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Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study

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ABSTRACT

OBJECTIVE

To study the effectiveness and safety of the non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) dabigatran, rivaroxaban, and apixaban compared with warfarin in anticoagulant naïve patients with atrial fibrillation.

DESIGN

Observational nationwide cohort study.

SETTING

Three Danish nationwide databases, August 2011 to October 2015.

PARTICIPANTS

61 678 patients with non-valvular atrial fibrillation who were naïve to oral anticoagulants and had no previous indication for valvular atrial fibrillation or venous thromboembolism. The study population was distributed according to treatment type: warfarin (n=35 436, 57%), dabigatran 150 mg (n=12 701, 21%), rivaroxaban 20 mg (n=7192, 12%), and apixaban 5 mg (n=6349, 10%).

MAIN OUTCOME MEASURES

Effectiveness outcomes defined a priori were ischaemic stroke; a composite of ischaemic stroke or systemic embolism; death; and a composite of ischaemic stroke, systemic embolism, or death. Safety outcomes were any bleeding, intracranial bleeding, and major bleeding.

RESULTS

When the analysis was restricted to ischaemic stroke, NOACs were not significantly different from warfarin. During one year follow-up, rivaroxaban was associated with lower annual rates of ischaemic stroke or systemic embolism (3.0% *v* 3.3%, respectively) compared with warfarin: hazard ratio 0.83 (95% confidence interval 0.69 to 0.99). The hazard ratios for dabigatran and apixaban (2.8% and 4.9% annually, respectively) were non-significant compared with warfarin. The annual risk of death was significantly lower with apixaban (5.2%) and dabigatran (2.7%) (0.65, 0.56 to 0.75 and 0.63, 0.48 to 0.82, respectively) compared with warfarin (8.5%), but not with rivaroxaban (7.7%). For the combined endpoint of any bleeding, annual rates for apixaban (3.3%) and dabigatran (2.4%) were significantly lower than for warfarin (5.0%) (0.62, 0.51 to 0.74). Warfarin and rivaroxaban had comparable annual bleeding rates (5.3%).

CONCLUSION

All NOACs seem to be safe and effective alternatives to warfarin in a routine care setting. No significant difference was found between NOACs and warfarin for ischaemic stroke. The risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran compared with warfarin.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The use of non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) has been increasing since their introduction

Based on data from clinical practice, however, limited evidence exists on effectiveness and safety of NOACs compared with warfarin

WHAT THIS STUDY ADDS

No significant difference in risk of ischaemic stroke was evident between NOACs and warfarin

Rivaroxaban was associated with a lower risk of ischaemic stroke or systemic embolism than warfarin, but with comparable major bleeding rates

Dabigatran and apixaban had non-significant hazard ratios compared with warfarin for ischaemic stroke or systemic embolism, whereas major bleeding rates were significantly lower with reference to warfarin

Introduction

Oral anticoagulant treatment with either vitamin K antagonists or non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) is essential for the prevention of stroke or systemic embolism and all cause mortality in patients with atrial fibrillation and one or more risk factors for stroke. The four currently available NOACs are dabigatran, rivaroxaban, apixaban, and edoxaban.[1-4] In clinical studies these drugs show similar efficacy and safety to warfarin, but with more convenience such as no requirement of meticulous dose adjustment to achieve optimal treatment. NOACs are therefore the preferred treatment option in some guidelines, especially where anticoagulation control with warfarin is suboptimal.[5]

A meta-analysis showed that NOACs at standard dose have a favourable risk-benefit profile compared with warfarin, with significant reductions in stroke or systemic embolism, intracranial haemorrhage, and mortality, but a similar major bleeding profile to warfarin, apart from increased gastrointestinal bleeding.[6] The relative efficacy and safety of NOACs were consistent across a wide range of patients.

Thus the use of NOACs in daily clinical practice has been increasing since their introduction.[7] Only large scale real world comparisons of a single NOAC versus warfarin have been published or presented. Evidence relating to the comparative effectiveness and safety of all oral anticoagulant drugs used in clinical practice is currently lacking.

We assessed and compared the effectiveness and safety of dabigatran, rivaroxaban, and apixaban compared with warfarin in clinical practice using a nationwide Danish cohort of patients with atrial fibrillation who were naïve to oral anticoagulants.

Methods

This study is based on data from three Danish nationwide databases: the Danish national prescription registry,[8] which holds information on purchase date, Anatomical Therapeutic Chemical (ATC) classification code, and package size for every prescription claimed since 1994; the Danish national patient register[9] established in 1977, which includes admission and discharge dates, and discharge diagnoses (international classification of diseases) for more than 99% of hospital admissions; and the Danish civil registration system,[10] with information on sex, date of birth, and vital and emigration status. Any individual in Denmark has a unique identification number, allowing linkage at individual level between databases.

Study population

We identified people with a first time purchase of a NOAC: apixaban (introduced 10 December 2012), dabigatran (1 August 2011), rivaroxaban (1 February 2012), as well as patients who started warfarin treatment (from 1 August 2011) up to 30 November 2015. All prescribed drugs in Denmark are partially reimbursed, based on a patient's level of drug expenses.

To study a cohort of patients treated for atrial fibrillation, we applied several criteria. We restricted the consumption of NOACs to standard doses (apixaban 5 mg twice daily, dabigatran 150 mg twice daily, and rivaroxaban 20 mg once daily). Warfarin is only available in 2.5 mg dose tablets in Denmark. We decided to focus our analyses on patients receiving standard dosages of apixaban, dabigatran, and rivaroxaban, because patients who receive reduced dosage regimens have more comorbidities and are of more advanced age (>80 years). Thus, comparisons across various dosing regimens and choices of antithrombotic agent could result in comparisons on mixed cohorts in terms of comorbidities, age, and concomitant treatment. Confining the analysis to patients receiving standard dosages only will thus allow for easier interpretation and a more robust comparison of cohorts. To establish a cohort of patients who were naïve to oral anticoagulant treatment, we excluded those who had used any oral anticoagulant within one year. We also excluded patients with hospital diagnoses indicating valvular atrial fibrillation (mitral stenosis or mechanical heart valves) or venous thromboembolism (pulmonary embolism or deep vein thrombosis) to narrow the included patients to only those who were likely to have been prescribed oral anticoagulants because of a diagnosis of atrial fibrillation in either hospital or general practice. The entire cohort comprised patients with atrial fibrillation. We also analysed a subgroup of patients who had been admitted to hospital with a diagnosis of atrial fibrillation.

Endpoints and variable definitions

Participants were followed until 30 November 2015 in the Danish national patient register for the occurrence of ischaemic stroke or systemic embolism and for ischaemic stroke separately (see supplementary table 1 for specific international classification of diseases, 10th revision codes). The outcome of ischaemic stroke has been validated, with a positive predictive value of more than 97%.[11] Because oral anticoagulants reduce the risk of both stroke and death, we included all cause mortality as a lone endpoint and as a combined endpoint with stroke.[12]

We recorded bleeding events as intracranial, major, gastrointestinal, and traumatic intracranial, reported in total as "any bleeding" and specific for intracranial and extracranial major bleeding. Extracranial major bleeding was defined as bleeding with anaemia, haemothorax, haematuria, epistaxis, and bleeding in the eye (see supplementary material for details).

Demographic data were obtained from the Danish civil registration system. Comorbidities and co-treatments (listed in table 1) were ascertained from the Danish national patient registry and the Danish national prescription registry (see supplementary table 1 for definitions of codes). We combined covariate information into the CHA_2DS_2VASc score[13] for assessing stroke risk, and a HAS-BLED score[14] as a measure of bleeding risk (see supplementary table 2 for definitions of scores).

Statistical analysis

To compare the risk of an endpoint between treatment groups we used time to event analysis, measuring risk time from initial prescription and until the relevant event, emigration, death, or end of follow-up, whichever came first. An intention to treat approach was applied for the analyses of all endpoints. The supplementary material shows the results of a continuous treatment analysis, by censoring follow-up if the patient was prescribed another treatment than that initiated.

We calculated crude incidence as the number of events divided by person time. Cox regression was used to compare event rates between the treatment groups, with warfarin as the primary reference. To deal with confounding by indication of treatment, we applied an inverse probability of treatment weighted analysis. Such an approach is suitable in situations with several treatment alternatives.[15,16] We used generalised boosted models, based on 10 000 regression trees, to calculate weights for optimal balance between the treatment populations.[17] The weights were derived to obtain estimates representing population average treatment effects. The underlying propensity models included the treatment predictors of age (continuous); binary indicators for sex; ischaemic stroke or systemic embolism or transient ischaemic attack; vascular disease; hypertension; diabetes; cancer; recent prescription of aspirin, β blockers, non-steroidal anti-inflammatory drugs, or statins; and CHA_2DS_2-VASc and HAS-BLED scores.

The treatments should be contrasted on comparable populations, and any patient must have a positive

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Table 1 | Participant characteristics according to treatment. Values are numbers (percentages) unless stated otherwise

Characteristics	NOAC			Warfarin	All	Maximum standardised difference*	
	Apixaban	Dabigatran	Rivaroxaban			Before	After
No in group				35 436	61 678	-	-
Women	39.7 (2522)	33.9 (4304)	43.1 (3100)	41.2 (14 598)	39.8 (24 524)	0.19	0.02
Median (interquartile range) age (years)	71.3 (65.8-77.2)	67.6 (62.0-72.4)	71.8 (65.7-78.9)	72.4 (64.7-79.8)	70.9 (64.3-77.7)	0.45	0.02
Age >65	78.2 (4967)	64.4 (8180)	77.7 (5590)	74.2 (26 295)	73.0 (45 032)	0.31	0.02
Age >75	33.7 (2140)	13.9 (1766)	38.1 (2737)	41.4 (14 655)	34.5 (21 298)	0.58	0.03
Previous atrial fibrillation diagnose	68.9 (4374)	70.0 (8889)	60.2 (4333)	51.5 (18 243)	58.1 (35 839)	0.38	0.02
Mean (SD) CHA_2DS_2VASc score†	2.8 (1.6)	2.2 (1.4)	2.8 (1.6)	2.8 (1.7)	2.7 (1.6)	0.39	0.02
Mean (SD) HAS-BLED score‡	2.3 (1.2)	2.0 (1.1)	2.2 (1.2)	2.2 (1.2)	2.2 (1.2)	0.25	0.01
Cancer	16.1 (1021)	11.8 (1495)	16.1 (1159)	16.5 (5862)	15.5 (9537)	0.13	0.02
Ischaemic stroke, or systemic embolism, or TIA	21.1 (1339)	13.2 (1674)	16.8 (1209)	14.8 (5241)	15.3 (9463)	0.22	0.03
Heart failure or LVD	15.9 (1009)	9.3 (1187)	12.6 (908)	10.4 (3699)	11.0 (6803)	0.13	0.03
Vascular disease	13.9 (882)	10.4 (1319)	12.2 (879)	18.1 (6407)	15.4 (9487)	0.21	0.02
Renal dysfunction	2.4 (155)	1.1 (145)	1.8 (131)	6.6 (2346)	4.5 (2777)	0.26	0.04
COPD	8.9 (564)	6.2 (787)	8.8 (636)	9.6 (3403)	8.7 (5390)	0.12	0.02
Previous bleeding	14.0 (886)	9.9 (1257)	12.8 (923)	11.8 (4185)	11.8 (7251)	0.13	0.02
Hypertension	48.8 (3099)	47.0 (5971)	48.6 (3492)	50.6 (17 932)	49.4 (30 494)	0.07	0.01
Diabetes	15.8 (1000)	13.8 (1754)	14.0 (1006)	15.6 (5513)	15.0 (9273)	0.05	0.03
Aspirin	37.8 (2400)	38.2 (4853)	38.3 (2751)	42.0 (14 895)	40.4 (24 899)	0.09	0.01
β blocker	38.6 (2450)	40.1 (5093)	38.9 (2801)	41.0 (14 518)	40.3 (24 862)	0.05	0.01
NSAIDs	22.4 (1422)	24.5 (3114)	22.1 (1586)	24.3 (8616)	23.9 (14 738)	0.06	0.01
Statins	40.6 (2577)	37.8 (4805)	38.4 (2764)	40.0 (14181)	39.4 (24 327)	0.06	0.02

TIA=transient ischaemic attack; LVD=left ventricular dysfunction; COPD=chronic obstructive pulmonary disease; NSAIDs=non-steroidal anti-inflammatory drugs.
*Maximum standardised pairwise difference, before and after inverse probability of treatment weighting.
†Scores range from 0-9, reflecting risk of stroke in patients with atrial fibrillation not receiving anticoagulants (see supplementary table 2).
‡Scores range from 0-9, reflecting risk of bleeding in patients with atrial fibrillation receiving anticoagulants (see supplementary table 2).

probability for any treatment, hence substantial overlap between the scores for each treatment should be present. This was assessed by graphical inspection of the weight distributions.[16] We evaluated the balance between treatment populations by standardised differences of all baseline covariates, using a threshold of 0.1 to indicate imbalance.[18] Ordinary logistic regression was used to evaluate the association of baseline characteristics on treatment choice versus any of the alternatives.

We assessed the sensitivity of inclusion criteria and analytical method. The analyses were repeated by restricting to the cohort of patients with a hospital discharge diagnosis of atrial fibrillation either before or within 30 days of the first prescription of a NOAC. Selection bias could be suspected at introduction of dabigatran as this initial group may have had an excess of patients with special conditions making warfarin intractable. To avoid this potential bias we carried out an analysis where inclusion of patients using dabigatran was postponed to February 2012. We compared the results of the inverse probability of treatment weighted analysis with an ordinary crude and adjusted analysis as well as a standardised morbidity ratio weighted analysis, weighting the warfarin stratum with the expected odds of receiving treatment with a NOAC. To account for baseline differences and potential confounding we used the same covariates as for the propensity models to adjust the standardised morbidity ratio and the ordinary analyses. The results are provided in the supplementary material.

The analyses on the entire population were supplemented by stratified analyses on the populations younger and older than 65, as well as stratified according to previous experience of stroke, systemic embolism, or transient ischaemic attack. These two classifications represented primary and secondary prevention treatment groups, respectively.

Stata/MP version 14 and R version 3.1.1 was used for the statistical analysis. We considered a two sided P value of less than 0.05 to be significant.

Patient involvement

No patients were involved in setting the research question, the outcome measures, or the study design; there are no plans to actively involve patients in dissemination of the results. Ethical approval for observational studies using Danish nationwide registries is not required in Denmark.

Results

We identified 122 068 patients as new users of oral anticoagulant treatment, including 35 035 patients receiving one of the non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) with reduced doses, who were excluded. Overall, we excluded 25 355 patients with an indication for valvular atrial fibrillation or venous thromboembolism (see supplementary figure 1). The study population (n=61 678) was distributed according to treatment type: warfarin (n=35 436, 57%), dabigatran (n=12 701, 21%), rivaroxaban (n=7192, 12%), and apixaban (n=6349, 10%). Supplementary figure 2 shows

the progress of patients new to oral anticoagulants. The average follow-up was 1.9 years, with the shortest in the apixaban group (average 0.9 years), owing to its later introduction to the market.

Table 1 presents the baseline information of the initial study population before weighting. Patients who started dabigatran were slightly younger (<14% aged ≥75) and had fewer risk factors for stroke, as summarised by a CHA_2DS_2-VASc score of 2.2, than other groups (older, with >33% aged ≥75 and a CHA_2DS_2-VASc score of 2.8). More patients in the apixaban (69%) and dabigatran (70%) groups had a diagnosis of atrial fibrillation before (or in connection with) the initiation of treatment, compared with patients in the rivaroxaban and warfarin groups (60% and 52%, respectively). Patients treated with apixaban had a higher prevalence of previous ischaemic stroke, systemic embolism, or transient ischaemic attack (21%), whereas previous vascular disease was most prevalent among patients who started with warfarin. Patients treated with dabigatran had the lowest proportion of renal impairment (1.1%) in contrast with warfarin users (6.6%).

After the study populations had been weighted using the inverse probability of treatment weighted method, all baseline differences were less than 0.04 standardised differences at maximum. Inspection of individual propensity score distributions showed sufficient overlap between treatment populations to obtain valid comparisons (data not shown).

Baseline characteristics and treatment choices

Supplementary table 3 shows the odds ratios for treatment compared with any of the alternatives. The likelihood of apixaban use (contrasted to the three other alternatives) was increased (odds ratio >1.1) in the presence of previous ischaemic stroke, systemic embolism, or transient ischaemic attack; vascular disease; bleeding; and hospital confirmed atrial fibrillation, but it was reduced (odds ratio <0.9) by renal impairment and aspirin use. Choice of dabigatran was increased with a hospital diagnosis of atrial fibrillation but reduced if the patient was female, and had vascular disease, renal impairment, chronic obstructive pulmonary disease (COPD), heart failure, or cancer. The probability for selecting rivaroxaban was increased by female sex, previous ischaemic stroke, systemic embolism, or transient ischaemic attack, or bleeding but reduced by vascular disease, renal impairment, heart failure, or use of non-steroidal anti-inflammatory drugs. Treatment with warfarin was more likely if the patient was female, had vascular disease, hypertension, renal impairment, COPD, heart failure, or cancer, or used aspirin but less likely in patients with a confirmed hospital diagnosis of atrial fibrillation.

Ischaemic stroke and systemic embolism

During the first year of follow-up, 1702 ischaemic stroke or systemic embolism events were observed. Crude cumulative incidence curves for the endpoint (fig 1)

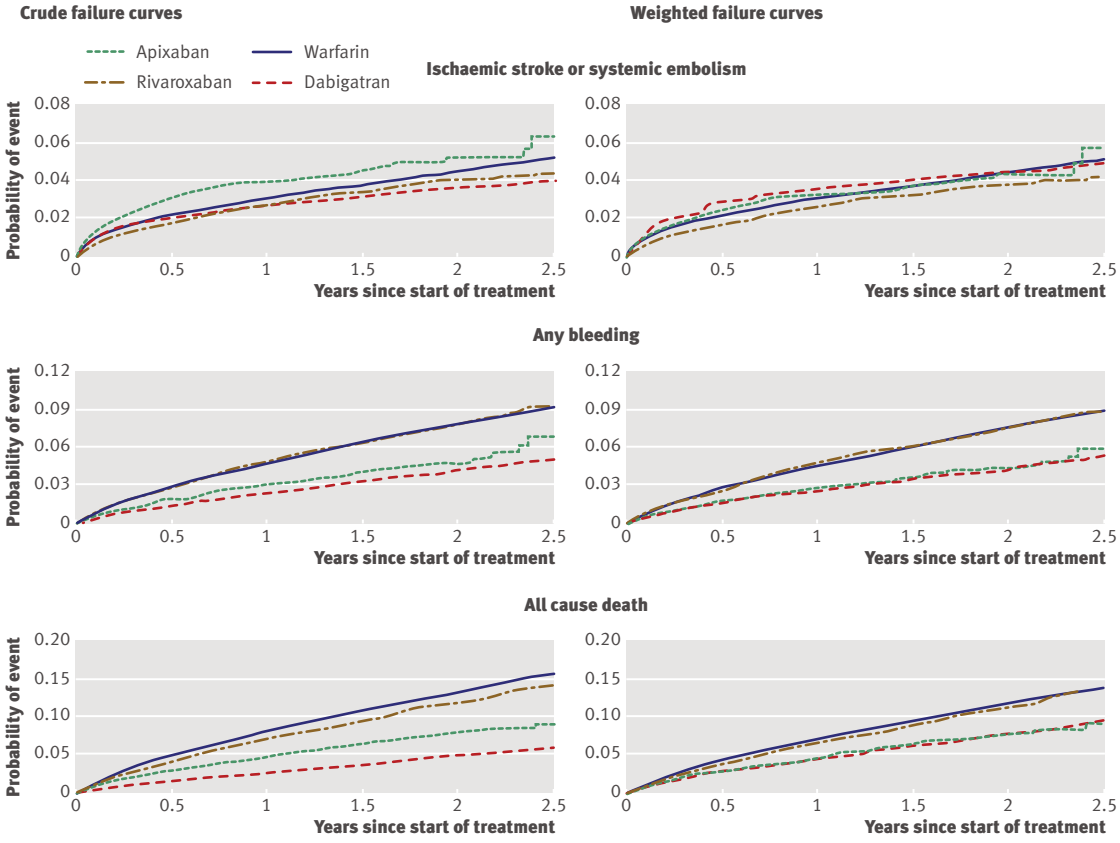

Fig 1 | Crude cumulative incidence curves of stroke, any bleeding, and all cause mortality according to initiated treatment. See supplementary material for corresponding curves for individual endpoints and for combined endpoints

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Table 2 | Number of events, and crude and weighted event rates according to initiated treatment

	Apixaban			Dabigatran			Rivaroxaban			Warfarin		
Variables	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†
One year follow-up:												
Ischaemic stroke or systemic embolism	210	4.86	3.92	327	2.77	3.73	161	3.04	2.89	1004	3.28	3.25
Ischaemic stroke	204	4.71	3.72	321	2.72	3.68	156	2.95	2.79	920	3.00	3.01
All cause mortality	232	5.23	5.01	319	2.66	4.62	413	7.69	7.02	2652	8.52	7.41
Ischaemic stroke, systemic embolism, or death	424	9.81	8.71	623	5.28	7.92	537	10.15	9.38	3483	11.39	10.28
Any bleeding	121	3.78	3.13	253	2.77	2.85	186	5.57	4.83	959	5.53	4.71
Major bleeding	90	2.80	2.29	203	2.22	2.04	149	4.44	3.92	725	4.16	3.58
Intracranial bleeding	15	0.46	0.40	19	0.21	0.22	14	0.41	0.31	118	0.66	0.55
2.5 years' follow-up:												
Ischaemic stroke or systemic embolism	225	4.08	3.32	441	1.84	2.32	201	2.34	2.21	1447	2.39	2.33
Ischaemic stroke	219	3.97	3.17	427	1.78	2.26	196	2.28	2.15	1337	2.20	2.17
All cause mortality	274	4.82	4.69	600	2.44	4.04	592	6.74	6.31	4469	7.17	6.20
Ischaemic stroke, systemic embolism, or death	473	8.58	7.75	992	4.13	6.10	733	8.53	8.03	5524	9.11	8.13
Any bleeding	143	3.52	2.90	461	2.48	2.67	252	4.60	4.09	1579	4.60	3.93
Major bleeding	109	2.67	2.15	376	2.01	2.02	200	3.63	3.27	1198	3.46	2.98
Intracranial bleeding	18	0.43	0.41	35	0.18	0.17	23	0.40	0.31	190	0.53	0.44

*Events divided by 100 person years.
†Inverse probability of treatment weighted and expressed as population average treatment rates per 100 years.

showed no distinct differences between the four treatments after applying weights. Weighted rates for ischaemic stroke or systemic embolism ranged from 2.9 to 3.9 per 100 person years among the NOACs and 3.3 specifically for warfarin (table 2).

When restricting the analysis to ischaemic stroke only, no significant differences were evident for the NOACs compared with warfarin across strata (fig 2, table 2). Rivaroxaban was associated with lower rates of ischaemic stroke or systemic embolism compared with warfarin: the hazard ratio at one year was 0.83 (95% confidence interval 0.69 to 0.99) and after 2.5 years was 0.80 (0.69 to 0.94, see supplementary fig 4a). When we restricted the analysis to patients with hospital diagnosed atrial fibrillation only or stratified according to age or primary or secondary stroke protection, the associations were similar, with hazard ratios between 0.79 and 0.86; statistical significance was not reached (fig 2).

The differences in rates of ischaemic stroke or systemic embolism were non-significant for apixaban and dabigatran compared with warfarin in the first year of treatment (fig 2).

Bleeding events

The cumulative incidence curves for the combined endpoint of any bleeding (fig 1) displayed comparable bleeding rates for warfarin and rivaroxaban, which were higher than for both apixaban and dabigatran. The incidence curves for the last two treatments overlapped. The weighted one year incidence rates were around five events per 100 person years for warfarin and rivaroxaban and three per 100 person years for apixaban and dabigatran (table 2).

Weighted Cox regressions yielded significantly lower hazard ratios with reference to warfarin for apixaban (0.63, 0.53 to 0.76) and dabigatran (0.61, 0.51 to 0.74, fig 3). After 2.5 years' follow-up these significant reductions remained (see supplementary figure 4b). The subgroup analyses (fig 3) showed consistency of these results, although the differences where less pronounced and non-significant for the secondary stroke prevention group.

The effect sizes for major bleeding were comparable to those for the overall combined bleeding endpoint (fig 3). The rate for dabigatran was significantly lower than for warfarin (0.50, 0.33 to 0.75) for the secondary stroke prevention group.

Intracranial bleeding was observed, with a one year weighted rate of 0.6 per 100 person years for warfarin; all NOACs had lower rates than warfarin. The main analysis showed lower rates for dabigatran (0.40, 0.25 to 0.65) and for rivaroxaban (0.56, 0.34 to 0.90) at one year follow-up (fig 2). The corresponding hazard ratios after 2.5 years' follow-up were 0.39 (0.27 to 0.56) and 0.66 (0.45 to 0.98, see supplementary figure 4b). The hazard ratios for apixaban ranged between 0.60 and 0.85 for all strata, with confidence intervals crossing unity.

Death

The cumulative incidence curves for warfarin and rivaroxaban overlapped and were higher than the overlapping curves for apixaban and dabigatran (fig 2). Table 2 shows the rates for death and the combined endpoint of ischaemic stroke, systemic embolism, or death. Death rates at one year follow-up were significantly lower for apixaban (0.65, 0.56 to 0.75) and for dabigatran (0.63, 0.48 to 0.82) compared with warfarin (fig 2). These differences remained consistent when stratified on subgroups.

The combined endpoint of ischaemic stroke, systemic embolism, or death displayed lower relative risks for all NOACs compared with warfarin, with general consistency in the entire cohort and the cohort of patients admitted to hospital (fig 2). After 2.5 years' follow-up, these differences were maintained (see supplementary figure 4a).

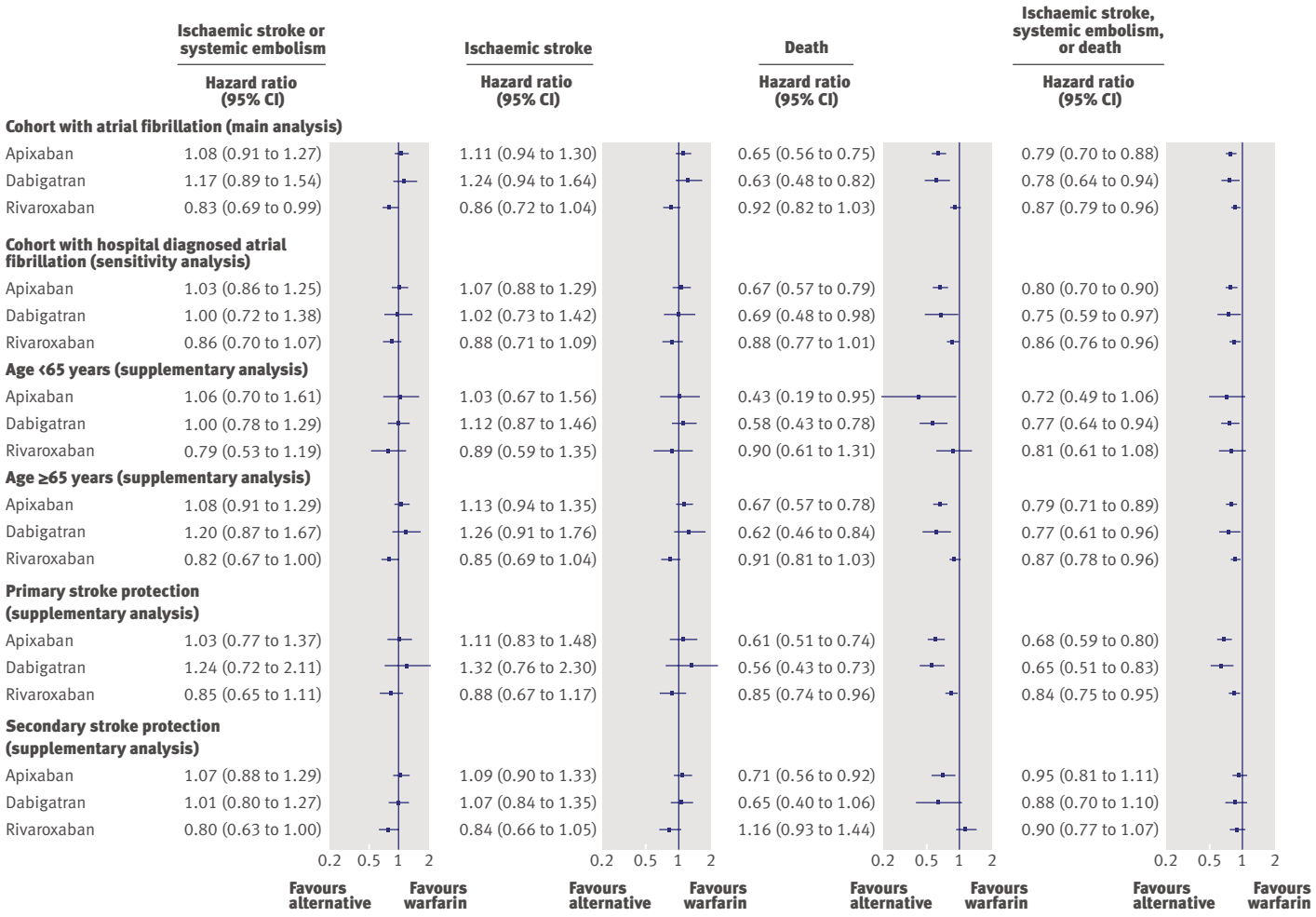

Fig 2 | Propensity weighted (inverse probability of treatment weighted) Cox hazard ratios for one year follow-up (intention to treat) for non-vitamin K antagonist oral anticoagulants (NOACs) compared with warfarin for stroke and death endpoints. Supplementary material provides corresponding results for follow-up of 2.5 years and for continuous treatment analysis

Sensitivity analyses

The adjusted analyses, the standardised morbidity ratio weighted analysis, and the subgroup analyses on patients with confirmed atrial fibrillation agreed with the weighted analyses (see supplementary figures 5a and 5b). The results were not altered when the analyses were repeated under a continuous treatment approach (see supplementary figures 6a, 6b, 7a, and 7b). The exclusion of patients who started dabigatran during the first five months after its introduction in Denmark did not materially change the effect estimates and conclusions (results not shown).

Discussion

In this large comparative effectiveness and safety analysis of NOAC drugs and warfarin from routine care setting, we found that non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) are overall safe and effective alternatives to warfarin treatment.

We observed differential prescribing of different non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) in relation to patient characteristics was evident. For example, dabigatran was preferentially prescribed in younger patients with a lower risk of stroke and less renal impairment. For ischaemic stroke only, no significant differences were evident (hazard ratios) between NOACs and warfarin; however, for the combined endpoint of ischaemic stroke or systemic embolism, rivaroxaban was associated with a lower risk than warfarin, with dabigatran and apixaban showing no significant differences. Apixaban and dabigatran were associated with a significantly lower risk of death compared with rivaroxaban or warfarin. The endpoints of any bleeding or major bleeding were significantly lower for apixaban and dabigatran than for rivaroxaban or warfarin; the last two drugs had similar profiles for bleeding risk.

Comparison with other studies

Some selective prescribing, as seen in this study, is perhaps unsurprising and consistent with other reports from small cohorts, often single centre studies.[19] With the availability of various NOACs, there is an opportunity to fit the particular NOAC to the patient's clinical profile.[20-22] Thus, dabigatran users were slightly younger than users of the other NOACs,

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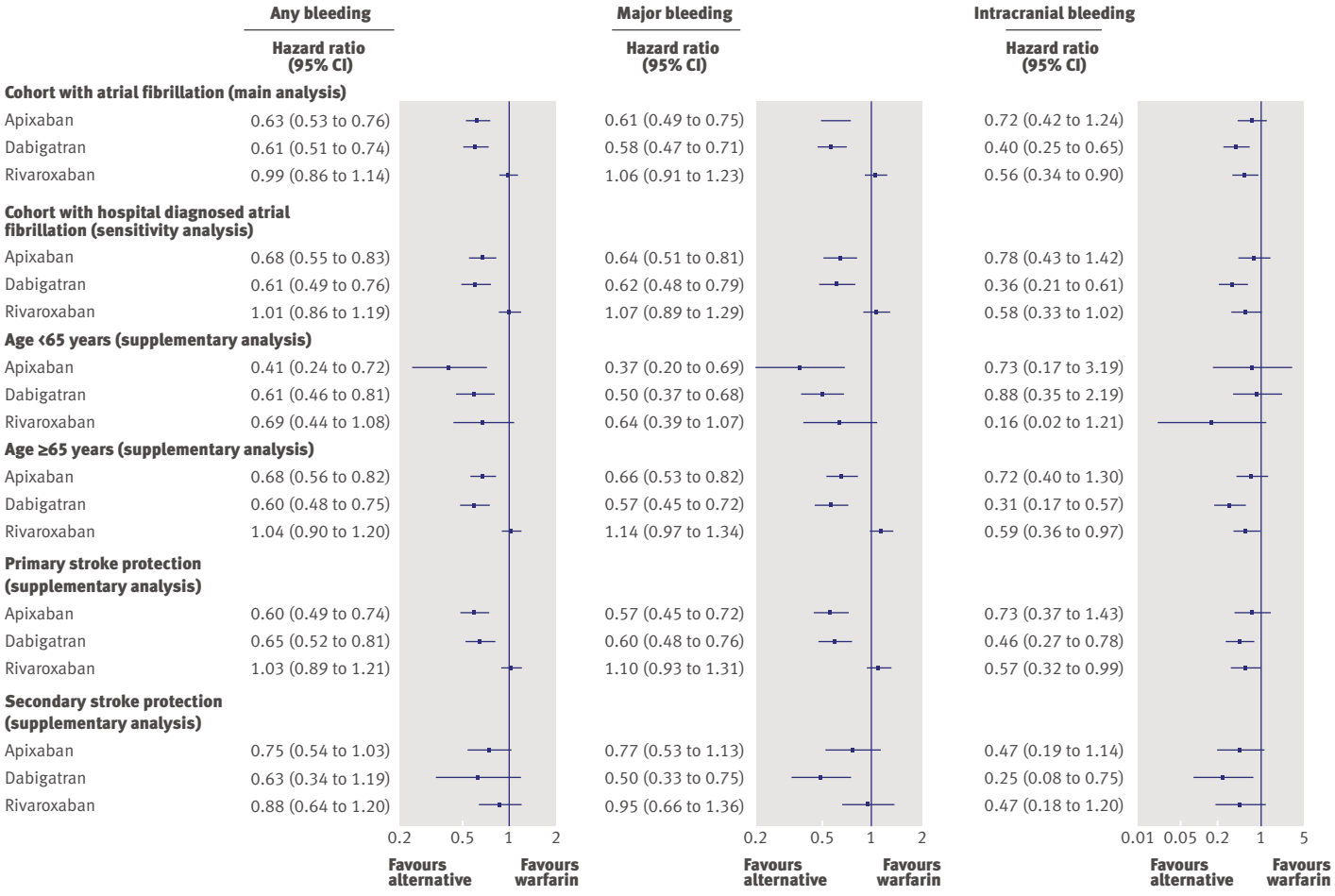

Fig 3 | Propensity weighted (inverse probability of treatment weighted) Cox hazard ratios for one year follow-up (intention to treat) for non-vitamin K antagonist oral anticoagulants (NOACs) compared with warfarin for bleeding endpoints. Supplementary material provides corresponding results for follow-up of 2.5 years and for continuous treatment analysis

but this may reflect our study focus on standard dose dabigatran (150 mg twice daily), which is not recommended for elderly patients (>80 years). NOACs were generally less used in patients with vascular disease, whereas warfarin was more commonly prescribed. This could reflect previous concerns of a numerical increase in cardiac ischaemic events with dabigatran treatment compared with warfarin, and the cardioprotective effect of warfarin.[23] The lower use of dabigatran in patients with renal impairment pertains to the caution with this NOAC, given its relative high renal excretion.[24] The higher use of rivaroxaban and apixaban in patients with previous ischaemic stroke or systemic embolism may possibly reflect the high proportion of such patients in their respective clinical trials.[2 3] In addition, throughout the past three to five years, NOACs have gained increasing attention, as healthcare authorities and caregivers learn the benefits and limitations of these new drugs. These include, for example, ease of being administered, continuous monitoring of renal function, and patient preferences. However, our analysis was not designed to take into account these facts and thus should be viewed in this perspective.

Our methodological approach accounted for such '"real world" selective prescribing through propensity weights.

In our analysis, mortality risks were similar in patients treated with warfarin and rivaroxaban, and higher than with apixaban or dabigatran. Mortality is a relevant endpoint in stroke prevention studies, and even in the historical trials, warfarin significantly reduced all cause mortality (by 26%) compared with placebo or control.[12] A meta-analysis of NOAC trials found a 10% reduction in all cause mortality with standard dose NOACs compared with warfarin.[25] Our analysis extends these observations, showing a differential effect of NOACs with a similar all cause mortality with rivaroxaban compared with warfarin, whereas dabigatran and apixaban had similar mortality that were significantly lower than warfarin. Indeed, mortality was not significantly different between rivaroxaban and warfarin in ROCKET-AF (the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), whereas the mortality reduction was significant for apixaban (11% reduction) and borderline significant for dabigatran 150 mg twice daily

(10% reduction, P=0.05), compared with warfarin in their respective phase 3 trials.[2 26 27]

We found comparable bleeding rates for warfarin and rivaroxaban that were noticeably higher than for both apixaban and dabigatran. Apixaban and dabigatran both yielded statistically significantly lower risks for any bleeding or major bleeding with reference to warfarin, even after 2.5 years of follow-up. These associations remained present in most subgroups. Again, these data are consistent with the results of the NOAC phase 3 clinical trial. In ROCKET-AF, for example, the rates of major and clinically relevant non-major bleeding were similar for rivaroxaban and warfarin. Nevertheless, the validity of the data from the ROCKET-AF trial has recently been questioned owing to use of an inaccurate point-of-care device (Hemosense INratio; HemoSense, San Jose, CA).[28] A US Food and Drug Administration mandated post hoc analysis of the trial data examined bleeding outcomes in patients with chronic inflammation, acute inflammation, or hematocrit levels out of range.[29] Specifically for the outcome of major bleeding, treatment with rivaroxaban was favoured compared with warfarin (hazard ratio 0.87, 95% confidence interval 0.70 to 1.08) in the subgroup of patients with none of the conditions; whereas the hazard ratio in patients with any of the conditions was 1.18 (0.98 to 1.42). As discussed elsewhere,[28] these results are counterintuitive, as the patients with the mentioned conditions could have received a higher dose of warfarin due to the inaccurate point-of-care devices resulting in an increased risk of bleeding. Notwithstanding the trial results, biased or not, rivaroxaban displayed similar bleeding risks to warfarin. Our comparisons on relative bleeding risks contrasting rivaroxaban with warfarin using data from clinical practice support this observation. For dabigatran, the endpoint "all bleeding" was significantly lower with both doses of dabigatran versus warfarin, whereas dabigatran 150 mg twice daily was associated with a non-significant reduction in major bleeding compared with warfarin. For apixaban, all bleeding and major bleeding were significantly lower compared with warfarin in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial.[3] In their respective trials, all NOACs were associated with significantly decreased intracranial bleeding compared with warfarin, but our data did only yield significant results for dabigatran and rivaroxaban. This, however, might reflect the smaller number of events and the shorter follow-up for (especially) patients treated with apixaban.

Limitations of this study

The present study has several limitations, which mainly relate to the observational nature of the data. Some unmeasured and residual confounding is likely to persist. For example, the differences in stroke and bleeding could potentially be related to selective prescribing. Although we applied propensity weighting to account for baseline differences, we are unlikely to have captured the full extent and effect of different prescribing behaviour. We did not have access to information on time in therapeutic range among warfarin users; nor did we have information on laboratory, anthropometric, or socioeconomic factors. However, our sensitivity analyses did not change the conclusions from the main analyses, suggesting a limited potential for further adjustment for confounding within the setting of Danish administrative registry data. Our data also apply to a predominantly white European population, and differential efficacy and safety benefits are seen between people of Asian and non-Asian origin, which we were unable to investigate.[30 31] Finally, there is the risk of misclassification, and various limitations of comparative effectiveness studies of newly marketed drugs have been noted previously[32] that would also apply to the present study. Our analyses were not focused on direct comparisons of one NOAC agent against another; further research is warranted to establish comparative effectiveness and safety within the NOAC agent group. Moreover, in accordance with the described methods we chose to exclude patients treated with a non-standard (that is, reduced) dose of NOAC. It remains to be established whether each of the NOACs provide comparative effectiveness and safety compared with warfarin when prescribing a reduced dose of a specific NOAC drug.

Conclusions

All NOACs are generally safe and effective alternatives to warfarin in a clinical care setting. For ischaemic stroke, our weighted analysis suggests no significant differences between the NOACs and warfarin. The risks for death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran, compared with warfarin.

Contributors: TBL and had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He is the guarantor. All authors contributed to the design; analysed and interpreted the data; drafted the article or revised it critically for important intellectual content; and approved the final version to be published.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at ww.icmje.org/coi_disclosure.pdf and declare: TBL has served as an investigator for Janssen Scientific Affairs, LLC, and Boehringer Ingelheim and has served as a speaker for Bayer, Bristol-Myers Squibb/Pfizer, and Boehringer Ingelheim. PBN has served as a speaker for Boehringer Ingelheim. GYHL has served as a consultant for Bayer, Astellas, Merck, Sanofi, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Biotronik, Portola, and Boehringer Ingelheim and has served as a speaker for Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, and Sanofi Aventis.

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Data sharing: Not possible owing to legislation by the Danish government. The Danish Health Data Authority provided the data material.

Transparency: The lead author (TBL) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

1 Connolly SJ, Ezekowitz MD, Yusuf S, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51. doi:10.1056/NEJMoa0905561.
2 Patel MR, Mahaffey KW, Garg J, et al. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91. doi:10.1056/NEJMoa1009638.
3 Granger CB, Alexander JH, McMurray JJV, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92. doi:10.1056/NEJMoa1107039.
4 Giugliano RP, Ruff CT, Braunwald E, et al. ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093-104. doi:10.1056/NEJMoa1310907.
5 Camm AJ, Lip GYH, De Caterina R, et al. ESC Committee for Practice Guidelines-CPG Document Reviewers. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;14:1385-413. doi:10.1093/europace/eus305.
6 Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955-62. doi:10.1016/S0140-6736(13)62343-0.
7 Olesen JB, Sørensen R, Hansen ML, et al. Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naïve atrial fibrillation patients: Danish nationwide descriptive data 2011-2013. *Europace* 2015;17:187-93. doi:10.1093/europace/euu225.
8 Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39(Suppl):38-41. doi:10.1177/1403494810394717.
9 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39(Suppl):30-3. doi:10.1177/1403494811401482.
10 Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39(Suppl):22-5. doi:10.1177/1403494810387965.
11 Krarup L-H, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology* 2007;28:150-4. doi:10.1159/000102143.
12 Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857-67. doi:10.7326/0003-4819-146-12-200706190-00007.
13 Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999;18:695-706. doi:10.1002/(SICI)1097-0258(19990330)18:6<695::AID-SIM60>3.0.CO;2-O.
14 Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138:1093-100. doi:10.1378/chest.10-0134.
15 Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11:550-60. doi:10.1097/00001648-200009000-00011.
16 Stürmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. *J Intern Med* 2014;275:570-80. doi:10.1111/joim.12197.
17 McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Stat Med* 2013;32:3388-414. doi:10.1002/sim.5753.
18 Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. *Biom J* 2009;51:171-84. doi:10.1002/bimj.200810488.
19 Lee SI, Sayers M, Lip GYH, Lane DA. Use of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients: insights from a specialist atrial fibrillation clinic. *Int J Clin Pract* 2015;69:1341-8. doi:10.1111/ijcp.12712.
20 Shields AM, Lip GYH. Choosing the right drug to fit the patient when selecting oral anticoagulation for stroke prevention in atrial fibrillation. *J Intern Med* 2015;278:1-18. doi:10.1111/joim.12360.
21 Diener H-C, Aisenberg J, Ansell J, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2. *Eur Heart J* 2016;:ehv643; Epub ahead of print. doi:10.1093/eurheartj/ehw069.
22 Diener H-C, Aisenberg J, Ansell J, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1. *Eur Heart J* 2016;:ehv643; Epub ahead of print. doi:10.1093/eurheartj/ehv643.
23 Lip GYH, Lane DA. Does warfarin for stroke thromboprophylaxis protect against MI in atrial fibrillation patients?*Am J Med* 2010;123:785-9. doi:10.1016/j.amjmed.2010.01.031.
24 Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2015;17:1467-507. doi:10.1093/europace/euv309.
25 Ruff CT, Giugliano RP, Antman EM, et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). *Am Heart J* 2010;160:635-41. doi:10.1016/j.ahj.2010.06.042.
26 Connolly SJ, Ezekowitz MD, Yusuf S, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51. doi:10.1056/NEJMoa0905561.
27 Connolly SJ, Eikelboom J, Joyner C, et al. AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;364:806-17. doi:10.1056/NEJMoa1007432.
28 Cohen D. Rivaroxaban: can we trust the evidence?*BMJ* 2016;352:i575. doi:10.1136/bmj.i575.
29 Patel MR, Hellkamp AS, Fox KAA. ROCKET AF Executive Committee and Investigators. Point-of-Care Warfarin Monitoring in the ROCKET AF Trial. *N Engl J Med* 2016;374:785-8. doi:10.1056/NEJMc1515842.
30 Wang K-L, Lip GYH, Lin S-J, Chiang C-E. Non-Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Asian Patients With Nonvalvular Atrial Fibrillation: Meta-Analysis. *Stroke* 2015;46:2555-61. doi:10.1161/STROKEAHA.115.009947.
31 Chiang C-E, Wang K-L, Lip GYH. Stroke prevention in atrial fibrillation: an Asian perspective. *Thromb Haemost* 2014;111:789-97. doi:10.1160/TH13-11-0948.
32 Schneeweiss S, Gagne JJ, Glynn RJ, Ruhl M, Rassen JA. Assessing the comparative effectiveness of newly marketed medications: methodological challenges and implications for drug development. *Clin Pharmacol Ther* 2011;90:777-90. doi:10.1038/clpt.2011.235.

Supplementary material