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Title

Risk factors for stroke and choice of oral anticoagulant in atrial fibrillation

Authors

Lars J Kjerpeseth, MD[1], Hanne Ellekjær, MD, PhD[2,3], Randi Selmer, PhD[4], Inger Ariansen, MD, PhD[4], Kari Furu, MPH, PhD[4], Eva Skovlund, PhD[1,4]

[1] Department of Public Health and Nursing, Norwegian University of Science and Technology, Trondheim, Norway

[2] Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway

[3] Stroke Unit, Department of Internal Medicine, St. Olav's Hospital, Trondheim, Norway

[4] Department of Chronic Diseases and Ageing, Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway

Abstract

Purpose To investigate risk factors for stroke in patients initiating oral anticoagulants for atrial fibrillation in Norway and their association with receiving DOACs versus warfarin.

Methods From nationwide registries we identified naïve users initiating treatment with warfarin, dabigatran, rivaroxaban or apixaban for atrial fibrillation from 2010 to 2015 in Norway. We studied temporal changes in the CHA_2DS_2-VASc score and its component risk factors. We used multiple logistic regression to identify CHA_2DS_2-VASc risk factors associated with receiving DOACs versus warfarin in 2015.

Results From 2010 to 2015, the yearly number of new oral anticoagulant users increased from 7588 to 13344. All new users initiated warfarin in 2010, while 86% initiated a DOAC in 2015. The mean CHA_2DS_2-VASc score decreased from 3.2 (SD 1.7) to 3.1 (SD 1.6) in the same period. Vascular disease (0.56 [0.49-0.63]), congestive heart failure (OR 0.65 [95% CI 0.58-0.72]) and diabetes (0.83 [0.73-0.95]) decreased the odds of receiving DOACs instead of warfarin, and ischemic stroke/transient ischemic attack/arterial thromboembolism (1.31 [1.12-1.54]), age 65-74 (1.23 [1.06-1.43]) and female sex (1.22 [1.10-1.36]) increased it. Age ≥75 (reference age <65) and hypertension had no impact.

Conclusions The uptake of DOACs was rapid and spurred an increase in new users of oral anticoagulants for atrial fibrillation from 2010 to 2015 in Norway. The mean CHA_2DS_2-VASc score did not change substantially during this period. Vascular disease, heart failure and diabetes were associated with initiation of warfarin, and previous stroke, age 65-74 and female sex with initiation of DOACs.

Keywords

Atrial fibrillation, anticoagulation treatment, risk factors, stroke

Word count

Main text excluding abstract, tables, figure legends and references: 3669.
Abstract: 245.

Introduction

Atrial fibrillation is associated with an elevated stroke risk [1]. Depending on the presence of other risk factors for stroke, the absolute stroke risk can vary 20-fold between patients [2]. Clinical risk assessment tools such as the $CHADS_2$ score (congestive heart failure, hypertension, age >75, diabetes, stroke [doubled]) and the more recent CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke/transient ischemic attack/arterial thromboembolism [doubled], vascular disease, age 65–74, and sex category [female]) are commonly used to predict the risk of stroke and systemic embolism in individual patients; a higher score associated with a higher risk [3,4].

The $CHADS_2$ scheme was introduced in the 2006 joint guidelines on atrial fibrillation by the American College of Cardiology, the American Heart Association and the European Society of Cardiology [5], and in the 2010 guidelines by the European Society of Cardiology it was endorsed as the primary tool to assess stroke risk in patients [6]. The 2010 guidelines further recommended oral anticoagulation for patients with valvular heart disease or a $CHADS_2$ score of ≥2, or additional risk stratification with the CHA_2DS_2-VASc score if the patient had a $CHADS_2$ score of 0-1. Oral anticoagulation or aspirin was recommended with a CHA_2DS_2-VASc score of 1, with a preference for the former except in women (were aspirin was slightly preferred). For a CHA_2DS_2-VASc score of 0, aspirin or no antithrombotic therapy was recommended, with a preference for the latter. The updated 2012 European Society of Cardiology guidelines recommending oral anticoagulation for $CHAD_2S_2$-VASC ≥2 in women and ≥1 in men were incorporated into Norwegian national guidelines in 2013 [7,8], thereby potentially increasing the target population for treatment [9].

Oral anticoagulation was traditionally synonymous with vitamin K antagonists such as warfarin which has been demonstrated to reduce the stroke risk by two-thirds [10]. Since 2009, the direct-acting oral antagonists (DOACs) dabigatran, rivaroxaban, apixaban and edoxaban have proven at least as effective and safe as warfarin for stroke prevention in non-valvular atrial fibrillation in large randomized trials [11-14]. In 2010 dabigatran, and in 2012 rivaroxaban and apixaban, were introduced in the European guidelines as alternatives to vitamin K antagonists for non-valvular atrial fibrillation [6,7]. Dabigatran, rivaroxaban and apixaban were authorized for non-valvular atrial fibrillation in August 2011, December 2011 and November 2012, respectively. Preapproved reimbursement for atrial fibrillation was granted for dabigatran and rivaroxaban in January 2013 and for apixaban in July 2013. A shift from warfarin to DOACs for anticoagulation in atrial fibrillation from 2010 to 2015 has been seen in Norway [15].

Following these major treatment changes, we set out to investigate the stroke risk profile in patients starting on one of the four oral anticoagulants commonly available in Norway during this period; warfarin, dabigatran, rivaroxaban and apixaban.

Materials and methods

Data sources

We used nationwide data from the Norwegian Prescription Database, the Norwegian Patient Registry and the National Registry. The latter administrates the national identification number unique to all Norwegian residents together with information on birth year, sex and date of emigration, death and other changes in resident status. The Norwegian Prescription Database has complete coverage of all prescriptions filled at Norwegian pharmacies since 2004 by non-institutionalized individuals, including national ID number, drug, dispensing date and reimbursement code. The prescriber applies for reimbursement from a list of preapproved indications kept for each drug and coded according to the International Classification of Diseases, 10th revision (ICD10) and the International Classification of

Primary Care, 2nd Edition (ICPC2). Most drugs have preapproved reimbursement for one or more chronic conditions. If the indication is not preapproved, or the drug does not have marketing authorization, the prescriber can apply for reimbursement and/or use of the drug on a case-by-case basis. The Norwegian Patient Register includes information on up to two primary and nineteen secondary ICD10 discharge diagnosis codes made at government-funded in- and outpatient visits at hospitals and private specialist practices since 2008, together with the national ID number.

Study population

We received an encrypted version of the datasets. We excluded individuals that did not match the person-identifier in the National Registry or that could not be tracked (e.g. citizens living abroad). We then identified all adult oral anticoagulant-naïve users with at least one dispensing of an oral anticoagulant for atrial fibrillation from 2010 to 2015. Naïve users meant that no vitamin K antagonist, direct thrombin inhibitors or direct factor Xa inhibitors had been dispensed from 2004 until the first dispensing of either warfarin, dabigatran, rivaroxaban or apixaban. We will refer to the date of the first dispensing as the index date. Inclusion criteria were a reimbursement code for atrial fibrillation/-flutter and age 18 years or older when the drug was dispensed. We excluded individuals who received more than one type of oral anticoagulant on index date.

Defining risk factors for stroke

We calculated age as year of oral anticoagulant dispensing minus birth year. We used diagnoses up to 730 days before or on index date from the Norwegian Patient Register and defined concomitant medicine use as drugs dispensed up to 365 days before or on index date. We defined hypertension as concomitant use of blood pressure medication with reimbursement code for hypertension, diabetes as concomitant use of anti-diabetic drugs, and congestive heart failure, vascular disease and ischemic stroke, transient ischemic attack or arterial thromboembolism as concomitant use of relevant drugs with reimbursement code for one of the conditions or a previous discharge diagnosis of one of the conditions. We defined arterial thromboembolism as embolism or thrombosis in the aorta, iliac artery or the extremities, and vascular disease as the presence of ischemic heart disease, atherosclerosis, peripheral vascular disease, aortocoronary bypass graft or coronary, peripheral or other intravascular prosthesis. See Supplementary Table 1 for further details.

Statistical analyses

We estimated the $CHADS_2$ and the CHA_2DS_2-VASc score for each study participant at index date. Using descriptive statistics, we describe patterns of CHA_2DS_2-VASc score and its component risk factors for stroke among new users according to year and oral anticoagulant dispensed. We first give an overview of changes from 2010 to 2015 and then focus on 2015 to get the most updated and settled picture of prescribing practices since the DOACs probably would have become familiar to most prescribers towards the end of follow-up. We used multiple logistic regression analyses to estimate odds ratios (OR) with 95% confidence intervals (CI) of being initiated on dabigatran, rivaroxaban or apixaban compared to warfarin according to the CHA_2DS_2-VASc component risk factors for stroke. The analyses were adjusted for the other risk factors making up the score. We considered p-values <0.05 as statistically significant. As a sensitivity analysis, we repeated the logistic regression analyses without restricting diagnosis codes from the Norwegian Patient Registry to 730 days before index date, thus including diagnoses recorded since 2008. We used Stata/SE version 15.0 to analyze the data.

Ethical considerations

The Regional Committee for Medical and Health Research Ethics in Central Norway approved the study protocol before the study commenced. The Norwegian Data Protection Authority gave a license to link registry data.

Results

Trends over time

We identified 62865 individuals naïve for oral anticoagulant who filled a first prescription for warfarin, dabigatran, rivaroxaban or apixaban for atrial fibrillation from 1 January 2010 to 31 December 2015 (Supplementary Figure 1). Cohort characteristics according to the year of first use are described in Table 1. The number of new users increased nearly each year, with an especially prominent increase from 2012 to 2013. The share of new oral anticoagulant users who started on warfarin decreased from ~100% in 2010 to 14% in 2015. Apixaban was the most frequently initiated oral anticoagulant in 2015, dabigatran the least.

The mean age increased slightly during follow-up, from 73.2 years in 2010 to 73.9 years in 2015. In the same period, the share of new users aged 65-74 years increased slightly, mainly at the expense of the share <65 years. The percentage of female users rose somewhat also. Among the pre-existing diseases predisposing for stroke, the prevalence remained relatively stable for diabetes and previous ischemic stroke, TIA or arterial thromboembolism throughout the study period, while the prevalence of congestive heart failure, hypertension and vascular disease decreased. The mean and median $CHADS_2$ and CHA_2DS_2-VASc score remained stable. However, the percentage of patients with a $CHADS_2$ score of 0-1 increased from 44% in 2010 to 47% in 2015. Of note, a growing majority of these patients received ≥2 points in the CHA_2DS_2-VASc scheme (62% in 2010 and 66% in 2015).

Differences between initiators of warfarin, dabigatran, rivaroxaban and apixaban

In 2015, the number of new oral anticoagulant users was 13344 (Table 2). The prevalence of risk factors for stroke varied for patients starting the different oral anticoagulants. Dabigatran and rivaroxaban users were generally younger and healthier with a lower CHA_2DS_2-VASc score than users of warfarin and apixaban. Men starting dabigatran and rivaroxaban had a lower median score (median 2) than the men initiating warfarin or apixaban (median 3). Women scored a median of CHA_2DS_2-VASc points across all four oral anticoagulants (Supplementary Figure 2).

Apixaban was the most frequently prescribed oral anticoagulant regardless of the individual stroke risk factors (Table 2) and CHA_2DS_2-VASc score (Figure 1). The percentage who initiated apixaban, and to some degree warfarin, increased with higher CHA_2DS_2-VASc score. Conversely, the percentage who started dabigatran decreased with a higher score. A score of 3 was most common, and only eight users scored 9.

Of the risk factors, the prevalence of hypertension ranked highest and a history of ischemic stroke, transient ischemic attack or arterial thromboembolism lowest (Table 2). Multiple logistic regression analyses of the association between each risk factor constituting the CHA_2DS_2-VASc and the choice of DOAC versus warfarin, revealed that in 2015 patients with vascular disease or congestive heart failure had increased odds of receiving warfarin rather than dabigatran, rivaroxaban, apixaban or DOACs combined compared to patients without these risk factors (Figure 2). Age 65-74 (reference age <65), increased the odds of initiating dabigatran, rivaroxaban, apixaban and DOACs combined instead of warfarin. An age of ≥75 tended to favor apixaban and disfavor dabigatran and rivaroxaban instead of warfarin (reference age <65), but the associations were not statistically significant. A history of

ischemic stroke, transient ischemic attack or arterial thromboembolism was significantly associated with receiving DOACs combined, but this finding was driven by a significant association with apixaban only. Women had higher odds than men of receiving rivaroxaban, apixaban and DOACs combined, but not dabigatran, rather than warfarin. Diabetes mellitus skewed the odds towards initiating warfarin instead of a DOAC, although the results were only statistically significant for rivaroxaban and DOACs combined versus warfarin. Preexisting hypertension did not play a substantial role in the decision between a DOAC versus warfarin.

Sensitivity analyses included diagnosis codes from the Norwegian Patient Register since 2008 instead of the last 730 days before index date in the risk factor definitions (Supplementary Table 1). They revealed comparable results, except for a slightly stronger effect of diabetes mellitus (Supplementary Figure 3).

Discussion

In this population-based cohort study, we compared current guideline-recognized risk factors for stroke in atrial fibrillation patients initiating dabigatran, rivaroxaban or apixaban versus warfarin. In addition to the observed increase in total number of new oral anticoagulant users almost every year from 2010 to 2015, the percentage of the new users initiating a DOAC increased yearly also (reaching 86.3% in 2015). The increase in new users was particularly large from 2012 to 2013, possibly spurred by the introduction of DOACs, the use of which also increased abruptly in 2013. The transition from $CHADS_2$ to CHA_2DS_2-VASc for stroke risk assessment could also have increased the share of atrial fibrillation patients that were anticoagulated [9]. Supporting this view, we observed an increase in the percentage of users with a $CHADS_2$ score of 0-1, who would be considered to have a low to moderate stroke risk according to the old scheme, and most of these users qualified for a high stroke risk score of ≥2 in the newer CHA_2DS_2-VASc scheme.

The reasons for apixaban's quick ascend as the preferred DOAC in Norway from 2013 to 2015, especially at the expense of dabigatran, are somewhat elusive since neither the European nor the Norwegian guidelines gave preference to any DOAC over the others [7,8]. A similar trend has been observed in neighboring countries [16,17]. Perhaps dabigatran's renal clearance of 80%, much higher than rivaroxaban's 35% and apixaban's 25% [18], discouraged its use in the often elderly atrial fibrillation patients who can have multiple comorbidities and concomitant drug therapies. Marketing and key opinion leaders could also have influenced the prescribing patterns.

Prescribers and patients discussing the pros and cons of an oral anticoagulant were perhaps motivated by the DOACs ease of use and fewer food and drug interactions compared to warfarin [11-13]. In a small retrospective Canadian study, perceptions of fewer side effects (by the patient) and superior efficacy (by the physician) were strongly associated with using a DOAC instead of warfarin in atrial fibrillation [19]. Citing a net clinical benefit, the 2012 update to the European guidelines gives DOACs a slight preference over vitamin K antagonists for stroke prevention in most non-valvular atrial fibrillation patients [7].

Increased odds of selecting a DOAC compared to warfarin for patients with a history of ischemic stroke, transient ischemic attack or arterial thromboembolism is seen in the present study and other studies [20-24], albeit not consistently [25-27]. This was perhaps motivated by the lower rates of ischemic and unspecified strokes reported with rivaroxaban, apixaban and high-intensity dabigatran (150 mg twice daily) compared to warfarin in non-valvular atrial fibrillation in clinical trials [11-13]. While this effect was only significant for the latter

combination, it is somewhat outweighed by the non-significantly higher rates seen for low-intensity dabigatran (110 mg twice daily) [11].

The proportion aged 65 to 74 years when initiating oral anticoagulation increased from 29% in 2010 to 33% in 2015, while the proportion younger than 65 years and older than 74 years declined by about 3% and 1%, respectively. This may have been driven by the replacement of the $CHADS_2$ scheme with the CHA_2DS_2-VASc scheme for stroke risk assessment, thus emphasizing age 65-74 years as a risk factor [3]. In the current study, we found that patients aged 65-74 years were more likely than younger patients to initiate a DOAC rather than warfarin. Age ≥75 years (reference age <65 years) seemed to favor apixaban and disfavor the other DOACs instead of warfarin, but the associations were not statistically significant. The latter result is in concordance with expert reviews finding apixaban the most beneficial oral anticoagulant in the elderly; the other DOACs were either ranked similarly to warfarin or preferred to it [28,29]. Two contemporary studies reported that in Denmark the odds of initiating rivaroxaban and apixaban increased incrementally with age 65-74 years and ≥75 years, while the trend was opposite for dabigatran [17,20].

Female sex drove the choice of oral anticoagulant from warfarin towards rivaroxaban, apixaban and DOACs combined in the present study, and men had equal odds as women of receiving dabigatran instead of warfarin. Other Nordic registry studies report similar findings [20,21,30]. However, no or a negative predictive effect of female sex on selecting DOACs versus warfarin have been described in other regions [24,26,31,32] and in a global study [25]. Favoring DOACs in female patients is in line with a meta-analysis of clinical trials that found that compared to men women have fewer bleeding complications on DOACs and higher rates of stroke and systemic embolism on warfarin [33].

Congestive heart failure decreased the odds of receiving DOACs instead of warfarin in the current study. Most studies describe a similar result as the present study [21,23,26,27,34], but a few find no effect [22,25]. Gundlund et al. reported that heart failure lowered the odds of receiving dabigatran and rivaroxaban, but not apixaban, compared to vitamin K antagonists in Denmark [20]. In another study based on the Norwegian Prescription Database, concomitant use of digoxin or diuretics, both typically prescribed in heart failure, increased the odds of receiving warfarin instead of a DOAC in atrial fibrillation [30].

Although heart failure is not a contraindication for DOACs, a preference for warfarin could have been motivated by heart failure caused or augmented by valvular heart disease, which coexists in ~30% of atrial fibrillation patients [18,35]. Unlike warfarin, DOACs are only approved for so-called ‘non-valvular’ atrial fibrillation. While this term is not meant to exclude milder forms of valvular heart disease, this might be exactly what is happening in clinical practice since a clear distinction between the ‘non-valvular’ and ‘valvular’ terms does not exist even among highly specialized cardiologists [36]. These historic terms have been replaced by more specific terms in the 2016 European guidelines on atrial fibrillation [18]. Of note, since we lacked information on procedures such as heart valve replacement, we were not able to exclude patients with valvular disease from the study population.

It has been suggested that prescribers are more cautious of prescribing DOACs to the most vulnerable patients [22]. The presence of multimorbidity, high bleeding risk, frequent falls and polypharmacy, could favor warfarin since it allows personalized dosing, compliance can be monitored, drug interactions are well-established, and a specific antidote was available at the time of the study (unlike DOACs). Diabetes mellitus, like heart failure, vascular diseases and hypertension, is associated with frailty [37]. Thus, an accompanying frailty might explain why diabetes mellitus increase the odds of receiving warfarin instead of DOACs in the current study. Adding to this could be the presence of diabetic nephropathy, which would disfavor

the more renally straining DOACs. However, the results are conflicting regarding this covariate; some report similar findings as the current study [23-25], other find no effect of diabetes mellitus [20-22].

An underlying frailty might also explain why patients with vascular disease have higher odds than their counterparts to receive warfarin rather than DOAC in the current and other studies [19,20,27,25,22,21,23,31]. However, prescribers could also have been motivated by concerns about the risk of coronary disease in patients treated with DOACs, which were signaled by a (non-significantly) higher rate of myocardial infarction with dabigatran than with warfarin in the RE-LY trial [11], possibly relayed through a protective effect of warfarin [38]. In an expert opinion and review in 2016, Caldeira et al. reported that the best available data from both clinical trials and observational studies do not support the claim of an unfavorable coronary profile of DOACs, however a definitive conclusion could not be made, especially regarding dabigatran [39]. Similarly, the lack of routines and studies on the use of DOACs in the presence of platelet inhibition in vascular disease could have motivated the selection of warfarin. Of note, the increased bleeding risk with dual or triple antithrombotic therapy can be attenuated by dosing warfarin at the lower therapeutic range.

We found no association between hypertension, or more specifically the dispensing of antihypertensives, and initiation of DOACs versus warfarin, which is line with other Nordic registry studies [20,21,30] and an expert review by Diener et al. that does not give preference to a particular DOAC in hypertension [29]. We observed a slight decline in the prevalence of hypertension from 2010 to 2015, which is consistent with a trend of falling blood pressures in the general population in Norway [40].

A limitation of our study is the use of reimbursement codes to identify atrial fibrillation as the indication for initiation of oral anticoagulation. Validation studies on the reimbursement codes' ability to identify the actual indication of drugs dispensed in Norway have not been conducted to our knowledge. Unlike DOACs, warfarin can be reimbursed for ischemic heart disease, valvular disease and strokes in patients with coexisting atrial fibrillation, potentially resulting in selection bias. On the other hand, since reimbursement codes are used by all prescribers, the study cohort includes patients initiated on an oral anticoagulant by physicians in hospitals and private specialist practices as well as patients that were diagnosed and treated by their general practitioner only. Coupled with the nationwide coverage of our study, this ensures the inclusion of a wide range of patients from clinical practice.

The Norwegian Prescription Database does not register medicines used by patients in institutions. Therefore, our analyses are restricted to a non-institutionalized population, excluding for example permanent residents of nursing and retirement homes. In most Norwegian municipalities, general practitioners treat residents of local nursing and retirement homes in addition to patients of routine clinical practice. The effect of any risk factors for stroke on the prescription patterns would probably be similar irrespective of whether these general practitioners treat patients who are institutionalized or not. Hence, we believe our results are generalizable to residents of nursing and retirement homes.

We do not have information on other risk factors for stroke that might affect which oral anticoagulant is opted for, such as creatinine clearance, socioeconomic status and level of education, consumption of alcohol, tobacco and illegal drugs, race and ethnicity, and family history of stroke. However, the effect some of these factors have on prescribing is hopefully attenuated by the universal health care system in Norway. While oral anticoagulants are only partially reimbursed, individual total yearly medical expenses are capped, meaning the personal financial burden of the costlier DOACs is the same as for warfarin.

Conclusion

The uptake of DOACs was rapid and spurred an increase in new users of oral anticoagulants for atrial fibrillation from 2010 to 2015 in Norway. The mean CHA_2DS_2-VASc score did not change substantially during this period. Vascular disease, heart failure and diabetes were associated with initiation of warfarin, and previous stroke, age 65-74 and female sex with initiation of DOACs.

Authors' contribution

LJK did the analyses and wrote the manuscript. All authors helped plan and design the study, interpret findings, revise the manuscript, and approved the final version of the manuscript.

Conflict of interest statement

None to declare.

Disclaimer

Data from the Norwegian Patient Register has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Register is intended nor should be inferred.

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Table 1 Characteristics of new users of warfarin, dabigatran, rivaroxaban or apixaban for atrial fibrillation from 2010 to 2015 in Norway

Year	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
All	n=7588	n=8605	n=8476	n=12080	n=12772	n=13344
Oral anticoagulant (%)						
Warfarin	7583 (~100)	8582 (~100)	8441 (~100)	4697 (39)	3127 (24)	1826 (14)
Dabigatran	5 (<1)	23 (<1)	28 (<1)	4141 (34)	3113 (24)	1171 (9)
Rivaroxaban	0 (<1)	0 (<1)	7 (<1)	2888 (24)	3085 (24)	3428 (26)
Apixaban	0 (<1)	0 (<1)	0 (<1)	354 (3)	3447 (27)	6919 (52)
CHA_2DS_2-VASc risk factors for stroke (%)						
Age (years)						
Median (IQR)	75 (66-82)	74 (66-82)	74 (67-82)	74 (67-82)	74 (67-82)	74 (67-82)
Mean (SD)	73.2 (11.2)	73.1 (11.3)	73.3 (11.3)	73.5 (11.2)	73.7 (11.3)	73.9 (11.3)
<65	1574 (21)	1767 (21)	1627 (19)	2262 (19)	2298 (18)	2349 (18)
65-74	2186 (29)	2591 (30)	2626 (31)	3870 (32)	4160 (33)	4431 (33)
≥75	3828 (50)	4247 (49)	4223 (50)	5948 (49)	6314 (49)	6564 (49)
Congestive heart failure	2147 (28)	2347 (27)	2287 (27)	3073 (25)	3112 (24)	3266 (24)
Hypertension	4968 (65)	5426 (63)	5360 (63)	7647 (63)	7908 (62)	8138 (61)
Diabetes mellitus	1063 (14)	1215 (14)	1194 (14)	1689 (14)	1762 (14)	1853 (14)
Ischemic stroke, TIA or arterial thromboembolism	899 (12)	981 (11)	1009 (12)	1529 (13)	1702 (13)	1740 (13)
Vascular disease	1168 (15)	1241 (14)	1277 (15)	1771 (15)	1867 (15)	1961 (15)
Female sex	3131 (41)	3623 (42)	3672 (43)	5350 (44)	5637 (44)	5708 (43)
CHA_2DS_2-VASc score (%)						
Median (IQR)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)
Mean (SD)	3.2 (1.7)	3.1 (1.6)	3.2 (1.7)	3.2 (1.6)	3.2 (1.6)	3.1 (1.6)
0	442 (6)	498 (6)	473 (6)	576 (5)	603 (5)	624 (5)
1	836 (11)	950 (11)	918 (11)	1242 (10)	1375 (11)	1473 (11)
2	1355 (18)	1590 (18)	1571 (19)	2395 (20)	2472 (19)	2637 (20)
3	1709 (23)	2047 (24)	1938 (23)	2885 (24)	3062 (24)	3156 (24)
4	1656 (22)	1870 (22)	1833 (22)	2537 (21)	2734 (21)	2871 (22)
5	965 (13)	1010 (12)	1046 (12)	1498 (12)	1513 (12)	1586 (12)
6-9	625 (8)	640 (7)	697 (8)	947 (8)	1013 (8)	997 (7)
$CHADS_2$ score (%)						
Median (IQR)	2 (1-3)	2 (1-2)	2 (1-2)	2 (1-2)	2 (1-2)	2 (1-2)
Mean (SD)	1.8 (1.2)	1.7 (1.2)	1.7 (1.2)	1.7 (1.2)	1.7 (1.2)	1.7 (1.2)
0	1105 (15)	1346 (16)	1336 (16)	1830 (15)	2042 (16)	2247 (17)
1	2210 (29)	2651 (31)	2547 (30)	3802 (31)	3918 (31)	3968 (30)
2-6	4273 (56)	4608 (54)	4593 (54)	6448 (53)	6812 (53)	7129 (53)

IQR = interquartile range. SD = standard deviation. TIA = transient ischemic attack

Table 2 Characteristics of new users of warfarin, dabigatran, rivaroxaban or apixaban for atrial fibrillation by oral anticoagulant initiated in Norway in 2015

Baseline drug	**Warfarin**	**Dabigatran**	**Rivaroxaban**	**Apixaban**
All	n=1826	n=1171	n=3428	n=6919
CHA_2DS_2-VASc risk factors for stroke (%)				
Age (years)				
Median (IQR)	76 (67-83)	72 (66-80)	73 (66-81)	75 (68-83)
Mean (SD)	74.1 (12.2)	72.3 (10.9)	72.8 (11.1)	74.7 (11.1)
<65	333 (18)	234 (20)	679 (20)	1103 (16)
65-74	530 (29)	447 (38)	1229 (36)	2225 (32)
≥75	963 (53)	490 (42)	1520 (44)	3591 (52)
Congestive heart failure	621 (34)	194 (17)	649 (19)	1802 (26)
Hypertension	1128 (62)	663 (57)	2063 (60)	4284 (62)
Diabetes mellitus	313 (17)	142 (12)	424 (12)	974 (14)
Ischemic stroke, TIA or arterial thromboembolism	200 (11)	139 (12)	398 (12)	1003 (14)
Vascular disease	426 (23)	111 (9)	415 (12)	1009 (15)
Female	698 (38)	447 (38)	1438 (42)	3125 (45)
CHA_2DS_2-VASc score (%)				
Median (IQR)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)
Mean (SD)	3.3 (1.7)	2.8 (1.5)	2.9 (1.6)	3.3 (1.6)
0	104 (6)	82 (7)	184 (5)	254 (4)
1	181 (10)	163 (14)	438 (13)	691 (10)
2	309 (17)	265 (23)	763 (22)	1300 (19)
3	397 (22)	294 (25)	845 (25)	1620 (23)
4	386 (21)	223 (19)	675 (20)	1587 (23)
5	265 (15)	83 (7)	336 (10)	902 (13)
6-9	184 (10)	61 (5)	187 (5)	565 (8)
$CHADS_2$ score (%)				
Median (IQR)	2 (1-3)	1 (1-2)	1 (1-2)	2 (1-3)
Mean (SD)	1.8 (1.3)	1.5 (1.2)	1.6 (1.2)	1.8 (1.2)
0	291 (16)	263 (22)	658 (19)	1035 (15)
1	467 (26)	380 (32)	1124 (33)	1997 (29)
2-6	1068 (58)	528 (45)	1646 (48)	3887 (56)

IQR = interquartile range. SD = standard deviation. TIA = transient ischemic attack

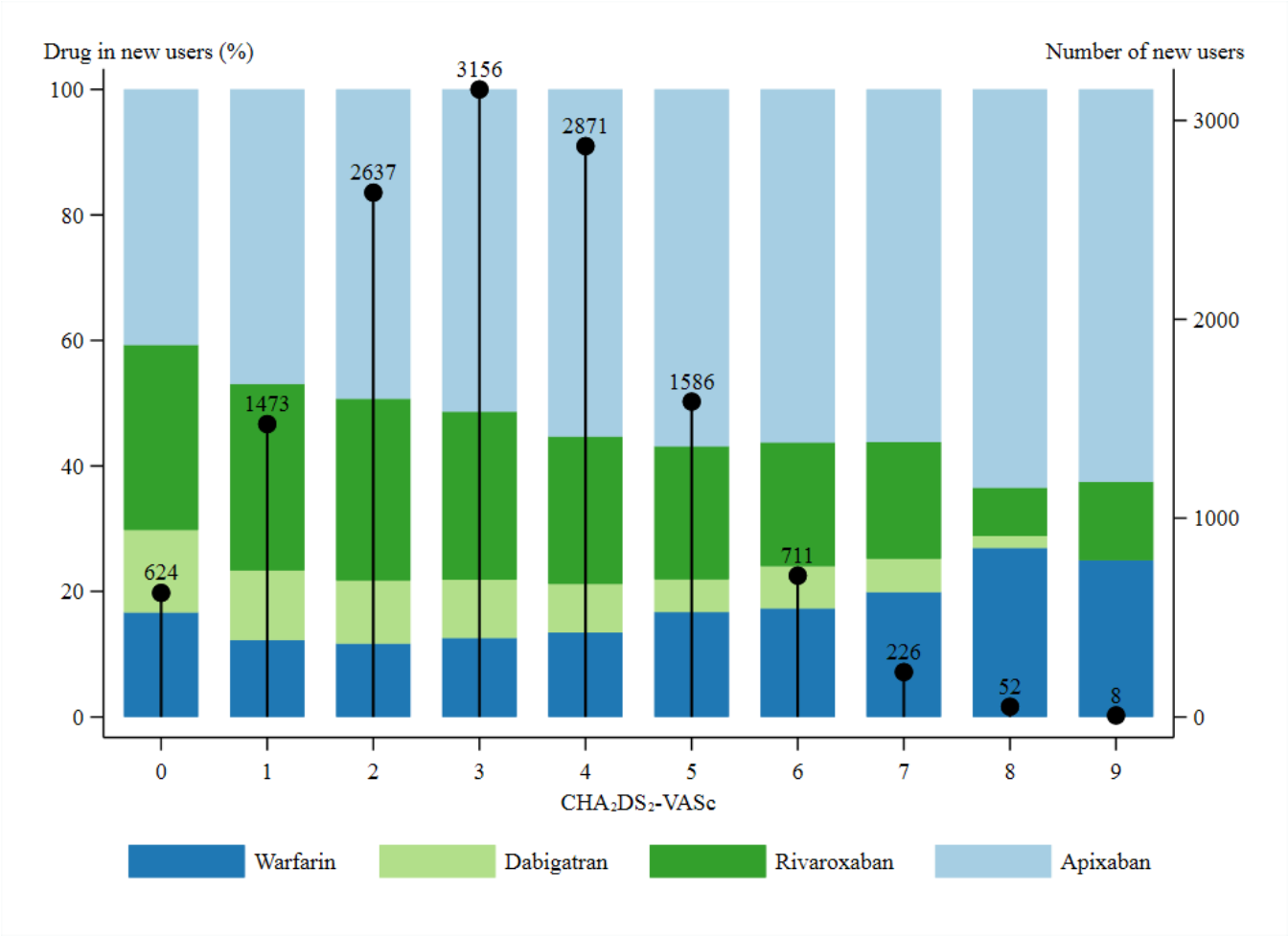


Fig. 1 The thick bars show the drug selected in percent of new users of warfarin, dabigatran, rivaroxaban or apixaban for atrial fibrillation according to CHA_2DS_2-VASc score. The narrow bars show the total number of new users per CHA_2DS_2VASc score. Norway, 2015

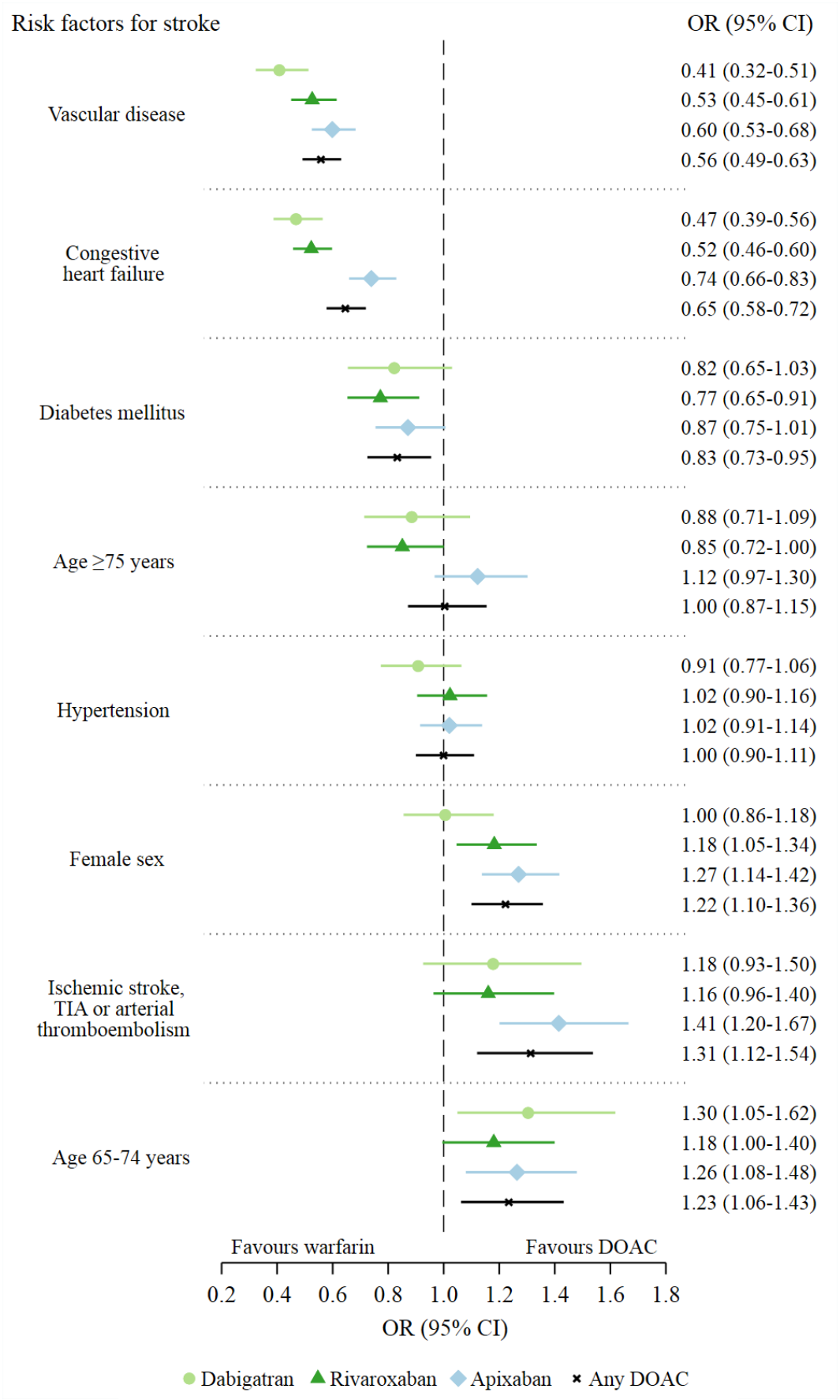


Fig. 2 CHA_2DS_2-VASc risk factors for stroke associated with choice of dabigatran, rivaroxaban or apixaban versus warfarin in new users of oral anticoagulants for atrial fibrillation. Results of multiple logistic regression analyses adjusting for the other risk factors: Odds ratio (OR) and 95% confidence interval (CI). Norway, 2015. Age groups are compared to age <65 years. TIA = transient ischemic attack

Online Resource 1 Definitions of comorbidities / risk factors

Comorbidity	NPR	NorPD		
	ICD10 codes	ATC codes	Reimbursement codes	
			ICD10 codes	ICPC2 codes
Atrial fibrillation		B01AA03 B01AE07 B01AF01 B01AF02	I48	K78
Congestive heart failure	I11.0 I42* I50* J81*	C01AA04 C01AA05 C01DA08 C01EB17 C02DB02 C03AA01 C03AA03 C03AB01 C03CA01 C03CA02 C03DA01 C03DA02 C03DA04 C03EA01 C07AA05 C07AB02 C07AB07 C07AG02 C09AA01 C09AA02 C09AA03 C09AA05 C09AA10 C09CA01 C09CA03 C09CA06 R03DA04	I11.0 I42 I50 I50.1 J81	K77
Hypertension		C02A C02C C02DB C02DC C03A C03CA01 C03CA04 C03DA01 C03DB01 C03E C07A C07B C08 C09 (÷ C07AA07 C08CA06)	I10 I11 I11.0 I12 I13 I15 O10 O11	K86 K87
Diabetes mellitus	E10* E11* E12* E13* E14* O24.0 O24.1 O24.2 O24.3	A10		
Ischemic stroke, transient ischemic attack, arterial thromboembolism	I63* I64* I74* G45.8 G45.9	B01AB04 B01AB05 B01AC04 B01AC05 B01AC07 B01AC30	G45 I63 I74	K89 K90
Vascular disease	I21* I22* I70* I73.9	(B01AB01) B01AB04 B01AB05 B01AC04 (B01AC07) B01AC22 B01AC24 (B01AC26 C01DA02 C01DA08 C01DA14) C04AD03 C07AA05 C07AB02 C07AB03 (C07AB07 C07AG01 C07AG02 C08CA01 C08CA02) C08CA05 (C08DA01 C08DB01) C09AA01 C09AA03 C09AA05 (C10)	-22 I21 I22 I70 I73.9	-22 K75 K92

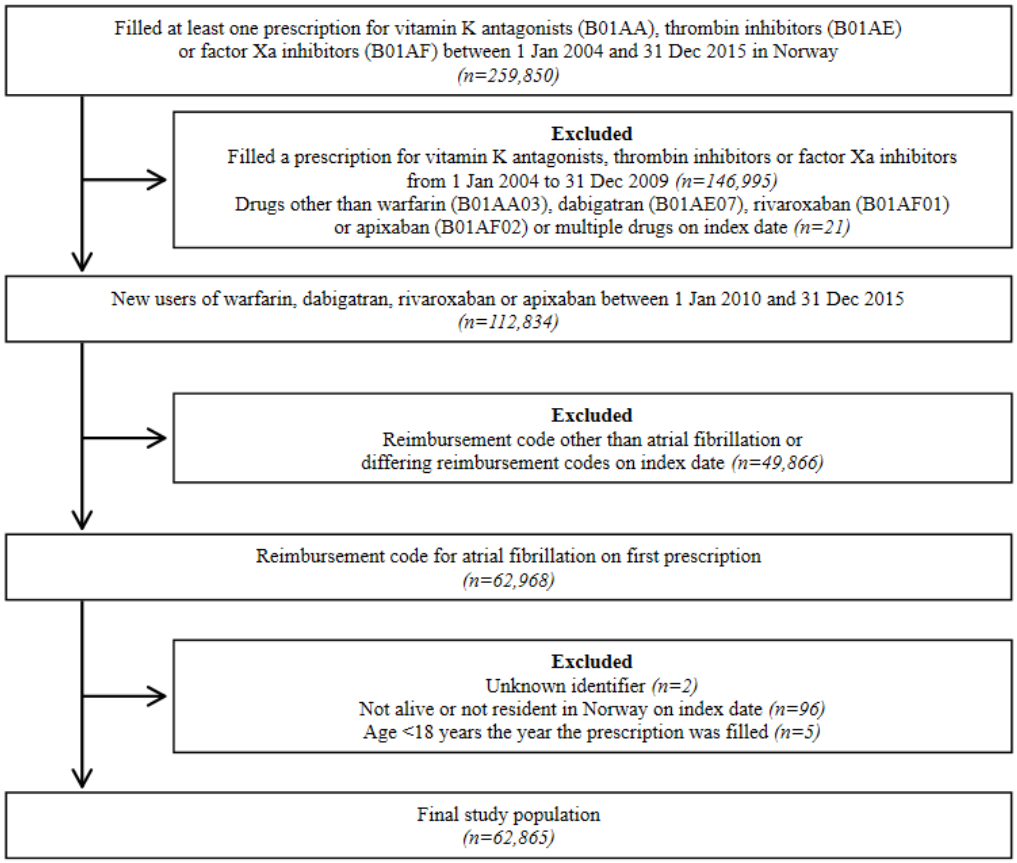
ICD10 = International Classification of Diseases, 10th revision

ICPC2 = International Classification of Primary Care, 2nd Edition

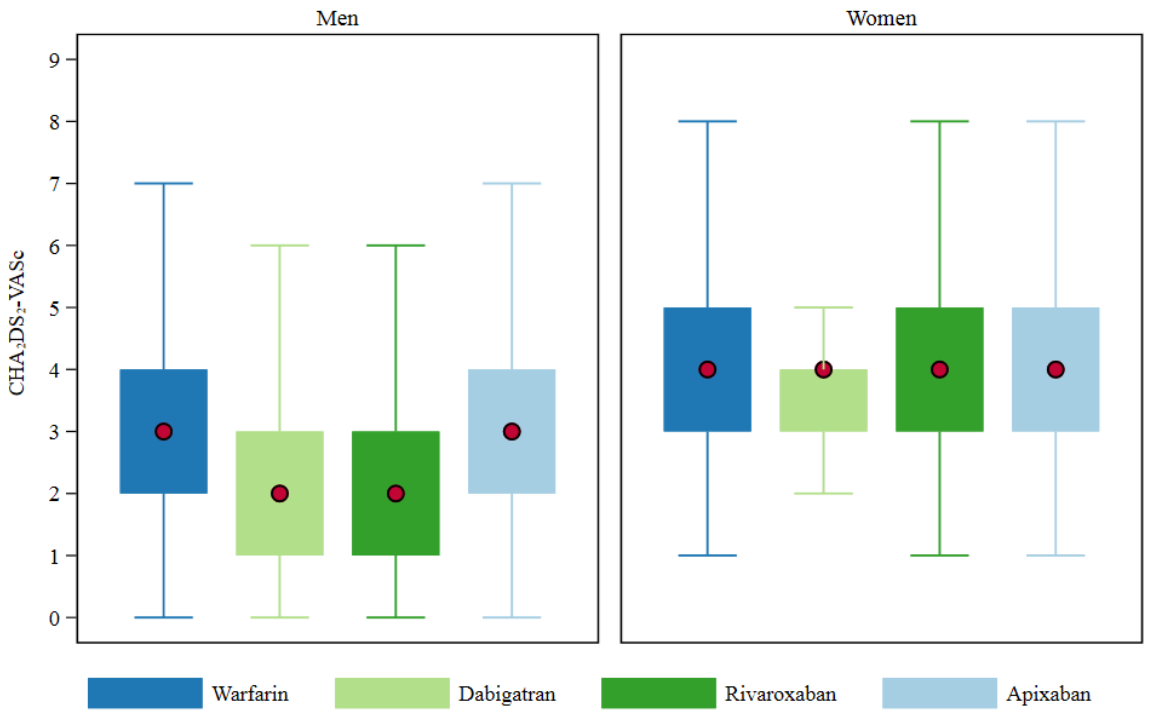
NPR = Norwegian Patient Registry

NorPD = Norwegian Prescription Database

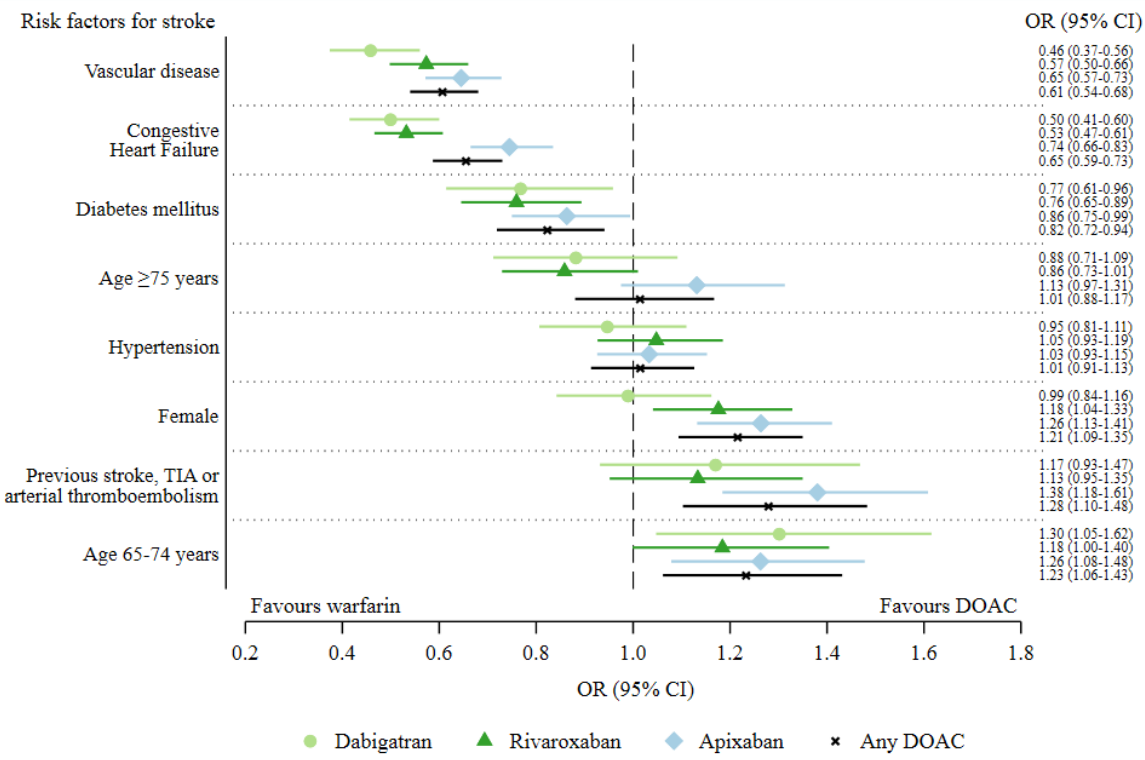
Atrial fibrillation was defined as a reimbursement code for atrial fibrillation on the first dispensing of either warfarin, dabigatran, rivaroxaban or apixaban (index date) in NorPD. Heart failure, vascular disease, and ischemic stroke, transient ischemic attack or systemic thromboembolism were defined as either an ATC code plus a reimbursement code on a dispensing within 365 days before or on index date, or a diagnosis code within 730 days before or on index date. Hypertension was defined as an ATC code plus a reimbursement code within 365 days before or on index date. Diabetes mellitus was defined as a diagnosis code within 730 days before or on index date or an ATC code within 365 days before or on index date.



Online Resource 2 Selection of the study population in the study period from 1 Jan 2010 to 31 Dec 2015 in Norway by linking the Norwegian Prescription Database and the National Registry



Online Resource 3 Boxplot of CHA_2DS_2-VASc by oral anticoagulant and gender in new users of warfarin, dabigatran, rivaroxaban or apixaban. Norway, 2015. Dot = median, box = interquartile range, whiskers = the most extreme values within the nearer quartile ± 1.5 interquartile range (Tukey, 1977)



Online Resource 4 CHA_2DS_2-VASc risk factors for stroke associated with choice of dabigatran, rivaroxaban or apixaban versus warfarin in new users of oral anticoagulants for atrial fibrillation: Odds ratio(OR) and 95% confidence interval (CI). Norway, 2015. Diagnosis codes since 2008 and co-medication since 365 days before index date were used to define the presence of risk factors. TIA = transient ischemic attack