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# Efficacy and Safety of Dabigatran Etexilate and Warfarin in "Real-World" Patients With Atrial Fibrillation

## A Prospective Nationwide Cohort Study

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**Objectives** The aim of this study was to assess the efficacy and safety in an "everyday clinical practice" population of anticoagulant-naïve patients with atrial fibrillation (AF) treated with dabigatran etexilate after its post-approval availability in Denmark, compared with warfarin.

**Background** Concerns have been raised about an excess of bleeding events or myocardial infarction (MI) among patients treated with the new oral direct thrombin inhibitor, dabigatran etexilate.

**Methods** From the Danish Registry of Medicinal Product Statistics, we identified a dabigatran-treated group and a 1:2 propensity-matched warfarin-treated group of 4,978 and 8,936, respectively. Comparisons on efficacy and safety outcomes were made on the basis of Cox-proportional hazards models stratified on propensity-matched groups.

**Results** Stroke and systemic embolism were not significantly different between warfarin- and dabigatran-treated patients. Adjusted mortality was significantly lower with both dabigatran doses (110 mg b.i.d., propensity-match group stratified hazard ratio [aHR]: 0.79, 95% confidence interval [CI]: 0.65 to 0.95; 150 mg b.i.d., aHR: 0.57, 95% CI: 0.40 to 0.80), when compared with warfarin. Pulmonary embolism was lower compared with warfarin for both doses of dabigatran. Less intracranial bleeding was seen with both dabigatran doses (110 mg b.i.d., aHR: 0.24, 95% CI: 0.08 to 0.56; 150 mg b.i.d., aHR: 0.08, 95% CI: 0.01 to 0.40). The incidence of MI was lower with both dabigatran doses (110 mg b.i.d., aHR: 0.30, 95% CI: 0.18 to 0.49; 150 mg b.i.d., aHR: 0.40, 95% CI: 0.21 to 0.70). Gastrointestinal bleeding was lower with dabigatran 110 mg b.i.d. (aHR: 0.60, 95% CI: 0.37 to 0.93) compared with warfarin but not dabigatran 150 mg b.i.d. The main findings were broadly consistent in a subgroup analysis of dabigatran users with ≥1-year follow-up (median follow-up 13.9 months [interquartile range: 12.6 to 15.3 months]).

**Conclusions** In this "everyday clinical practice" post-approval nationwide clinical cohort, there were similar stroke/systemic embolism and major bleeding rates with dabigatran (both doses) compared with warfarin. Mortality, intracranial bleeding, pulmonary embolism, and MI were lower with dabigatran, compared with warfarin. We found no evidence of an excess of bleeding events or MI among dabigatran-treated patients in this propensity-matched comparison against warfarin, even in the subgroup with ≥1-year follow-up. (J Am Coll Cardiol 2013;61:2264–73) © 2013 by the American College of Cardiology Foundation

Stroke is a serious complication of atrial fibrillation (AF), which is the most common sustained cardiac rhythm disorder. Effective prevention of stroke requires oral anticoagulation (OAC) therapy, and until recently, this was dependent upon the vitamin K antagonist class of drugs, for example, warfarin (1). The limitations of vitamin K antagonists include the need for regular monitoring and the possibility for food and drug interactions. This has led to the

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quest for new OACs that would be safe and effective alternatives to warfarin (1,2).

The new oral direct thrombin inhibitor, dabigatran etexilate, has been available in Denmark in 2 doses (either 150 mg b.i.d. or 110 mg b.i.d.) since August 2011 for stroke prevention in AF patients with 1 or more risk factors. The approval of this new OAC was based on the large Phase 3 clinical trial of stroke prevention in AF, the RE-LY (Randomized Evaluation of Long-Term Anticoagulant therapy) study (3). This trial compared 2 doses of dabigatran etexilate against warfarin in AF patients with 1 or more stroke risk factors and reported that dabigatran 110 mg b.i.d. was noninferior to warfarin for the primary endpoint of stroke and systemic embolism, with 20% less major bleeding events, whereas dabigatran 150 mg b.i.d. showed superiority for the primary efficacy endpoint over warfarin, with a similar rate of major bleeding (3). In the RE-LY trial, there were some concerns over a numerical increase in myocardial infarction (MI) events among dabigatran-treated patients, and after its introduction, various reports of major, trauma-related, and fatal bleeding events were published (4–7), leading to cautionary recommendations from some regulatory authorities.

The principal objective of this nationwide cohort study was to assess the efficacy and safety in an "everyday clinical practice" population of patients with AF treated with dabigatran etexilate after its post-approval availability in Denmark, compared with patients treated with warfarin. As a secondary objective, we investigated the feasibility of using linked healthcare databases for continuous surveillance of the benefit-risk balance after approval of a new indication.

## Methods

**Study design.** For this study we used information from 3 well-established (and well-validated) Danish nationwide datasets: the Danish Civil Registration system (8); the National Patient Register (9); and the Danish National Prescription Registry (10). The application of this nationwide cohort approach has recently been described in AF studies (11,12).

Information on birthday, sex, vital status, and emigration was available from the Danish Civil Registration System. The Danish National Patient Register, which was established in 1977, includes more than 99% of all discharges from public and private Danish medical hospitals and holds information on the dates of hospital admission and discharge and up to 20 discharge diagnoses, classified according to the Danish version of the International Classification of Diseases (ICD). In this study we used the 10th Revision (ICD-10). Also, all prescription drugs sold in Denmark since 1994 are registered in the Register of Medicinal Products Statistics maintained by the Danish Health and Medicines Authority and made available for research in the Danish National Prescription Registry. The availability of the unique personal identification number enables full linkage between the datasets. This study based on prescription data was updated up to June 30, 2012, and the information on hospital admissions and vital status was updated to December 31, 2012.

**Abbreviations and Acronyms**

aHR = propensity match group stratified hazard ratio
AF = atrial fibrillation
CI = confidence interval
HR = hazard ratio
ICD = International Classification of Diseases
MI = myocardial infarction
OAC = oral anticoagulation
PE = pulmonary embolism
TTR = time in therapeutic range

To be included in the treatment group of this study, treatment for AF with dabigatran etexilate (110-mg or 150-mg b.i.d. doses) should have been initiated after August 1, 2011. At that time dabigatran etexilate was formally approved and available for AF stroke prevention in Denmark. Transition to warfarin, emigration, or end-of-study (December 31, 2012) were considered as censoring events. A control group with initiated warfarin treatment between August 1, 2009, and June 30, 2010 was identified for comparison. To avoid treatment-dependent censoring December 31, 2010, was considered end-of-study for the control group. All included patients in both time periods were previously untreated (both warfarin and dabigatran) patients with AF.

Admissions relevant to this study were found with ICD-10 for admissions reflecting efficacy (thrombosis) and safety (bleeding or death) as well as comorbidity (see following).

The Danish National Prescription Registry was used to identify the anticoagulant treatment history as well as use of contraindicated or potential hazardous medication at baseline and after initiated dabigatran medication for the case group. For all medications indicating comorbidities (Online Table 1) except warfarin and dabigatran, baseline medication status was achieved if the time lapse between the dates of the last prescription to baseline was shorter than the number of daily dosages included in the last prescription. For all contraindicated or potentially hazardous medication usage, this was coded if a prescription during the observation period (warfarin or dabigatran treatment period) was observed (Online Table 2).

It was assumed that the dabigatran and warfarin treatment period was initiated at time of diagnosis. Treatment was assumed to be lifelong, and hence, treatment was assumed to end only if a prescription of an alternative was registered. Patients with mechanical heart valves as well as previous diagnoses of pulmonary embolism (PE), deep vein thrombosis, or mitral stenosis were excluded. Also, the patient was required to have permanent residence or be immigrated no later than 1 year before initiation of the treatment.

**Outcomes.** The primary study outcomes were stroke, systemic embolism, and intracranial bleeding. Secondary outcomes were death from any cause, gastrointestinal bleeding, traumatic intracranial bleeding, or major bleeding (Online Table 3). The definition of major bleeding is bleeding from or into an organ or a sudden drop in hemoglobin leading to hospital stay. Other outcomes were MI, PE, and hospital stay for whichever cause, except ambulatory visits related to AF.

**Statistical analysis.** Baseline characteristics of the dabigatran- and warfarin-treatment populations were reported by means and SDs for quantitative information and with frequencies and percentages for qualitative characteristics.

Dabigatran patients were matched 1:2 with patients selected randomly with no replacement from the control group with propensity score matching on the basis of the nearest neighbor in terms of Mahalanobis distance between the propensities for treatment type and for dabigatran dose (13). The propensity score models were obtained by logistic regressions. The first model on treatment type (warfarin or dabigatran) choice was based on the 2011 to 2012 population of warfarin and dabigatran patients; the latter model on dabigatran dose was based on all dabigatran patients. In both cases the following baseline information was included in the regression model: previous stroke, intracranial bleeding, or transient ischemic attack; heart failure; MI; diabetes mellitus; renal disease; and hepatic disease. Also, we included usage indicators of aspirin, clopidogrel, angiotensin receptor blocker/angiotensin converting enzyme inhibitor, beta-blocker, amiodarone, statins, proton-pump inhibitors, and H2-receptor antagonists, respectively. These comorbidities comprise both stroke and bleeding risk factors. All effects were included with interaction with sex and age category (<65, 65 to 69, 70 to 74, 75 to 79, 80 to 84, ≥85 years). These models were subsequently used to calculate the propensity for the treatment type and dose on the warfarin control population (2009 to 2010) and likewise for the dabigatran population. The matching was evaluated by reporting standardized distances between baseline characteristics of the treatment and control populations for each dose (14).

Incidence rates were calculated for all outcomes. Hazard ratios (HR) for dabigatran 110 mg and 150 mg versus warfarin on the basis of Cox proportional hazards model stratified in match groups were calculated with time since treatment initiation as time-scale (15). Crude HRs are provided for comparison. The analyses were performed with SAS/STAT software (version 9.2 for Windows, SAS Institute, Cary, North Carolina). The Cox regressions were performed with PROC PHREG (SAS). The propensity score models were estimated with PROC LOGISTIC (SAS).

Our study is not a randomized trial but is a nationwide cohort study sized with a case and control population of approximately 5,000 and 9,000 patients, respectively. The main endpoint of interest is stroke/thromboembolism, which in a Danish AF population has a 6-month incidence rate of approximately 4% (Olesen et al. [12] report 4.75% for 1-year follow-up for patients with $CHADS_2$ score = 1). With power 80% and 5% significance level, our study would be able to detect rate ratios down to 25%.

## Results

**Characteristics of the cohort.** Given the focus was on the treatment-naïve patients in the 2 study periods, we initially identified 13,131 and 18,654 patients, respectively. After excluding existing mechanical heart valves or previous PE, venous thromboembolism, and mitral stenosis and the requirement for at least 1 year residence in Denmark, we identified a warfarin-treated group and a dabigatran-treated group of n = 8,936 and n = 4,978, respectively (Fig. 1). Baseline characteristics are shown in Table 1. The median follow-up period after incident AF was 10.5 months (IQR: 7.9 to 13.4 months), with no patients lost to follow-up. Of the dabigatran-treated patients, 32% had a follow-up of ≥1 year, and overall this analysis was based on 4,086 patient-years of experience with dabigatran treatment.

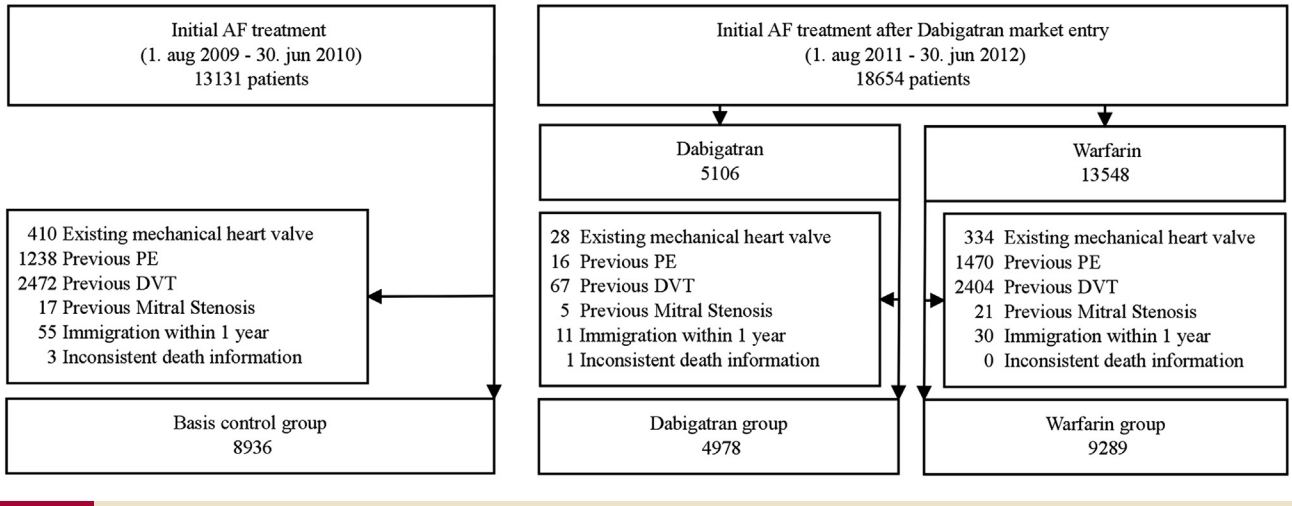


**Figure 1** Inclusion of the Study Population

AF = atrial fibrillation; DVT = deep vein thrombosis; PE = pulmonary embolism.

**Table 1 Baseline Characteristics According to Treatment Group**

| | 2009–2010* | 2011–2012† | | | | |
|---|---|---|---|---|---|---|
| | Warfarin (n = 8,936) | Warfarin and Dabigatran All (n = 14,267) | Dabigatran, 150 mg (n = 2,239) | Dabigatran, 110 mg (n = 2,739) | Warfarin (n = 9,289) | RE-LY Trial All (n = 18,113) |
| Age, yrs | 69.7 ± 12.5 | 70.8 ± 12.1 | 67.4 ± 8.5 | 74.7 ± 11.8 | 70.4 ± 12.6 | 71.8 ± 8.7 |
| ≥65 | 70.0 (6,242) | 73.8 (10,524) | 68.6 (1,536) | 80.5 (2,206) | 73.0 (6,782) | N/A |
| ≥75 | 37.0 (3,295) | 38.6 (5,508) | 18.3 (410) | 52.8 (1,445) | 39.3 (3,653) | N/A |
| ≥80 | 20.1 (1,797) | 23.0 (3,275) | 2.4 (54) | 40.9 (1,121) | 22.6 (2,100) | N/A |
| ≥85 | 7.6 (670) | 10.1 (1,437) | 0.8 (19) | 19.7 (540) | 9.5 (878) | N/A |
| Female | 40.2 (3,595) | 43.5 (6,203) | 38.5 (861) | 53.1 (1,455) | 41.9 (3,887) | 36.4 (6,599) |
| $CHADS_2$‡ | 1.17 ± 1.18 | 1.16 ± 1.18 | 0.96 ± 1.07 | 1.27 ± 1.27 | 1.18 ± 1.17 | 2.13 ± 1.13 |
| $CHADS_2$ 3–6 | 14.2 (1,271) | 14.3 (2,047) | 9.5 (212) | 18.9 (518) | 14.2 (1,317) | 32.5 (5,882) |
| Prior stroke, transient ischemic attack, or systemic embolism | 17.3 (1,542) | 16.1 (2,297) | 17.1 (383) | 17.5 (478) | 15.5 (1,436) | 20.0 (3,623) |
| Heart failure | 8.5 (764) | 8.3 (1,179) | 5.2 (116) | 6.9 (188) | 9.4 (875) | 32.0 (5,793) |
| Myocardial infarction | 9.6 (861) | 9.5 (1,362) | 6.1 (136) | 8.0 (218) | 10.9 (1,008) | 16.6 (3,005) |
| Diabetes mellitus | 12.3 (1,099) | 12.0 (1,713) | 12.1 (270) | 10.8 (295) | 12.4 (1,148) | 23.3 (4,221) |
| Hypertension | 19.3 (1,721) | 20.9 (2,977) | 22.7 (509) | 18.0 (493) | 21.2 (1,975) | 78.3 (14,183) |
| Moderate/severe renal disease | 4.0 (354) | 3.9 (552) | 1.2 (27) | 2.0 (55) | 5.1 (470) | N/A |
| Moderate/severe hepatic disease | 0.3 (29) | 0.2 (34) | 0.0 (0) | 0.2 (6) | 0.3 (28) | N/A |
| Medications in use at baseline | | | | | | |
| Aspirin | 37.4 (3,346) | 34.7 (4,946) | 35.2 (789) | 30.7 (841) | 35.7 (3,316) | 39.8 (7,198) |
| Clopidogrel | 3.2 (288) | 5.3 (756) | 5.0 (111) | 5.3 (144) | 5.4 (501) | N/A |
| ARB or ACE inhibitor | 34.8 (3,106) | 36.6 (5,226) | 39.9 (894) | 34.5 (945) | 36.4 (3,387) | 66.1 (11,979) |
| Beta-blocker | 19.7 (1,757) | 20.0 (2,848) | 20.9 (468) | 16.6 (454) | 20.7 (1,926) | 62.8 (11,375) |
| Amiodarone | 0.7 (58) | 0.5 (70) | 0.2 (9) | 0.2 (4) | 0.6 (57) | 10.7 (1,933) |
| Statin§ | 27.2 (2,433) | 29.8 (4,248) | 32.3 (724) | 27.2 (745) | 29.9 (2,779) | 44.4 (8,038) |
| Proton-pump inhibitor | 9.4 (838) | 12.7 (1,805) | 12.0 (268) | 14.4 (395) | 12.3 (1,142) | 13.8 (2,491) |
| H2-receptor antagonist | 0.2 (20) | 0.1 (9) | 0.0 (1) | 0.1 (2) | 0.1 (6) | 4.0 (722) |
| Rate of discontinuation for dabigatran | — | — | 6.5 (145) | 3.2 (92) | — | N/A or N/C |

Values are mean ± SD or % (n). Baseline defined as date of atrial fibrillation. *The warfarin control period data are from August 1, 2009 to June 30, 2010. †August 1, 2011 to June 30, 2012 is the period used to capture dabigatran data and to derive the propensity score. All dabigatran-treated patients for this analysis were warfarin-naïve. ‡The $CHADS_2$ score is a measure of the risk of stroke in which congestive heart failure, hypertension, an age of 75 years or older, and diabetes mellitus are each assigned 1 point and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient. §Statins are defined here as 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker.

When compared with the RE-LY trial population, our Danish cohort were broadly similar in age (70.8 years vs. RE-LY: 71.8 years), sex distribution (43.5% vs. RE-LY: 36.4%), and proportion who were secondary prevention (16.1% vs. RE-LY: 20.0%) but were overall at lower stroke risk (mean $CHADS_2$ score of 1.16 vs. RELY: 2.13) and had fewer comorbidities (e.g., heart failure, prior MI, diabetes mellitus, hypertension) (Table 1). Moderate/severe renal impairment was present in 3.9% of the Danish cohort.

**Evaluation of propensity-matched cohort.** The logistic regressions for the propensity score models achieved c-statistics of 0.6 and 0.8 for discriminating between warfarin and dabigatran groups and between dabigatran doses. The matched cohorts were compared on baseline characteristics (Online Table 4). The standardized distances ranged between −16.8% and 18.8% with average absolute distance of 6.7%. The dabigatran 110-mg b.i.d. group was matched to a slightly younger warfarin-treated group, with less frequent renal impairment. Both dabigatran-treated groups were compared with a warfarin group with less frequent treatment with proton-pump inhibitors.

**Primary study outcomes.** The primary study outcomes in terms of stroke and systemic embolism were similar in the warfarin group and in the dabigatran etexilate group in the adjusted analyses (Fig. 2).

In the adjusted analyses, mortality was significantly lower in the dabigatran 110-mg b.i.d. group versus warfarin users (propensity-match group stratified hazard ratio [aHR]: 0.79, 95% confidence interval [CI]: 0.65 to 0.95) (Fig. 2) and also in the dabigatran 150-mg b.i.d. group compared with warfarin (aHR: 0.57, 95% CI: 0.40 to 0.80). Overall, 8 deaths were reported to the Danish Health and Medicines Authority—7 of these 8 patients were >80 years of age (1 was a 76-year-old man taking dabigatran 150 mg b.i.d.); 6 of the 8 were female, and 7 of the 8 were taking dabigatran 110 mg b.i.d.

**Secondary outcomes.** Compared with warfarin, major bleeding was comparable with both dabigatran doses ($p = 0.21$). The incident event rates of intracranial and traumatic intracranial bleeding were low (Table 2) and lower intracranial bleeding rates were seen with both dabigatran doses (110 mg b.i.d., aHR: 0.24, 95% CI: 0.08 to 0.56; 150 mg b.i.d., aHR: 0.08, 95% CI: 0.01 to 0.40) (Fig. 2).

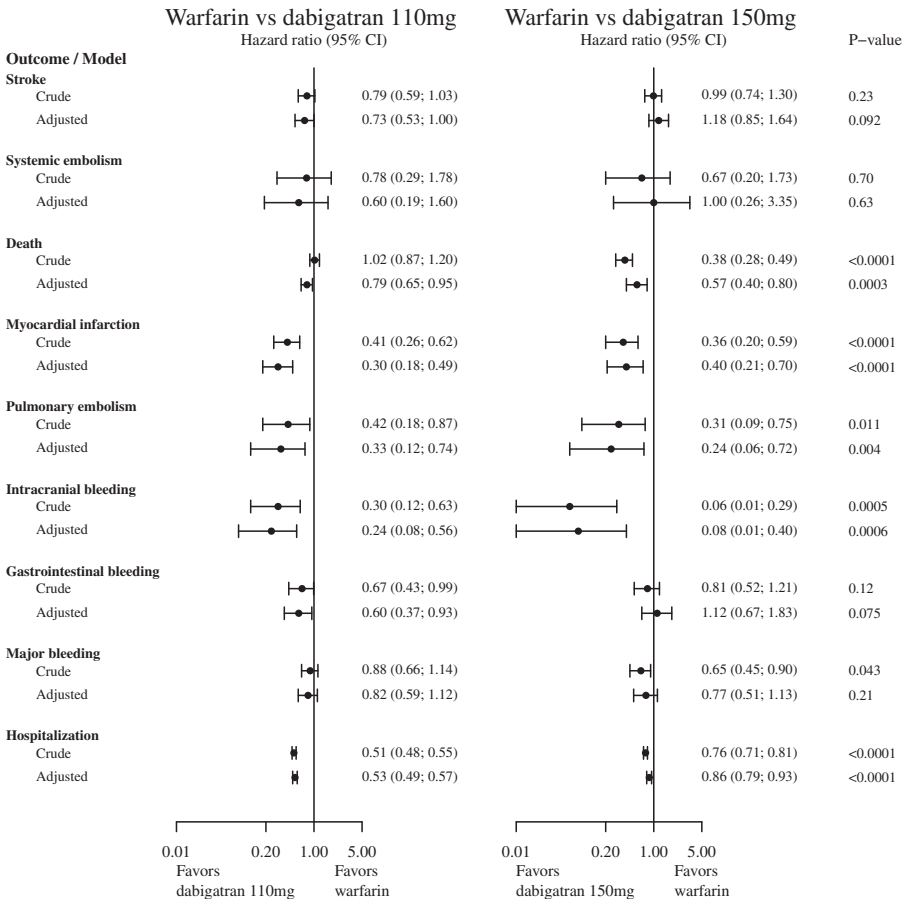


**Figure 2** **Main Outcome Measures**

Main outcome measures (hazard ratios, 95% confidence interval [CI]). The p value is for the hypothesis of no overall difference between treatments. Adjusted analysis is based on Cox proportional hazards model stratified on propensity match groups.

We observed trauma-related bleeding events in 25 patients (21 in warfarin- and 4 in dabigatran-treated patients, respectively). Gastrointestinal bleeding was not significantly different overall (p = 0.075) between dabigatran- and warfarin-treated patients (Fig. 2) but was significantly lower in the dabigatran 110-mg b.i.d. compared with warfarin (aHR: 0.60, 95% CI: 0.37 to 0.93).

The incidence of MI was low overall and lower with both dabigatran doses (110 mg b.i.d., aHR: 0.30, 95% CI: 0.18 to 0.49; 150 mg b.i.d., aHR: 0.40, 95% CI: 0.21 to 0.70) compared with warfarin. The risk of PE was lower in both the dabigatran doses (110 mg b.i.d., aHR: 0.33, 95% CI: 0.12 to 0.74; 150 mg b.i.d., aHR: 0.24, 95% CI: 0.06 to 0.72) compared with warfarin. The frequency of all-cause hospital stays was lower in both the dabigatran doses (110 mg b.i.d., aHR: 0.53, 95% CI: 0.49 to 0.57; 150 mg b.i.d., aHR: 0.86, 95% CI: 0.79 to 0.93) compared with warfarin (Fig. 2).

**Subgroup analysis on dabigatran users with ≥1-year follow-up.** Of the dabigatran-treated patients with a follow-up of ≥1 year, the primary study outcomes in terms of stroke and systemic embolism were broadly similar to that seen in the main cohort (Table 3). Median follow-up of this subgroup was 13.9 months (IQR: 12.6 to 15.3 months).

Mortality was significantly lower only in the dabigatran 150-mg b.i.d. group compared with warfarin (aHR: 0.58, 95% CI: 0.35 to 0.92). Major bleeding was comparable with both dabigatran doses versus warfarin, with point estimates of 0.74 and 0.66, for dabigatran110 mg b.i.d. and 150 mg b.i.d., respectively. Gastrointestinal bleeding was also not significantly different but with point estimates of 0.61 and 0.78, respectively. The incidence of MI was lower with both dabigatran doses, although only statistically significant for dabigatran 110 mg b.i.d. (aHR: 0.50, 95% CI: 0.26 to 0.89) compared with warfarin.

**Prescribing trends.** Prescribing trends for dabigatran after its approval in Denmark showed a rapid increase in prescriptions among new users, peaking in November 2011, followed by a slow decline and plateau effect (Fig. 3). Few patients with moderate/severe renal or liver disease (see Online Table 1 for definitions) have been treated with dabigatran: renal disease in 5.1% (warfarin), 2.0% (dabigatran

**Table 2** Efficacy and Safety for New Atrial Fibrillation Patients Treated With Dabigatran

| | Warfarin D150 Matched* (n = 3996) | Dabigatran 150 mg (n = 2239) | Warfarin D110 Matched (n = 4940) | Dabigatran 110 mg (n = 2739) |
|---|---|---|---|---|
| Primary endpoints | | | | |
| Stroke | 109/3,626/3.0 | 60/1,722/3.5 | 157/4,333/3.6 | 62/2,299/2.7 |
| Systemic embolism | 8/3,684/0.2 | 4/1,758/0.2 | 18/4,402/0.4 | 6/2,322/0.3 |
| Intracranial bleeding | 27/3,680/0.7 | 1/1,760/0.1 | 42/4,398/1.0 | 6/2,323/0.3 |
| Secondary endpoints | | | | |
| Death from any cause | 172/3,689/4.7 | 52/1,760/3.0 | 453/4,411/10.3 | 185/2,326/8.0 |
| Gastrointestinal bleeding | 53/3,661/1.5 | 26/1,749/1.5 | 90/4,369/2.1 | 28/2,311/1.2 |
| Traumatic intracranial bleeding | 11/3,684/0.3 | 0/1,760/0 | 10/4,408/0.2 | 4/2,324/0.2 |
| Major bleeding | 104/3,630/2.9 | 37/1,744/2.2 | 151/4,329/ 3.5 | 65/2,296/2.8 |
| Other endpoints | | | | |
| Myocardial infarction | 70/3,650/1.9 | 15/1,752/0.9 | 111/4,342/2.6 | 22/2,316/1.0 |
| Pulmonary embolism | 20/3,675/0.5 | 4/1,760/0.2 | 36/4,397/0.8 | 7/2,324/0.3 |
| Hospital stay | 2,438/2,082/117.1 | 1,003/1,129/88.8 | 2,981/2,534/117.6 | 970/1,726/56.2 |

Values are events/total person-year at risk/crude event rate/100 years. *Propensity score matched (Online Table 4).

110-mg), and 1.2% (dabigatran 150-mg). Table 4 shows that there were few patients who received any concomitant hazardous drugs or medications with potential interaction with dabigatran in the study period.

## Discussion

This is the first nationwide report from a large "everyday clinical practice" post-approval clinical cohort in terms of efficacy and safety outcomes with warfarin and dabigatran (110 mg b.i.d., 150 mg b.i.d.). We show that stroke was not significantly different between warfarin- and dabigatran-treated patients, but adjusted mortality was lower with both dabigatran doses compared with warfarin. Major bleeding was not significantly different between dabigatran and warfarin, but intracranial bleeding was markedly lower with both doses of dabigatran. Myocardial infarction was also significantly lower with dabigatran-treated patients (both groups) compared with warfarin. These main findings remained broadly consistent in a subgroup analysis of dabigatran users with ≥1-year follow-up. Thus, we found no evidence of an excess of bleeding events or MI among dabigatran-treated patients in this propensity-matched comparison against warfarin in a large post-approval registry study, even in the subgroup with ≥1-year follow-up.

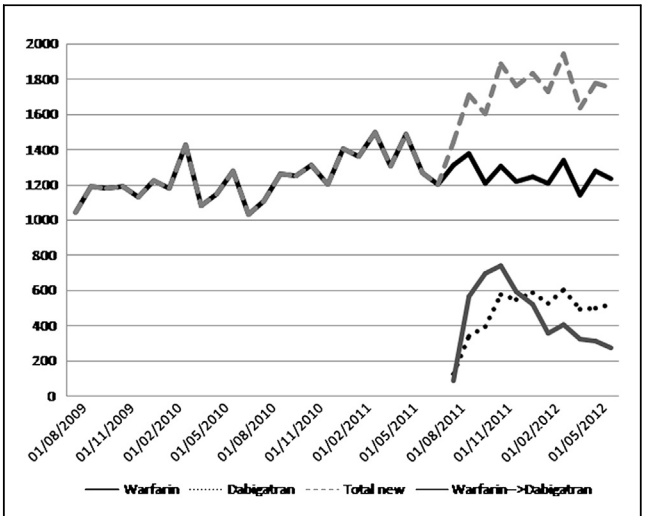


**Figure 3** Monthly New Users of Warfarin and Dabigatran Etexilate for AF

Monthly new users of warfarin and dabigatran etexilate for atrial fibrillation (AF) in the period August 2009 to June 2012 in Denmark.

The new oral anticoagulants have been recommended in recent international guidelines or position statements, because they offer efficacy, safety, and convenience (16–18). In the recent 2012 focused update of the ESC guidelines, novel oral anticoagulants such as dabigatran should be considered rather than a Vitamin K antagonist, whenever an oral anticoagulant is indicated (16). Initial global uptake of dabigatran was marred by case reports on fatal bleedings or thromboembolism, mostly related to inappropriate prescribing (e.g., in renal failure), as well as bleeding related to trauma (6,7). Regulatory authorities have even issued cautionary statements on its use, which were subsequently followed by reassuring updates highlighting that bleeding rates associated with new use of dabigatran do not seem to be higher than bleeding rates associated with new use of warfarin, consistent with observations from the large clinical trial used to approve the new drug (i.e., the RE-LY trial) (19,20). Of note, such initial frequent reporting of adverse events has previously been encountered with the introduction of new drugs (the so-called "Weber effect") (21).

In our cohort, the remarkable compliance with the medication guidance in Denmark is not coincidental. In contrast to other countries, the Danish Society of Cardiology has a policy of very early implementation of guidelines from the ESC to the equivalent Danish guidelines, and hence, there is great awareness about the use of dabigatran and the various safety issues right away from the start. Furthermore, a formal collaboration between the Danish Health and

**Table 3** Subgroup Analysis on Dabigatran Users With More Than 1-Year Follow-Up

| Outcome | Warfarin vs. Dabigatran 110 mg b.i.d. HR | 95% CI | Warfarin vs. Dabigatran 150 mg b.i.d. HR | 95% CI | p Value* |
|---|---|---|---|---|---|
| Stroke | | | | | |
| Crude | 0.95 | (0.62–1.41) | 1.58 | (1.06–2.30) | 0.05 |
| Adjusted | 0.84 | (0.53–1.31) | 1.53 | (0.96–2.43) | 0.15 |
| Death | | | | | |
| Crude | 0.93 | (0.72–1.18) | 0.39 | (0.25–0.59) | <0.0001 |
| Adjusted | 0.82 | (0.62–1.06) | 0.58 | (0.35–0.92) | 0.03 |
| Myocardial infarction | | | | | |
| Crude | 0.60 | (0.33–1.02) | 0.62 | (0.30–1.14) | 0.10 |
| Adjusted | 0.50 | (0.26–0.89) | 0.74 | (0.34–1.48) | 0.06 |
| Major bleeding | | | | | |
| Crude | 0.77 | (0.51–1.14) | 0.63 | (0.36–1.02) | 0.12 |
| Adjusted | 0.74 | (0.47–1.14) | 0.66 | (0.36–1.14) | 0.15 |
| Gastrointestinal bleeding | | | | | |
| Crude | 0.58 | (0.30–1.02) | 0.70 | (0.34–1.29) | 0.15 |
| Adjusted | 0.61 | (0.30–1.13) | 0.78 | (0.35–1.59) | 0.26 |

*The p value for the hypothesis of no overall difference between the treatments. Subgroup analysis was performed on n = 1,069 taking dabigatran 110 mg b.i.d. and n = 796 taking dabigatran 150 mg b.i.d.; these patients were matched 1:2 with n = 3,730 taking warfarin (initial dabigatran prescriptions between August 1, 2011 and December 31, 2011; control population was initiated on warfarin regimen between August 1, 2009 and December 31, 2009). Median follow-up of this subgroup was 13.9 months (interquartile range: 12.6 to 15.3 months). Adjusted analysis is based on Cox proportional hazards model stratified on propensity match groups.

CI = confidence interval; HR = hazard ratio.

Medicines Authority and our group at Aalborg University Hospital has led to consecutively issued formal guidance to all Danish doctors after the introduction of dabigatran to the Danish prescribing market.

In the RE-LY trial, the rates of the primary outcome were 1.69%/year in the warfarin group, as compared with 1.53%/year in the group that received dabigatran 110 mg b.i.d. and 1.11%/year with dabigatran 150 mg b.i.d. (22). For comparison, the present study reported fewer events (in terms of an event rate/100 person-years), but this might be reflective of the overall lower risk Danish population. Indeed, the Danish study had a mean $CHADS_2$ score of 1.2, which represents a lower stroke risk cohort compared with the RE-LY trial participants, where the average $CHADS_2$ score was 2.1.

**Table 4** Contraindicated or Potential Hazardous Co-Medication for Dabigatran Group

| | Baseline* | Follow-Up |
|---|---|---|
| Contraindicated drugs | | |
| Systemic ketoconazole | <0.1 (1) | 0 (0) |
| Cyclosporine | 0 (0) | 0 (0) |
| Itraconazole | <0.1 (1) | 0.1 (6) |
| Tacrolimus | 0 (0) | 0 (0) |
| Potential hazardous co-medication | | |
| Amiodarone | 0.3 (13) | 3.1 (155) |
| Dronedarone | 0.1 (5) | 0.4 (18) |
| Verapamil | 2.1 (105) | 4.3 (216) |
| Quinidine† | 0 (0) | 0 (0) |
| Clarithromycin | 0.1 (4) | 0.9 (42) |
| Coumarins | <0.1 (2) | 4.8 (239) |
| Concomitant drug use that can increase bleeding risk | | |
| Aspirin | 32.8 (1,630) | 16.3 (811) |
| Thienopyridines (clopidogrel, ticagrelor, prasugrel) | 5.3 (262) | 2.9 (141) |
| Low molecular weight heparins | 0.3 (13) | 0.3 (14) |
| Fondaparinux | 0 (0) | 0 (0) |
| GP IIb/IIIa antagonists (eptifibatide) | 0 (0) | 0 (0) |
| Sulfinpyrazone | 1.3 (66) | 2.3 (114) |
| NSAIDs | 11.7 (585) | 21.3 (1,059) |

Values are % (n). *Baseline is at start of treatment with dabigatran etexilate. †Probably not in use in Denmark anymore.

GP = glycoprotein; NSAID = nonsteroidal anti-inflammatory drug.

When compared with dabigatran 150 mg b.i.d., crude mortality was higher in the dabigatran 110-mg b.i.d. group, which was the recommended dose for elderly patients (>75 years of age); however, in the stratified or adjusted analyses, mortality was low and comparable between dabigatran 110 mg b.i.d. and warfarin users. Importantly, mortality was significantly lower with both dabigatran doses compared with warfarin. Patients prescribed dabigatran 110 mg b.i.d. were older than the warfarin-treated patients, and associated comorbidities could account in part for higher crude mortality in this cohort (given the nonrandomized trial design). Of note, approximately 18% of the patients >75 years of age were prescribed the 150-mg b.i.d. dose. In the analysis by Eikelboom et al. (23), there was a significant age interaction for the major bleeding endpoint, with less benefit on major bleeding apparent for dabigatran 110 mg b.i.d. in elderly patients compared with the overall trial result. The EU license is to use the 110-mg b.i.d. dose in elderly patients (>80 years of age), but in Denmark, prescribing recommendations suggest an "age >75 years" criterion.

Compared with warfarin, major bleeding was lower with dabigatran 150 mg b.i.d., whereas lower intracranial bleeding was seen with both dabigatran doses. The

observation with major bleeding was contrary to the RE-LY trial but might reflect the lower risk Danish cohort as well as the application of prescribing recommendations and guidelines, whereby the 150-mg b.i.d. dose was not recommended in elderly patients or those at high bleeding risk or with concomitant interacting medications (e.g., verapamil) (16). Our observation of lower intracranial bleeding with both doses of dabigatran reflects the findings of the main RE-LY trial and subsequent analyses (22,24).

Concerns over a numerical (but nonsignificant) increase in MI in the RE-LY trial (25) prompted discussions over whether dabigatran caused more MIs (26) or whether warfarin was more protective (4,27). Our Danish cohort provides some reassuring "everyday clinical practice" data that there was not an excess of MI, and in fact, the incidence of MI was lower with both doses of dabigatran compared with warfarin, even after adjustments for risk factors and propensity score. Compared with the RE-LY trial, our study cohort was lower risk and had a lower prevalence of prior MI or risk factors for the same (e.g., diabetes mellitus, hypertension). Our "everyday clinical practice" cohort design cannot account for the possibility that physicians could choose to avoid dabigatran in patients at higher risk of myocardial ischemia, although to minimize residual confounding, our findings still remain consistent even after adjustments for risk factors (i.e., comorbidities, including risk factors for MI) and propensity scores. Similarly, physicians might be either less likely to put high-risk patients on a regimen of dabigatran or more likely to switch them if they perceive them as having unstable international normalized ratios or being at high risk of bleeding. As shown in Table 3, thienopyridines were used in 5.3% of the patients at baseline but only in 2.9% during follow-up. If a higher degree of thienopyridine use should reflect that patients were at higher risk of MI at baseline, this would be in favor of warfarin, not the opposite (as we have seen). Also, there is no evidence that adding antiplatelet therapy reduces MI when added to dabigatran (28).

Another concern from the main RE-LY trial was an excess of gastrointestinal major bleeding events with dabigatran 150 mg b.i.d. compared with warfarin. Indeed, gastrointestinal bleeding was the most frequent side effect in the cohort from reports to the Danish Health and Medicines Authority, but in our cohort, there was no significant excess of gastrointestinal bleeding with dabigatran-treated patients compared with warfarin. This was despite similar proportions of patients in the RE-LY trial and the Danish cohort being on a regimen of aspirin or proton pump inhibitors. This could reflect that fewer side effects from warfarin were reported to the authorities because warfarin has been on the market for more than 50 years but re-emphasizes that a register-based, post-marketing surveillance study is a very powerful tool for surveillance of newly marketed drugs, because it makes it possible to compare 2 treatments. When reporting side effects of a new drug, the risk of surveillance bias is high.

This analysis also gives an insight into prescribing patterns with dabigatran. There was an initial rapid uptake among new users after the introduction of the drug, followed by a decline and a plateau effect. Reassuringly, only a minority of patients received any concomitant hazardous drugs or medications with potential interaction with dabigatran in the study period. However, there was a slight increase in nonsteroidal anti-inflammatory drugs during follow-up.

Our approach to monitoring the uptake of dabigatran for nonvalvular AF is one alternative for addressing the need for comparative-effectiveness data shortly after the approval of a drug or a new indication (29). Although the follow-up time was relatively short for a traditional academic/analytic study or trial, this report provides a new approach where, in a dynamic manner, we can study the introduction of a new drug treatment and generate data that are of relevance to regulators and public health officials. The objective and approach is clearly different from a classic cohort study (29–32). By regularly repeating the analyses conducted in this study, it would be possible to assess the dynamics of the uptake by observing changes over time in addition to improving the precision of the estimates. Furthermore, variants of this model for an enhanced continuous surveillance of the benefit-risk balance could potentially support new paradigms for licensing of medicinal products (30,32).

**Study limitations.** This analysis is limited by its dependence upon prescribing information (covering both general practice and hospital data), and selection of treatment options in the post-dabigatran world will be influenced by patient characteristics that might relate to outcome. Also, we cannot fully account for the impact of cardiovascular prevention strategies (e.g., statin and angiotensin-converting enzyme inhibitor use) or the differences in all the various subgroups (e.g., moderate-severe kidney disease was present in 1.2% of dabigatran 150-mg b.i.d. patients, compared with 5.1% of warfarin), given the "everyday clinical practice" nontrial setting of this dataset. Also, event ascertainment might be greater in warfarin-treated patients, simply because they are seen or communicated with more frequently in relation to international normalized ratio checks. However, such an "ascertainment bias" would draw the conclusion more in a direction in favor of warfarin and not toward dabigatran.

Because this was not a randomized trial dataset (but a registry-based cohort study), we had no information on time in therapeutic range (TTR) for the warfarin-treated patients, but the data from the present study reflect overall and national "best practice" with regard to anticoagulation with warfarin. Mean TTR in Denmark during the RE-LY study was good, at 72% (33), and has been reported to be generally adequate (>65%) in both hospitals and in general practice (34). Therefore this is in accordance with the overall average TTR for Denmark in the RE-LY trial. We also only included warfarin-naïve patients with incident AF, given the potential risk of selection bias toward dabigatran (previous compliance problems, poor TTR, bleeding, and so forth). Patients with a previous need for anticoagulant treatment of disorders other than AF were also excluded in the RE-LY trial. Of note, the RELY trial did not show any

heterogeneity in outcomes between warfarin experienced and warfarin-naïve patients (35).

Datasets from Denmark have been well-validated (10,36) and used in many previous pharmacovigilance studies (11,12). Also, prescribing coding from this nationwide cohort data have been validated for AF and its complications, although it does not have the individual detail on blood tests (e.g., serum creatinine, hemoglobin) or other investigations (e.g., detailed imaging data). For example, the positive predictive value for ischemic stroke in the Danish National Registry of Patients was 87.6% (95% CI: 80.1% to 93.1%) (37), and the ICD-10 codes for comorbidity in the Danish National Registry of Patients are consistently high, with a positive predictive value between 82% and 100% for the Charlson comorbidity index conditions (38). Not being 100% means that we could overestimate the study outcome and the influence from comorbidity, but this is probably similar between the treatment groups. Nonetheless, outcome definitions (e.g., major bleeding) in this "everyday clinical practice" cohort study and the RE-LY trial are unlikely to completely overlap. The outcomes addressed in this study cover hospital diagnosis (major bleeding, thrombosis, and stroke) and are not treated by general practitioners. Information on death comes from the population register, and this covers all deaths in Denmark, including those not referred to hospital. Consequently, these data reflect "real world" use data from an entire country, and no one is ruled out (except users of dabigatran that were not warfarin-naïve; see Methods). This should provide the best conditions for a nondifferential comparison between warfarin and dabigatran, strengthened by our propensity score matching.

Our strength is the 4,086 patient-year experience with dabigatran treatment from this first "everyday clinical practice" post-approval experience of using dabigatran in a nationwide cohort study with comprehensive prescribing data ever since the introduction of the drug for AF in Denmark only approximately 18 months ago. Long-term data on efficacy and safety events from dabigatran-treated patients from the RE-LY trial have recently been presented (RELY-ABLE), where during 2.3 years of additional treatment after the RE-LY trial (total mean follow-up 4.3 years), the rates of stroke, MI, and major bleeding remained low on a regimen of dabigatran and were consistent with those seen during the RE-LY trial (22). We also did not report (or compare) dabigatran use with rivaroxaban, because the latter was approved much later than dabigatran in Denmark, and low numbers ($n = \sim 500$) and a much shorter patient-year experience in our dataset preclude a meaningful analysis. Finally, we have to a large extent eliminated most possibilities for residual confounding in this study, by using propensity-matched analysis. The results of this analysis were also compared with alternative approaches with risk factor (i.e., comorbidity) adjustment and age stratification, and similar results as those reported were found. Excluding matched pairs with distance above a caliber of 0.2 did not alter the reported conclusions and HRs.

## Conclusions

Efficacy in terms of stroke and systemic embolism prevention was similar between warfarin and dabigatran (both doses), whereas mortality, PE, and MI were lower with both doses of dabigatran, in this "everyday clinical practice" post-approval clinical cohort. With regard to safety, major bleeding was similar between dabigatran and warfarin, whereas intracranial bleeding was lower with both dabigatran doses, compared with warfarin. Also, the rate of gastrointestinal bleeding was significantly lower in the dabigatran 110-mg b.i.d. treated groups compared with warfarin. The previous concerns about an excess of bleeding events or MI among dabigatran-treated patients were not evident in this propensity-matched comparison against warfarin in a large post-approval registry study, even in the subgroup with ≥1-year follow-up.

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**Key Words:** atrial fibrillation ■ dabigatran ■ oral anticoagulation ■ stroke.

**APPENDIX**

**For supplementary tables, please see the online version of this article.**