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propensity weighted nationwide cohort study

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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

Torben Bjerregaard Larsen,1,2 Flemming Skjøth,2,3 Peter Brønnum Nielsen,2 Jette Nordstrøm Kjældgaard,2 Gregory Y H Lip2,4

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 \( (n=35436, 57\%) \), dabigatran 150 mg \( (n=12701, 21\%) \), 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; 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 \( (3.0\% v 3.3\%, \text{respectively}) \) compared with warfarin: hazard ratio 0.83 \((95\% \text{confidence interval 0.69 to 0.99})\). The hazard ratios for dabigatran and apixaban \((2.8\% \text{and} 4.9\%, \text{respectively})\) were non-significant compared with warfarin. The annual risk of death was significantly lower with apixaban \((5.2\%)\) and dabigatran \((2.7\%)\) \((0.65, 0.56 \text{to} 0.75 \text{and} 0.63, 0.48 \text{to} 0.82, \text{respectively})\) 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 \((5.0\%)\) \((0.62, 0.51 \text{to} 0.74)\). 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.

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, 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 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, 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%. 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.

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 CHA2DS2-VASc score for assessing stroke risk, and a HAS-BLED score 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. We used generalised boosted models, based on 10 000 regression trees, to calculate weights for optimal balance between the treatment populations. 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 CHA2DS2-VASc and HAS-BLED scores.

The treatments should be contrasted on comparable populations, and any patient must have a positive
‡Scores range from 0-9, reflecting risk of bleeding in patients with atrial fibrillation receiving anticoagulants (see supplementary table 2).

†Scores range from 0-9, reflecting risk of stroke in patients with atrial fibrillation not receiving anticoagulants (see supplementary table 2).

*Maximum standardised pairwise difference, before and after inverse probability of treatment weighting.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NOAC</th>
<th>Warfarin</th>
<th>All</th>
<th>Mean (SD) HAS-BLED score‡</th>
<th>Mean (SD) CHA 2DS2VASc score†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No in group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>39.7 (2522)</td>
<td>33.9 (4304)</td>
<td>43.1 (3100)</td>
<td>2.3 (1.2)</td>
<td>2.8 (1.6)</td>
</tr>
<tr>
<td>Median (interquartile range) age (years)</td>
<td>71.3 (65.8-77.2)</td>
<td>67.6 (62.0-72.4)</td>
<td>71.8 (65.7-78.9)</td>
<td>2.0 (1.1)</td>
<td>2.2 (1.2)</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>78.2 (9697)</td>
<td>64.6 (8180)</td>
<td>77.7 (5590)</td>
<td>43.1 (4100)</td>
<td>74.2 (26295)</td>
</tr>
<tr>
<td>Age &gt;75</td>
<td>33.7 (2140)</td>
<td>13.9 (1766)</td>
<td>38.1 (2737)</td>
<td>41.4 (4655)</td>
<td>73.0 (45052)</td>
</tr>
<tr>
<td>Previous atrial fibrillation diagnose</td>
<td>68.9 (4374)</td>
<td>70.0 (8889)</td>
<td>60.2 (4333)</td>
<td>51.5 (1824)</td>
<td>58.1 (35839)</td>
</tr>
<tr>
<td>Mean (SD) CHA 2DS2VASc score†</td>
<td>2.3 (1.2)</td>
<td>2.2 (1.1)</td>
<td>2.0 (1.2)</td>
<td>2.3 (1.2)</td>
<td>2.2 (1.2)</td>
</tr>
</tbody>
</table>

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 122068 patients as new users of oral anticoagulant treatment, including 35035 patients receiving one of the non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) with reduced doses, who were excluded. Overall, we excluded 25355 patients with an indication for valvular atrial fibrillation or venous thromboembolism (see supplementary figure 1).

The study population (n=6378) was distributed according to treatment type: warfarin (n=35436, 57%), dabigatran (n=12701, 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 CHA2DS2-VASc score of 2.2, than other groups (older, with >33% aged ≥75 and a CHA2DS2-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)
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 figure 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).
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.15 With the availability of various NOACs, there is an opportunity to fit the particular NOAC to the patient’s clinical profile.20,21 Thus, dabigatran users were slightly younger than users of the other NOACs,

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

<table>
<thead>
<tr>
<th>Ischaemic stroke or systemic embolism</th>
<th>Ischaemic stroke</th>
<th>Death</th>
<th>Ischaemic stroke, systemic embolism, or death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort with atrial fibrillation (main analysis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.08 (0.91 to 1.27)</td>
<td>1.11 (0.94 to 1.30)</td>
<td>0.65 (0.56 to 0.75)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1.17 (0.89 to 1.54)</td>
<td>1.24 (0.94 to 1.64)</td>
<td>0.63 (0.48 to 0.82)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.83 (0.69 to 0.99)</td>
<td>0.86 (0.72 to 1.04)</td>
<td>0.92 (0.82 to 1.03)</td>
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<tr>
<td>Cohort with hospital diagnosed atrial fibrillation (sensitivity analysis)</td>
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<tr>
<td>Apixaban</td>
<td>1.03 (0.86 to 1.25)</td>
<td>1.07 (0.88 to 1.29)</td>
<td>0.67 (0.57 to 0.79)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1.00 (0.72 to 1.38)</td>
<td>1.02 (0.73 to 1.42)</td>
<td>0.69 (0.48 to 0.98)</td>
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<tr>
<td>Rivaroxaban</td>
<td>0.86 (0.70 to 1.07)</td>
<td>0.88 (0.71 to 1.09)</td>
<td>0.88 (0.77 to 1.01)</td>
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<tr>
<td>Age &lt;65 years (supplementary analysis)</td>
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<tr>
<td>Apixaban</td>
<td>1.06 (0.70 to 1.61)</td>
<td>1.03 (0.67 to 1.56)</td>
<td>0.43 (0.19 to 0.95)</td>
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<tr>
<td>Dabigatran</td>
<td>1.00 (0.78 to 1.29)</td>
<td>1.12 (0.87 to 1.46)</td>
<td>0.58 (0.43 to 0.78)</td>
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<tr>
<td>Rivaroxaban</td>
<td>0.79 (0.53 to 1.19)</td>
<td>0.89 (0.59 to 1.35)</td>
<td>0.90 (0.61 to 1.31)</td>
</tr>
<tr>
<td>Age ≥65 years (supplementary analysis)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.08 (0.91 to 1.29)</td>
<td>1.13 (0.94 to 1.35)</td>
<td>0.67 (0.57 to 0.78)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1.20 (0.87 to 1.67)</td>
<td>1.26 (0.91 to 1.76)</td>
<td>0.62 (0.46 to 0.84)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.82 (0.67 to 1.00)</td>
<td>0.85 (0.69 to 1.04)</td>
<td>0.91 (0.81 to 1.03)</td>
</tr>
<tr>
<td>Primary stroke protection (supplementary analysis)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.03 (0.77 to 1.37)</td>
<td>1.11 (0.83 to 1.48)</td>
<td>0.61 (0.51 to 0.74)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1.24 (0.72 to 2.11)</td>
<td>1.32 (0.76 to 2.30)</td>
<td>0.56 (0.43 to 0.73)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.85 (0.65 to 1.11)</td>
<td>0.88 (0.67 to 1.17)</td>
<td>0.85 (0.74 to 0.96)</td>
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<tr>
<td>Secondary stroke protection (supplementary analysis)</td>
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<tr>
<td>Apixaban</td>
<td>1.07 (0.88 to 1.29)</td>
<td>1.09 (0.90 to 1.33)</td>
<td>0.71 (0.56 to 0.92)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1.01 (0.80 to 1.27)</td>
<td>1.07 (0.84 to 1.35)</td>
<td>0.65 (0.40 to 1.06)</td>
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<tr>
<td>Rivaroxaban</td>
<td>0.80 (0.63 to 1.00)</td>
<td>0.84 (0.66 to 1.05)</td>
<td>1.16 (0.93 to 1.44)</td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI)
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.23 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.20 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 (1% reduction) and borderline significant for dabigatran 150 mg twice daily.

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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.
have received a higher dose of warfarin due to the inac-
scious. For example, the differences in stroke and bleeding
some limitations of this study
risks contrasting rivaroxaban with warfarin using data
patients with chronic inflammation, acute
Specifically for the outcome of major bleeding, treat-
rivaroxaban was favoured compared with
in patients with none of the conditions; whereas the hazard ratio in patients
inflammation, or hematocrit levels out of range.29
As discussed elsewhere,28 these results are counterintuitive,
instead of major bleeding with reference to warfarin.
results, biased or not, rivaroxaban displayed similar bleeding
databases with rivaroxaban and warfarin. Nevertheless, the validity
In ROCKET-AF, for example, the rates of major
rates of major bleeding with reference to warfarin,
even after 2.5 years of follow-up. These associations
remaining present in most subgroups. Again, these data
are consistent with the results of the NOAC phase 3 clini-
cal evidence from clinical practice support this observation. For dab-
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
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 intracra-
nial bleeding compared with warfarin, but our data did
only yield significant results for dabigatran and rivarox-
abrilisation, or hematocrit levels out of range.29

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 signifi-
cantly lower for apixaban and dabigatran, compared
with warfarin.

Contributors: TBL and had full access to all of the data in this study and
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
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Bristol-Myers Squibb/Pfizer, and Boehringer Ingelheim. GRHL has served as a
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Data sharing: Not possible owing to legislation by the Danish
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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.

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(10% reduction, P=0.05), compared with warfarin in
their respective phase 3 trials.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 warfa-
rin, even after 2.5 years of follow-up. These associations

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 per-
sist. 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 cap-
tured 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 anal-
yses 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.60 31 Finally, there is the
risk of misclassification, and various limitations of
comparative effectiveness studies of newly marketed
drugs have been noted previously32 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 estab-
lish 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 spe-
cific 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
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with warfarin.
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Supplementary material