sensitiviteitsanalyses om de robuustheid van de resultaten te testen. Deze benaderingen en sensitiviteitsanalyses geven een voorbeeld van een aanpak voor het bepalen van gebruik, de veiligheid en de effectiviteit van een nieuw geneesmiddel in de klinische praktijk op een internationaal niveau.

6.3

SAMMANFATTNING PÅ SVENSKA

INTRODUKTION

I en randomiserad kontrollerad studie (RCT) avgör slumpen vilken patient som får vilken behandling. På det sättet finns det inget samband mellan patientens egenskaper och valet av behandling. I observationell forskning är det inte slumpen utan den behandlande läkaren som gör valet vilken patient som får vilken behandling. Patientens motivation, övriga sjuklighet och prognos kan spela en stor roll i dessa val. Om patientegenskaperna som spelar en roll i valet av behandling också påverkar risken för ett resultat, kallas detta "confounding bias". Eftersom RCT förhindrar confounding genom randomisering utgör de standarden för att bestämma effektivitet och säkerhet för ett nytt läkemedel. Därför krävs RCTinnan ett läkemedel tillåts på marknaden.

Icke-vitamin K-antagonist orala antikoagulantia (NOAC) är en grupp läkemedel som nyligen testats i stora randomiserade stuider, varefter de har godkänts på marknaden. Efter detta har flera observationsstudier bekräftat deras effektivitet och säkerhet i klinisk praxis. NOAC är alternativ till vitamin K-antagonister (VKA) vid förebyggande av stroke hos patienter med förmaksflimmer. Båda läkemedelsgrupperna fungerar genom att hämma koagulationskaskaden, vilket minskar risken för stroke, men ökar samtidigt risken för blödning.

Resultaten av en RCT kan undersökas i klinisk praxis med observationella studier. Dessutom finns det efter en RCT ofta obesvarade frågor kvar som också måste besvaras med hjälp av observationell forskning. Syftet med denna avhandling var att med avancerade farmakoepidemiologiska metoder studera användningen, effektiviteten och säkerheten av NOAC-behandling för att förebygga stroke hos patienter med förmaksflimmer.

INFÖRANDET AV NOAC-BEHANDLING I KLINISK PRAXIS

Efter att ett läkemedel har godkänts spelar flera faktorer en roll i läkemedlets upptagning i klinisk praxis. I Stockholmsregionen hade de lokala riktlinjerna, som rekommenderade apixaban, störst inflytande på förskrivningen av NOAC (kapitel 2.1). Innan dessa riktlinjer publicerades ordinerades alla tre NOAC-preparaten ungefär lika mycket. Tre månader efter publicering av de lokala riktlinjerna ordinerades apixaban fyra gånger så mycket som de två andra NOAC-preparaten tillsammans. Vi använde en s.k. "interrupted time series" tidsserieanalys för att kvantifiera denna ökning och fann att fem månader efter publiceringen av riktlinjerna ökade den asboluta användningen av apixaban med 19,5% (95% konfidensintervall (KI): 13,3-22,7). Hos patienter som påbörjade antikoagulantbehandling mellan mars 2015 och februari 2016, när NOAC ade börjat etablera sig i klinisk praxis, fick patienter med hög risk för stroke och blödning oftare ordinerat aspirin eller VKA istället för en NOAC (kapitel 2.2). Detta resultat var oroande, eftersom aspirin är mindre effektivt för att förhindra stroke än NOAC- eller VKA-behandling.

Introduktionen av NOAC åtföljdes av en förbättring av antikoagulantbehandling av förmaksflimmer i Stockholmsregionen (kapitel 2.3). När vi jämförde en kohort av patienter med förmaksflimmer 2012, d.v.s. före NOAC-introduktionen, med en kohort från 2017, d.v.s. efter NOAC-introduktionen, såg vi en ökning av oral antikoagulantbehandling hos patienter med förmaksflimmer från 51,6% till 73,8%. Detta var associerat med en minskad risk för ischemisk stroke med 42% utan ökad risk för blödning. Efter att ha upprepat denna studie i Stockholm, Danmark,

Skottland och Norge såg vi en liknande förbättring av antikoagulantbehandling (kapitel 2.4). Minskningen av antalet stroke var dock bara synlig i Stockholm, Danmark och Norge, medan i Skottland var risken för ischemisk stroke något högre efter NOAC-introduktionen. På liknande sätt var det för allvarliga blödningar; risken var oförändrad i Stockholm, Danmark och Norge medan den hade ökat i Skottland.

När ett läkemedel blivit godkänt är det fortfarande okänt hur behandlingen kommer att fungera i daglig praxis. Följsamheten till behandling kan definieras som adherens och persistens. Adherens är i vilken utsträckning en patient tar den föreskrivna dosen och persistens i vilken utsträckning en patient fortsätter att använda ett läkemedel. Hos patienter med förmaksflimmer i Stockholmsregionen som började med NOAC använde 70% NOAC kontinuerligt i fem år medan 85% av patienterna använde någon NOAC (inkluderat de som hade avbrutit och senare återupptagit behandling) (kapitel 2.5). "Medication possession rate" (MPR), ett mått på adherens, var cirka 90% hos de patienter som var persistenta med sin NOAC-behandling. Genom en fallkontrollanalys fann vi i samma studie att patienter med dålig adherens hade ungefär dubbelt så stor risk för stroke. Adherensen var också hög i fem västeuropeiska länder när denna studie upprepades (Stockholm, Danmark, Norge, Skottland och Tyskland) (kapitel 2.6). 20% av patienterna hade dock suboptimal följsamhet, vilket innebär att en av fem patienter inte hade optimalt strokeskydd. Både persistens och adherens var lägre under det första behandlingsåret hos patienter som startade dabigatran (persistens: 77%, adherens: 65%) jämfört med apixaban (86% och 75%) och rivaroxaban (83% och 75%). Dessa skillnader var statistiskt signifikanta efter justering för skillnader i patientegenskaper. Både persistens och adherens med dabigatran förblev lägre under hela studietiden.

SÄKERHET OCH EFFEKT MED NOAC-BEHANDLING I KLINISK PRAXIS

För patienter med förmaksflimmer och måttlig strokerisk (dvs. CHA2DS2-VASc-poäng 1 för manliga och 2 för kvinnliga patienter) finns det ingen tydlig rekommendation i riktlinjerna avseende behandling med orala antikoagulantia. I en studie med patienter från Stockholm, Danmark, Norge och Skottland fann vi att behandling med NOAC medförde en positiv klinisk nytta jämfört med behandling med VKA i denna patientgrupp (kapitel 3.1). Detta berodde främst på att NOAC-behandling inte ökade risken för intrakraniell blödning (HR: 0,84; KI: 0,54-1,40) men resulterade i en minskad risk för ischemisk stroke (HR: 0,72; KI: 0,56-0,94) jämfört med ingen behandling. VKA-behandling tycktes också minska risken för stroke (HR: 0,81; CI: 0,59-1,09) men ökade risken för intrakaniell blödning (HR: 1,41; CI: 0,88-2,14), vilket inte resulterade i någon positiv nettoeffekt för VKA-behandling jämfört med ingen behandling i denna patientgrupp.

Behandling med antidepressiva medel kan öka risken för både blödning och ischemisk stroke. Hos patienter med förmaksflimmer i Stockholm som behandlades med VKA eller NOAC fanns det en signifikant ökad blödningsrisk när dessa patienter hade samtidig antidepressiva medel (HR: 1,42; KI: 1,12-1,80) men inte en signifikant ökad risk för ischemisk stroke (HR: 1,23; CI: 0,93-1,62) (kapitel 3.2). Extra uppmärksamhet rekommenderas därför hos patienter som ordineras kombinationen av dessa två läkemedelsgrupper.

Behandling med en protonpumpshämmare (PPI) kan minska risken för gastrointestinal blödning, medan behandling med NOAC ökar risken. Hos patienter med förmaksflimmer från Stockholm, Danmark och Nederländerna som använde en NOAC var det en lägre risk för en gastrointestinal blödning om dessa patienter samtidigt använde PPI (incidens rate ratio (IRR): 0,75; KI: 0,59-0,95) (kapitel 3.3). Resultaten av denna studie visar att man kan rekommendera PPI för att minska risken för gastrointestinala blödningar hos NOAC-behandlade patienter.

PROPENSITY SCORE MATCHNING INOM FARMAKO-EPIDEMIOLOGIN

En av de mest använda algoritmerna för matchning med propensity score är s.k. "greedy" matchning. I vår systematiska litteraturöversikt fann vi att greedy matchning användes i 71% av de utvalda studierna (kapitel 4.1). De flesta former av denna matchningsalgoritmen beror på den slumpmässiga ordning i vilken observationerna sorteras innan matchningen äger rum. Detta slumpmässiga steg ger variation i resultaten när PS-matchningsproceduren upprepas. När PS-matchningsproceduren upprepades 1000 gånger i samma kohort med 500 observationer varierade oddskvoterna från 0,53 till 10,0, med ett interkvartilintervall mellan 1,11 och 1,67. För att hantera denna spridning föreslår vi ett nytt sätt att matcha observationer, där greedy matchning upprepas och det genomsnittliga resultatet efter de upprepade matcherna används som slutresultat. Med en Monte-Carlo-simulering visade vi att denna nya metod överträffar alla standardmatchningsmetoder som vi jämförde med mer exakta resultat utan ökad bias (kapitel 4.2).

DISKUSSION

I observationella studier finns det två sätt att minimera risken för bias, nämligen genom god studiedesign och genom statistisk korrigering, varav det första är det viktigaste. I denna avhandling utförde vi en mängd känslighetsanalyser för att testa i vilken utsträckning våra studieresultat skulle ha varit annorlunda om vi hade gjort en annan statistisk analys. Ingen av dessa analyser visade signifikanta skillnader, vilket talar för att valet av statistisk analys inte är så viktigt när en korrekt studiedesign redan har använts. Å andra sidan finns det många tidigare exempel som har visat att en felaktig studiedesign kan leda till stora problem inom observationell forskning. Därför bör det vara mycket mer fokus på att välja rätt studiedesign, eftersom detta har en mycket större inverkan på de slutliga studieresultaten.

I denna avhandling visade vi att det är möjligt att utföra högkvalitativ observationell forskning i olika länder med hjälp av en gemensam datamodell och ett gemensamt protokoll. Detta gör det möjligt att drastiskt öka antalet patienter i studier, vilket ger möjlighet att undersöka sällsynta resultat eller resultat i specifika populationer. Dessutom säkerställer kombinationen av resultat från olika länder att studieresultaten kan generaliseras till andra länder och patienter.

Denna avhandling ger ett exempel på hur introduktionen av nya läkemedel systematiskt kan studeras i ett flertal europeiska länder som har liknande databaser med observationella metoder. Detta arbetssätt har visat sig vara användbart för både beskrivande och

avancerade associeringsstudier och var tillräckligt flexibelt för att inkorporera data från olika länder i samma analyser.

SLUTSATS

Sammanfattningsvis har de studier som presenterats i denna avhandling bidragit till förståelsen för användning, säkerhet och effektivitet med NOAC-behandling hos patienter med förmaksflimmer. Nästan ett decennium efter marknadsintroduktionen av NOAC används NOAC nu i stor utsträckning i klinisk praxis i Europa. I de flesta länder har detta resulterat i bättre förebyggande av stroke. Denna avhandling ger ett exempel på hur observationell forskning av nya läkemedel kan, och möjligen även bör, bedrivas. Studierna tillämpade avancerade metoder i stora databaser från ett eller flera europeiska länder för att svara på kliniskt relevanta frågor. Studierna inkluderade en mängd olika metoder för att hantera confounding tillsammans med olika känslighetsanalyser för att testa resultatens robusthet. Dessa tillvägagångssätt och känslighetsanalyser ger exempel på ett ramverk för att undersöka användning, säkerhet och effektivitet av nya läkemedel i klinisk praxis på internationell nivå.

6.4

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ABOUT THE AUTHOR

Joris Jan Komen was born on September 21st, 1990 in 's-Hertogenbosch and currently lives in Amsterdam. He obtained his master's degree in Pharmacy from Utrecht University in 2017 (cum laude). He performed his master's thesis at the Karolinska Institutet in Stockholm, which formed the basis for his PhD-project.

Joris started his PhD at the Division of Pharmacoepidemiology and Clinical Pharmacology at Utrecht University, in a collaboration with the Karolinska Institutet and the Stockholm County Council, under the supervision of Aukje Mantel-Teeuwisse, Olaf Klungel, Tomas Forslund, and Björn Wettermark. His research focussed on the utilization, safety, and effectiveness of anticoagulant therapy in patients with atrial fibrillation. He started his PhD project by performing studies in the Stockholm Healthcare Database, after which he set-up and led a collaboration between five universities from Sweden, Denmark, Norway, Scotland, and Germany to perform several international studies. During his PhD, he obtained his postgraduate master's degree in Epidemiology from the Julius Centre, University Medical Centre Utrecht (cum laude).

Joris won the yearly Utrecht Institute for Pharmaceutical Sciences (UIPS) PhD competition in 2019 and the Stanley A. Edlavitch for best rated abstract at the International Conference for Pharmacoepidemiology in 2020. He presented his research on several occasions, such as the European Society for Cardiology Conference and the International Conference for Pharmacoepidemiology. At the latter, he also organised a symposium, served as a moderator, and was a teacher in a pre-conference course. In addition, he was an invited speaker at several post-academic courses on anticoagulant therapy for the Royal Dutch Pharmacists Association (KNMP).