Rivaroxaban versus warfarin and dabigatran in atrial fibrillation: comparative effectiveness and safety in Danish routine care†

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ABSTRACT

Purpose To evaluate effectiveness and safety of rivaroxaban versus warfarin or dabigatran etexilate in a prospective cohort of routine care non-valvular atrial fibrillation (AF) patients during February 2012 to August 2014.

Methods We identified in nationwide health registries a cohort of AF patients who were new-users of rivaroxaban 15 mg (R15) or 20 mg (R20); dabigatran 110 mg (D110) or 150 mg (D150); or warfarin. Propensity-adjusted Cox regression was used to compare outcome rates in four settings: ‘R15 vs. warfarin’; ‘R15 vs. D110’; ‘R20 vs. warfarin’; and ‘R20 vs. D150’.

Results Rivaroxaban users (R15: n = 776; R20: n = 1629) were older and with more comorbidities than warfarin (n = 11,045) and dabigatran users (D110: n = 3588; D150: n = 5320). Rivaroxaban 15-mg users had the overall highest crude mortality rate. After propensity adjustment, rivaroxaban had lower stroke rates vs. warfarin (R15: hazard ratio [HR] 0.46, 95% confidence interval [CI]: 0.26–0.82; R20 HR: 0.72, 95% CI: 0.51–1.01), and similar stroke rates vs. dabigatran. The bleeding rate was similar to warfarin and moderately higher vs. dabigatran (R15 vs. D110 HR: 1.28, 95% CI: 0.82–2.01; R20 vs. D150 HR: 1.81, 95% CI: 1.25–2.62). The mortality rate was higher vs. dabigatran (R15 vs. D110 HR: 1.43, 95% CI: 1.13–1.81; R20 vs. D150 HR: 1.52, 95% CI: 1.06–2.19).

Conclusions Rivaroxaban was associated with similar or lower stroke rates, but higher bleeding and mortality rates. Channeling of rivaroxaban towards elderly and less healthy patients may have generated residual confounding. In particular, our findings cannot stand alone when deciding which oral anticoagulant to prescribe. Copyright © 2016 John Wiley & Sons, Ltd.

INTRODUCTION

Non-vitamin K antagonist oral anticoagulants (NOACs) are fast becoming the mainstay therapy for stroke prevention in patients with non-valvular atrial fibrillation (AF). Observational studies of comparative effectiveness, despite their potential for inherent biases, are important tools for confirming safety and effectiveness of NOACs in routine care.1 For dabigatran etexilate, the first NOAC marketed in AF, observational studies have corroborated trial findings,2 confirming that dabigatran provides noninferior stroke protection, and similar or lower bleeding risk compared to warfarin.3,4 However, for rivaroxaban, the second NOAC marketed in AF, large-scale observational studies are more limited. Findings from the Dresden NOAC registry suggest non-inferior or lower major bleeding rates with rivaroxaban than with vitamin K antagonists.5,6 A propensity-based comparison of rivaroxaban and warfarin based on US health claims data concurred with the ROCKET-AF trial,7 which reported non-inferiority of rivaroxaban vs. warfarin for stroke/systemic embolism (event rate 1.71% vs. 2.16%; p < 0.001) and bleeding events (3.60% vs. 3.45%, p = 0.58).8
Reconfirming such observational findings in other study populations is important, not least in light of the concerns regarding ROCKET-AF which enrolled a very high-risk population (87% of the intention-to-treat population had CHADS2 ≥ 3). Moreover, with several NOACs currently approved in AF, a clinician will not only want to know *if* to use a NOAC, but also *which* NOAC to use. Indirect comparisons based on trial data have been inconclusive, and head-to-head comparisons, based on trial data and observational evidence alike, are needed.

In this study, data from nationwide Danish registries on prescription purchases and hospital discharges were used to perform propensity-adjusted analyses of outcome rates, following a first-time purchase of rivaroxaban, warfarin, or dabigatran in the period February 2012–August 2014 (apixaban was not considered because of limited data).

### METHODS

#### Study population

Study data were obtained by merging three nationwide Danish registries, using the civil registration number assigned to all Danish residents: the Danish National Prescription Registry (containing information on all prescription purchases in Denmark since 1995, coded using Anatomical Therapeutic Chemical [ATC] classification codes); The Danish National Patient Register11 (containing information on all prescription purchases and hospital discharges in Denmark since 1976, coded according to the International Classification of Diseases [ICD]), and the Danish Civil Registration System (containing information on date of birth, sex, and residency).12

We identified all patients with an existing diagnosis of atrial fibrillation (ICD10 code: 148) who had purchased rivaroxaban (15 mg: R15; or 20 mg: R20), warfarin (any dose), or dabigatran (110 mg: D110; or 150 mg: D150) in the period from 1 February 2012 to 30 July 2014 (ATC codes in Supplementary Table 1). The date of purchase was designated the baseline date.

To obtain a new-user cohort (to reduce ‘healthy user bias’), we excluded patients who had purchased oral anticoagulants (warfarin, rivaroxaban, dabigatran, or apixaban) within two years of baseline. We subsequently excluded patients for which either of the following applied: immigrated within one year before baseline; prior venous thromboembolism diagnosis; knee or hip surgery within 30 days before baseline; prior valvular surgery; and prior diagnosis of mitral stenosis.

**Outcomes and baseline characteristics**

Patients were followed from baseline and until the occurrence of an outcome of interest, death, emigration, or end of study (31 July 2014), whichever came first. Endpoints were ascertained according to the International Classification of Disease, 10th revision (ICD10).

Primary endpoints were: ischemic stroke/systemic embolism (SE)/transient ischemic attack (TIA) (ICD10: I63–64, I74, G45); any bleeding (intracranial bleeding, gastrointestinal, major bleeding events: ICD-10 codes in the Supporting Information); and all-cause death.

Secondary endpoints were: intracranial bleeding (ICD10: I60-I62); gastrointestinal bleeding (ICD10: K25-K29); myocardial infarction (ICD10: I21-I23); and venous thromboembolism (ICD-10 codes in the Supporting Information).

Other baseline characteristics were obtained from the Danish National Patient Register and the Danish National Prescription Registry (Supplementary Table 1). For quantifying stroke and bleeding risk, we combined baseline characteristics into CHADS2/CHA2DS2-VASc, HAS-BLED risk scores (Supplementary Tables 1–2).

#### Statistical analysis

Baseline characteristics were summarized descriptively. We calculated crude event rates for all endpoint and treatment combinations. For the primary endpoints, enough events were available to pursue adjusted comparisons. We anticipated substantial systematic differences in baseline characteristics between treatment groups. For example, D150 is contraindicated in decreased renal function (creatinine clearance <30 ml/min); whereas R15 can be used in patients with relatively low renal function (creatinine clearance 15–30 ml/min). Comparing treatment effects under principally different indications is problematic because it violates the positivity assumption needed for valid inference. We therefore restricted attention to contrasts between clinically meaningful treatment alternatives: ‘R15 vs. warfarin’, ‘R15 vs. D110’, ‘R20 vs. warfarin’, and ‘R20 vs. D150’.

Propensity score (PS) methods were subsequently used to control for baseline differences. Specifically, each of the four contrasts ‘R15 vs. warfarin’, ‘R15 vs. D110’, ‘R20 vs. warfarin’, and ‘R20 vs. D150’ defined a sub-cohort of patients receiving either rivaroxaban or a comparison treatment. Within each sub-cohort, we derived a PS for the probability of rivaroxaban therapy using boosted logistic regression models, a flexible
regression method which automatically learns nonlinearities and interactions among included covariates. Variables listed in Table 1 were used as candidate covariates in PS models, alongside time since rivaroxaban market introduction. To ensure that sufficient data was available to support a formal treatment comparison and to further reduce the risk of violating the positivity assumption, we used asymmetric trimming, discarding patients with a PS <2.5 percentile of the PS among rivaroxaban users, respectively >97.5 percentile among comparison users. Standardized mean differences were used to check balance of treatment groups. Cox proportional hazards models stratified by deciles of the trimmed PS were then used to compare event rates within each sub-cohort.

Net clinical benefit was assessed as in Renda et al., using Cox models stratified by deciles of the trimmed PS to compare rates of the composite endpoint ‘ischemic stroke or intracranial bleeding’, respectively, ‘ischemic stroke or intracranial bleeding or death’, with rivaroxaban vs. the comparison treatment.

R version 3.0.2 with the add-on ‘twang’ was used for analysis. A two-sided P-value less than 0.05 was considered statistically significant.

**Sensitivity analyses**

We conducted various sensitivity analyses to challenge our findings. First, we entered the trimmed PS in ‘standardized mortality reweighted’ Cox models estimating the average treatment effect on the treated. Second, we obtained an alternative PS, using the high-dimensional propensity score technique to screen the full Danish National Patient Register and the Danish National Prescription Registry for putative confounders (details in Supplementary Table 3). We then stratified Cox models for the primary endpoints by deciles of this PS, after performing asymmetric trimming as previously described.

Third, we repeated the primary analysis after truncation of follow-up when there was evidence of discontinuation; censoring patients if deemed to having been off treatment for more than 30 days; or if they switched treatment.

**Ethical considerations**

No ethical approval is required for anonymous register studies in Denmark. The study was approved by the Danish Data Protection Agency (J. No. File No. 2012-41-0633).

### Table 1. Baseline characteristics by treatment group.

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th></th>
<th>Dabigatran</th>
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<th>Warfarin</th>
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<tbody>
<tr>
<td></td>
<td>15 mg</td>
<td>20 mg</td>
<td>110 mg</td>
<td>150 mg</td>
<td>11 045</td>
</tr>
<tr>
<td>N</td>
<td>776</td>
<td>1629</td>
<td>3588</td>
<td>5320</td>
<td>11 045</td>
</tr>
<tr>
<td>Female</td>
<td>59.7 (463)</td>
<td>48.9 (797)</td>
<td>56.8 (2039)</td>
<td>36.5 (1941)</td>
<td>43.0 (4745)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>82.8 (8.7)</td>
<td>72.8 (9.9)</td>
<td>80.8 (8.0)</td>
<td>66.0 (8.5)</td>
<td>72.6 (11.3)</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>96.1 (746)</td>
<td>82.0 (1336)</td>
<td>95.5 (3427)</td>
<td>62.4 (3319)</td>
<td>78.3 (8649)</td>
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<tr>
<td>Age ≥ 75 years</td>
<td>82.6 (641)</td>
<td>39.2 (639)</td>
<td>81.4 (2921)</td>
<td>12.4 (659)</td>
<td>45.1 (4984)</td>
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<td>Comorbidities</td>
<td></td>
<td></td>
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<tr>
<td>CHADS2*, mean (SD)</td>
<td>2.3 (1.2)</td>
<td>1.5 (1.3)</td>
<td>2.0 (1.2)</td>
<td>1.0 (1.0)</td>
<td>1.6 (1.3)</td>
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<td>CHA2DS2-VaSC†, mean (SD)</td>
<td>4.2 (1.5)</td>
<td>3.0 (1.7)</td>
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<td>2.1 (1.4)</td>
<td>3.1 (1.7)</td>
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<tr>
<td>HAS-BLED‡, mean (SD)</td>
<td>2.8 (1.1)</td>
<td>2.3 (1.1)</td>
<td>2.6 (1.1)</td>
<td>1.9 (1.2)</td>
<td>2.4 (1.2)</td>
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<td>Prior bleeding</td>
<td>17.0 (132)</td>
<td>14.3 (233)</td>
<td>16.8 (603)</td>
<td>10.1 (539)</td>
<td>14.3 (1581)</td>
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<td>Prior stroke</td>
<td>20.9 (162)</td>
<td>18.2 (297)</td>
<td>16.9 (605)</td>
<td>9.4 (500)</td>
<td>12.2 (1344)</td>
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<td>Heart failure</td>
<td>17.4 (135)</td>
<td>5.3 (86)</td>
<td>8.6 (310)</td>
<td>3.7 (196)</td>
<td>9.9 (1095)</td>
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<td>Hypertension</td>
<td>38.4 (298)</td>
<td>35.2 (574)</td>
<td>36.5 (1310)</td>
<td>27.7 (1475)</td>
<td>35.3 (3903)</td>
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<td>Renal disease</td>
<td>10.1 (78)</td>
<td>1.5 (25)</td>
<td>2.5 (88)</td>
<td>1.1 (60)</td>
<td>6.5 (716)</td>
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<td>Liver disease</td>
<td>0.5 (4)</td>
<td>0.2 (3)</td>
<td>0.3 (11)</td>
<td>0.2 (8)</td>
<td>0.3 (34)</td>
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<tr>
<td>Diabetes</td>
<td>17.4 (135)</td>
<td>13.8 (225)</td>
<td>14.0 (504)</td>
<td>12.9 (686)</td>
<td>16.8 (1852)</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>22.2 (172)</td>
<td>12.2 (199)</td>
<td>18.1 (648)</td>
<td>9.9 (527)</td>
<td>20.5 (2259)</td>
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<tr>
<td>Comedication</td>
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</tr>
<tr>
<td>Aspirin</td>
<td>55.8 (433)</td>
<td>44.0 (717)</td>
<td>48.9 (1756)</td>
<td>36.1 (1920)</td>
<td>48.1 (5314)</td>
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<tr>
<td>Clopidogrel</td>
<td>11.5 (89)</td>
<td>10.2 (166)</td>
<td>10.8 (388)</td>
<td>6.1 (327)</td>
<td>8.9 (980)</td>
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<td>NSAID</td>
<td>21.5 (167)</td>
<td>21.2 (345)</td>
<td>22.4 (804)</td>
<td>24.7 (1312)</td>
<td>23.1 (2547)</td>
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</tbody>
</table>

Data are shown as ‘percent (count)’ unless otherwise indicated.

*CHADS2: score ranging from 0 to 5 which reflect the stroke risk in atrial fibrillation patients not in anticoagulant therapy (see Supplementary Table).
†CHA2DS2-VaSC: score ranging from 0 to 9 which reflect the risk of stroke in atrial fibrillation patients not in anticoagulant therapy (see Supplementary Table 2).
‡HAS-BLED: score ranging from 0 to 9 which reflect the risk of bleeding in atrial fibrillation patients undergoing anticoagulant therapy (see Supplementary Table 2). Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; SD, standard deviation
RESULTS

Characteristics of the study population

A flowchart is provided in Figure 1. After exclusions, the patient population comprised 2405 rivaroxaban users (10.8%), 8908 dabigatran users (39.8%), and 11,045 warfarin users (49.4%).

Baseline characteristics according to treatment group are shown in Table 1. Patients in the R15 group were older than patients in the other treatment groups (mean age: 82.8 years) and had a high predicted stroke and bleeding risk (mean CHA2DS2-VASc 4.2; mean HAS-BLED 2.8). Patients in the R20 group were younger than those in the R15 group (mean age: 72.8 years), with a perceived stroke and bleeding risk similar to warfarin (mean CHA2DS2-VASc: 3.0 vs. 3.1 for warfarin; mean HAS-BLED 2.3 vs. 2.4 for warfarin) but higher than D150. Renal disease was prevalent in the rivaroxaban 15-mg group (10.1%) but almost absent in the R20 group (1.5%) and D150 group (1.1%). Aspirin usage was more frequent in the R15 group (55.8% vs. 36.1%–48.9% in the other treatment groups).

PS model

Within sub-cohorts, we derived a PS corresponding to each contrast of interest, ‘R15 vs. warfarin’, ‘R15 vs. D110’, ‘R20 vs. warfarin’, and ‘R20 vs. D150’. Mean standardized differences were all below 0.10, indicating acceptable balance (data not shown). However, visual inspection of PS distributions indicated lack of overlap between the rivaroxaban group and comparison groups (Supplementary Figure 1). Upon inspection, we found that the subgroup of patients with high PS for rivaroxaban therapy (PS > 0.5) were almost...
exclusively actual rivaroxaban users, and were also substantially older and with more comorbidities (Supplementary Table 4). Asymmetric trimming of the PS improved overlap but reduced the number of patients in the four sub-cohorts with 30%–45% (‘R15 vs. warfarin’, n = 496 vs. n = 6110; ‘R15 vs. D110’ n = 480 vs. n = 2231; ‘R20 vs. warfarin’, n = 1218 vs. n = 7630; ‘R20 vs. D150’ n = 1044 vs. n = 3936). After trimming, treatment groups were more comparable in terms of baseline characteristics (Supplementary Tables 5a–d).

Outcomes

Patients were followed for stroke/SE/TIA for a median of 1.08 years (interquartile range: 0.52–1.72 years). Event rates are shown in Table 2. Stroke rates ranged from an annual 3.0% in the D150 to 4.6% and 4.7% in the R15, respectively, D110 group. Bleeding rates were slightly higher in the rivaroxaban groups compared to the other treatment groups, with the highest rate observed in the R15 group (6.0% annually). The mortality rate was also high in the R15 group (25.7% annually), being more than double that of the next-highest mortality rate (D110, 12.6% annually). Rates of secondary endpoints were generally low.

Propensity-adjusted hazard ratios for primary endpoints are shown in Figure 2 (R15 vs. comparison treatments) and Figure 3 (R20 vs. comparison treatments). The primary analyses indicated that rivaroxaban was superior, or at least non-inferior, to warfarin in terms of stroke rate (R15, hazard ratio [HR]: 0.46, 95% confidence interval [CI]: 0.26–0.82; R20, HR: 0.72, 95%CI: 0.51–1.01) but that the overall bleeding rate was comparable to that of warfarin. These findings were corroborated by sensitivity analyses; although R15 was no longer superior to warfarin for prevention of stroke/SE/TIA in the high-dimensional propensity score analysis (Figure 2).

When comparing rivaroxaban with dabigatran, the rate of all-cause death was higher in the R15 group (vs. warfarin, HR: 1.47, 95%CI: 1.19–1.82; vs. D110, HR: 1.43, 95%CI: 1.13–1.81) and in the R20 group compared to D150 (HR: 1.52, 95%CI: 1.06–2.19). Stroke rates were similar while bleeding rates were non-significantly higher for R15 compared to D110 (HR: 1.28, 95%CI: 0.82–2.01), and significantly higher for R20 compared to D150 (HR: 1.81, 95%CI: 1.25–2.62). Sensitivity analyses yielded similar findings for rivaroxaban vs. dabigatran, with hazard ratios for bleeding being attenuated slightly compared to the primary analysis (Figures 2, 3).

In terms of net clinical benefit, rivaroxaban was noninferior to both warfarin and dabigatran, except for the composite endpoint combining ischemic stroke, intracranial bleeding, and death, where both warfarin and D110 were superior to R15 (Figure 4).

In adherence-adjusted sensitivity analyses (Supplementary Table 4), directions of associations were unchanged and effect sizes materially similar to the primary analysis, although generally slightly further from the null.

DISCUSSION

In this observational comparative effectiveness and safety study, we observed selective prescribing in a prospective cohort of 22,358 routine care Danish AF patients initiating anticoagulant therapy in the period February 2012–August 2014. Rivaroxaban users had a higher prevalence of prior stroke than warfarin or dabigatran users, while renal disease and cardiovascular comorbidities were more prevalent among rivaroxaban 15-mg users. The crude mortality rate among rivaroxaban 15-mg users was more than double those of comparators. Accounting for

<table>
<thead>
<tr>
<th>Events per 100 person-years (number of events)</th>
<th>Rivaroxaban 15 mg</th>
<th>Rivaroxaban 20 mg</th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
<th>Warfarin 15 mg</th>
<th>Warfarin 150 mg</th>
</tr>
</thead>
<tbody>
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<td><strong>Primary endpoints</strong></td>
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<td></td>
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<tr>
<td>Stroke/SE/TIA</td>
<td>4.6 (28)</td>
<td>4.2 (60)</td>
<td>4.7 (191)</td>
<td>3.0 (185)</td>
<td>3.9 (515)</td>
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<tr>
<td>Any bleeding</td>
<td>6.0 (36)</td>
<td>5.2 (74)</td>
<td>4.1 (169)</td>
<td>2.2 (139)</td>
<td>4.8 (636)</td>
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<tr>
<td>Death</td>
<td>25.7 (160)</td>
<td>8.4 (123)</td>
<td>12.6 (529)</td>
<td>2.5 (162)</td>
<td>8.8 (1206)</td>
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<tr>
<td><strong>Secondary endpoints</strong></td>
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<td></td>
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<td>Intracranial bleeding</td>
<td>0.6 (4)</td>
<td>0.6 (9)</td>
<td>0.5 (19)</td>
<td>0.2 (13)</td>
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<td>Gastrointestinal bleeding</td>
<td>1.0 (6)</td>
<td>0.6 (9)</td>
<td>0.5 (19)</td>
<td>0.3 (17)</td>
<td>0.5 (74)</td>
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<tr>
<td>Myocardial infarction</td>
<td>1.5 (9)</td>
<td>0.9 (13)</td>
<td>1.3 (56)</td>
<td>0.8 (52)</td>
<td>1.7 (227)</td>
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<td>Venous thromboembolism</td>
<td>1.8 (11)</td>
<td>0.5 (7)</td>
<td>0.7 (29)</td>
<td>0.4 (24)</td>
<td>0.6 (88)</td>
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</tr>
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</table>

Abbreviations: SE, systemic embolism; TIA, transient ischemic attack.
selective prescribing via propensity-adjustment, we found that the stroke rate with rivaroxaban was lower than with warfarin, and similar to dabigatran; however, there were moderately higher bleeding rates compared to dabigatran, and a higher all-cause mortality rate.

There are few similar studies to compare with, but our results for rivaroxaban vs. warfarin are consistent with those from both the ROCKET-AF trial (stroke/systemic embolism HR 0.88, 95%CI 0.74–1.03; bleeding HR: 1.03, 95%CI 0.96–1.11), and a recent study utilizing routine care data (stroke/systemic embolism HR 0.77, 95%CI 0.55–1.09; bleeding HR: 1.08, 95%CI 0.71–1.64). Our finding that rivaroxaban is non-inferior to warfarin in terms of bleeding rates is consistent with reports from the routine care Dresden NOAC registry. Concerns have previously been raised about higher risk of gastrointestinal bleedings with rivaroxaban. In our study, gastrointestinal bleeding rates were low, and there were insufficient events to support adjusted comparisons with any useful precision.

A number of differences between our results and previous findings must be highlighted. Indirect comparisons have indicated that D150 is superior to rivaroxaban for the prevention of stroke and systemic embolism but this was not the case in the present study. Also, the higher all-cause mortality seen with R15 relative to warfarin is contrary to trial data, and was not evident from prior indirect comparisons. On the other hand, a higher bleeding rate with R20 compared to D150 is consistent with indirect comparisons. For example, Lip et al. found that rivaroxaban was associated with a higher risk of major bleeding compared to D110 and similar risk to D150.

The poorer bleeding and all-cause mortality prognosis with rivaroxaban in the present study are likely related to selective prescribing that we were unable to fully capture despite extensive confounder adjustment strategies. This is consistent with the finding that patients receiving the lower (and, perceivedly, safer) dose of rivaroxaban had the overall highest crude bleeding rate, and a crude mortality rate more than double those of comparators. Selective
Figure 3. Propensity-adjusted Cox hazard ratios and 95% confidence intervals for the comparison between rivaroxaban and warfarin, respectively, dabigatran. Abbreviations: CI, confidence interval; D150, dabigatran 150 mg; hd-PS: Cox regression, stratified on deciles of the high-dimensional propensity score (see Supplementary Table 3 for details); HR, hazard ratio; R15, rivaroxaban 15 mg; R20, rivaroxaban 20 mg; SMR: standardized mortality reweighted Cox regression, using the trimmed propensity score.

Figure 4. Propensity-adjusted Cox hazard ratios and 95% confidence intervals for the comparison between rivaroxaban and warfarin/dabigatran with respect to net clinical benefit. Abbreviations: CI, confidence interval; D150, dabigatran 150 mg; HR, hazard ratio; R15, rivaroxaban 15 mg; R20, rivaroxaban 20 mg; NCB: net clinical benefit; NCB endpoint 1 = ‘composite of ischemic stroke or intracranial bleeding’; NCB endpoint 2 = ‘composite of ischemic stroke or intracranial bleeding or death’.
prescribing was expected from the onset; for example, R15 is only licensed for those with creatinine clearance 15–49 ml/min, and significant renal impairment is associated with higher mortality. Although we applied state-of-the-art PS adjustment methods to account for baseline differences, we are unlikely to have captured the full extent and effect of selective prescribing. Indeed, the high mortality in the R15 group may suggest that the selective prescribing of this treatment is based on patient prognosis that may only be known between the patient and prescriber, so that unmeasured confounding is present. We were able to use the estimated PS to substantiate the assertion of selective prescribing, by identifying rivaroxaban-treated subgroups for which no comparison may be available in the data. Likely rivaroxaban candidates, according to the PS, were substantially older and with substantially more comorbidities, suggesting a preference for rivaroxaban in older and frailer patients, including patients with prior stroke. We can speculate that clinicians consider rivaroxaban a safer treatment option for higher-risk patients, following the ROCKET-AF trial which demonstrated efficacy and safety in a very high-risk population (87% of patients with CHADS$_2$ ≥3).

**Study limitations**

There are several limitations to the present study. Some unmeasured and residual confounding is likely to persist. For example, we did not have information on laboratory, anthropometric, or socioeconomic data. However, extensive sensitivity analyses did not change conclusions, suggesting a limited potential for further confounding adjustment within the setting of Danish administrative registry data.

A second limitation is the risk of misclassification and ascertainment error, including the problem of inferring drug usage from purchase data. We dealt with this problem by studying treatment initiation as the primary exposure. While sensitivity analyses of adherent usage were also performed, these should be interpreted cautiously because they relied on strong, unverifiable assumptions about daily dosing. Third, various limitations of comparative effectiveness studies of newly marketed drugs were noted by Schneeweiss et al.; they all apply to the present study.

**CONCLUSIONS**

This large-scale observational study provides reassurance that rivaroxaban is a safe and effective alternative to warfarin in a routine care setting. Evidence was more mixed relative to dabigatran, indicating a higher all-cause mortality and bleeding rate with rivaroxaban. It is plausible that channeling of rivaroxaban towards elderly and less healthy patients generated confounding that we were unable to fully capture, despite extensive confounder adjustment strategies. In particular, the present observational findings cannot stand alone when deciding which oral anticoagulant to prescribe.

**KEY POINTS**

- Head-to-head comparisons of new oral anticoagulants in atrial fibrillation are limited
- Using Danish nationwide health registries and propensity score methods, we compared outcome rates with rivaroxaban to outcome rates with dabigatran and warfarin
- We found similar or lower stroke rates with rivaroxaban, but higher a mortality
- Findings should be interpreted cautiously, as they may be driven by selective prescribing

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**DISCLOSURES**

Professor Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola, and Boehringer Ingelheim and has served as a speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, and Sanofi Aventis. Associate Professor Larsen has been on the speaker bureaus for Bayer, BMS/Pfizer, Janssen Pharmaceuticals, Takeda, Roche Diagnostics, and Boehringer Ingelheim. Dr. Gorst-Rasmussen has no disclosures.

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The Obel Family Foundation supported this study. TBL and GYHL conceived the idea for the study. AGR performed the statistical analysis and wrote the initial draft of the paper. All authors contributed to critically revising the initial draft and approved the final version.

**REFERENCES**

RIVAROXaban EFFECTIVENESS AND SAFETY IN DENMARK


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