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Published in:
Europace

DOI:
[10.1093/europace/euv397](https://doi.org/10.1093/europace/euv397)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Korenstra, J., Wijtvliet, E. P. J., Veeger, N. J. G. M., Geluk, C. A., Bartels, G. L., Posma, J. L., ... Tieleman, R. G. (2016). Effectiveness and safety of dabigatran versus acenocoumarol in 'real-world' patients with atrial fibrillation. *Europace*, 18(9), 1319-1327. DOI: 10.1093/europace/euv397

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Effectiveness and safety of dabigatran versus acenocoumarol in ‘real-world’ patients with atrial fibrillation

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Received 18 June 2015; accepted after revision 22 October 2015; online publish-ahead-of-print 3 February 2016

Aims

Randomized trials showed non-inferior or superior results of the non-vitamin-K-antagonist oral anticoagulants (NOACs) compared with warfarin. The aim of this study was to assess the effectiveness and safety of dabigatran (direct thrombin inhibitor) vs. *acenocoumarol* (vitamin K antagonist) in patients with atrial fibrillation (AF) in daily clinical practice.

Methods and results

In this observational study, we evaluated all consecutive patients who started anticoagulation because of AF in our outpatient clinic from 2010 to 2013. Data were collected from electronic patient charts. Primary outcomes were stroke or systemic embolism and major bleeding. Propensity score matching was applied to address the non-randomized design. In total, 920 consecutive AF patients were enrolled (442 dabigatran, 478 acenocoumarol), of which 2×383 were available for analysis after propensity score matching. Mean follow-up duration was 1.5 ± 0.56 year. The mean calculated stroke risk according to the CHA₂DS₂-VASc score was 3.5%/year in dabigatran vs. 3.7%/year acenocoumarol-treated patients. The actual incidence rate of stroke or systemic embolism was 0.8%/year [95% confidence interval (CI): 0.2–2.1] vs. 1.0%/year (95% CI: 0.4–2.1), respectively. Multivariable analysis confirmed this lower but non-significant risk in dabigatran vs. acenocoumarol after adjustment for the CHA₂DS₂-VASc score [hazard ratio (HR)_{dabigatran} = 0.72, 95% CI: 0.20–2.63, $P = 0.61$]. According to the HAS-BLED score, the mean calculated bleeding risk was 1.7%/year in both groups. Actual incidence rate of major bleeding was 2.1%/year (95% CI: 1.0–3.8) in the dabigatran vs. 4.3%/year (95% CI: 2.9–6.2) in acenocoumarol. This over 50% reduction remained significant after adjustment for the HAS-BLED score (HR_{dabigatran} = 0.45, 95% CI: 0.22–0.93, $P = 0.031$).

Conclusion

In ‘real-world’ patients with AF, dabigatran appears to be as effective, but significantly safer than *acenocoumarol*.

Keywords

Atrial fibrillation • Anticoagulation • Acenocoumarol • Dabigatran • Stroke • Bleeding

Introduction

Stroke is a very serious and common complication of atrial fibrillation (AF), which is the most prevalent clinically significant cardiac arrhythmia.¹ Effective prevention of stroke by means of oral anticoagulation therapy is vital.² Until recently, the vitamin K antagonists (VKAs), such

as warfarin and acenocoumarol, were the only available oral anticoagulants. These drugs effectively reduce the risk of stroke in patients with AF, but increase the risk of major bleeding, especially intracranial hemorrhage.³ In addition, the use of VKAs is cumbersome because of multiple food and drug interactions and a small therapeutic range, necessitating frequent laboratory monitoring and dose adjustments. In

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What's new?

- We compared dabigatran to another vitamin K antagonist (VKA) than warfarin, i.e. acenocoumarol.
- In 'real-world' atrial fibrillation patients, dabigatran is as effective, but significantly safer than acenocoumarol.
- We show detailed adjustment of endpoints for individual HAS-BLED and CHA₂DS₂-VASc scores, in a propensity score matching design.
- We evaluated switching from VKA therapy to dabigatran in real life.
- In the current cohort, the HAS-BLED score seems to underestimate the bleeding risk on acenocoumarol.

the Netherlands, anticoagulation therapy is monitored by well-organized anticoagulation clinics, called the Thrombosis Service.

The non-vitamin-K-antagonist oral anticoagulants (NOACs), both the direct thrombin inhibitors (dabigatran) and factor Xa blockers (rivaroxaban, apixaban, edoxaban), have emerged as an alternative for anticoagulation therapy with VKAs.^{4–8} They have predictable pharmacokinetics without the need for routine monitoring like VKAs. Secondly, they have a low potential for food and drug interactions. Finally, and probably most important, they have an improved efficacy/safety ratio.⁴ Randomized controlled trials showed non-inferior or superior efficacy and safety results of the NOACs compared with warfarin.^{5–8} For this reason, the ESC guideline for the management of AF accomplished by the European Society of Cardiology (ESC) was updated in 2012. This guideline now recommends NOACs as broadly preferable to VKAs in the vast majority of patients with non-valvular AF.⁹

In all randomized controlled trials, warfarin was used as the comparator of the different NOACs.^{5–8} However, in different parts of the world, other coumarin derivatives are widely used such as acenocoumarol and phenprocoumon. Although the working mechanism is similar, there are some important pharmacokinetic differences between warfarin, acenocoumarol, and phenprocoumon. In comparison with warfarin, acenocoumarol has a very short elimination half-life of 1.8 h for S-acenocoumarol and 6.6 h for R-acenocoumarol, where warfarin has an elimination half-life of 24–33 h for S-warfarin and 35–58 h for R-warfarin. Phenprocoumon has the longest elimination half-life of 110–130 h.¹⁰ The primary aim of the present study was to assess the effectiveness and safety of dabigatran vs. the VKA *acenocoumarol* in patients with AF in daily clinical practice.

Methods

Study design

This was a retrospective, single-centre, observational study conducted in the Martini Hospital Groningen, the Netherlands, comparing the effectiveness and safety of dabigatran with acenocoumarol in consecutive patients with AF in daily clinical practice.

Study population

We evaluated all consecutive patients who started with oral anticoagulation therapy because of non-valvular AF and an increased risk for

stroke according to the CHA₂DS₂-VASc score (score ≥ 1 point) in our outpatient clinic from 1 January 2010 till 31 December 2012. Patients were collected by a computerized search in the electronic patients registry for the combination of the diagnosis code 'atrial fibrillation' with initiated medication use of acenocoumarol or dabigatran within these years. Atrial fibrillation was confirmed on a 12-lead electrocardiogram. For the purpose of this study, all patients were allocated to either the acenocoumarol or the dabigatran study group. Patients who started with dabigatran were assigned to the dabigatran group and patients who started with acenocoumarol to the acenocoumarol group. Those patients that were already on VKA before 1 January 2010 and switched to dabigatran during study period were included in the dabigatran group. From January 2012, dabigatran 150 mg twice a day (b.i.d.) was preferably prescribed, following reimbursement in the Netherlands and according to the ESC guideline for the management of AF. Dabigatran dose was reduced to 110 mg b.i.d. according to renal function (estimated glomerular filtration rate 30–50 mL/min), concomitant use of verapamil, or age > 80 years. Patients who switched from acenocoumarol discontinued anticoagulation therapy for 2 days (5 half-lives) and then started dabigatran. Dabigatran was prescribed without extra compliance counselling. All patients had at least one follow-up visit after initiating the oral anticoagulation therapy at our outpatient clinic and were seen every 6–12 months thereafter. There were no exclusion criteria.

Study outcomes

The primary effectiveness outcome was stroke or systemic embolism. Primary safety outcome was major bleeding. Secondary effectiveness outcomes were stroke, transient ischaemic attack (TIA), systemic embolism, myocardial infarction, pulmonary embolism, death from vascular cause, and death from any cause. Secondary safety outcomes were intracranial bleeding, gastrointestinal bleeding, perioperative bleeding, and life-threatening bleeding. Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery caused by an arterial thrombus in this artery, categorized as ischaemic stroke and TIA. A TIA was defined as a transient stroke, whereby clinical symptoms disappeared within 24 h. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ, documented by means of imaging, surgery, or autopsy. Death from vascular cause was defined as death caused by cardiac, haemorrhagic, or other vascular pathologic conditions. Major bleeding was defined as an acute bleeding with a sudden reduction in the haemoglobin level of at least 20 g/L (1.2 mmol/L) or transfusion of at least 2 units of blood, a symptomatic acute bleeding in a critical area or organ, or an acute bleeding that required hospitalization. Life-threatening bleeding was a subcategory of major bleeding that consisted of fatal bleeding, symptomatic intracranial bleeding, bleeding with a sudden decrease in the haemoglobin level of at least 50 g/L (3.1 mmol/L), bleeding requiring transfusion of at least 4 units of blood or inotropic agents, or necessitating surgery. All other bleedings were considered minor. Intracranial bleeding consisted of haemorrhagic stroke and subdural or subarachnoid bleeding. These effectiveness and safety outcome definitions were based on the definitions used in the RE-LY study.⁵ For all dabigatran patients, we documented reasons to switch or stop dabigatran therapy.

In all patients, the CHA₂DS₂-VASc and HAS-BLED scores at baseline were calculated.^{11,12} Individual stroke risk per year at baseline was adapted from Lip *et al.*, according to the CHA₂DS₂-VASc scoring system.¹³ Bleeding risk per patient per year was adapted from Pisters *et al.*, according to the HAS-BLED scoring system.¹² The time in therapeutic range (TTR) for patient who received acenocoumarol was calculated according to the Rosendaal method.¹⁴

Procedures

This study was approved by the Medical Ethics Committee of the Martini Hospital. Need for informed consent was waived by this Medical Ethics Committee. Patient data were collected retrospectively from the electronic patient chart by a single investigator (J.K.) from date dabigatran or acenocoumarol was initiated. All effectiveness and safety outcomes were reviewed by another investigator, blinded for the treatment group (R.G.T.). Potential differences were solved by consensus. We followed the patients during time on therapy, i.e. until switch to another anticoagulation drug, quitting the anticoagulation drug, death, or a maximum follow-up duration of 2 years.

Statistical analysis

Variables were described using mean \pm standard deviation if distributed normally or median and range otherwise. Categorical variables were described using frequency counts and percentages. Comparative analyses were performed by using the independent samples *t*-test, the Mann–Whitney, or the χ^2 test, when appropriate.

To address potential selection bias due to the observational non-randomized study design, we implemented propensity score matching to achieve a more balanced study cohort. In this, patients treated with dabigatran were 1:1 matched to patients that received acenocoumarol, using their probability to receive dabigatran, i.e. the propensity score for dabigatran. Matching was performed with a 0.1 maximum allowed difference in the exact propensity scores in a 'pair of patients' treated with dabigatran and acenocoumarol. Propensity score of individual patients was estimated using multivariable logistic regression with covariates describing condition at baseline. In this, baseline variables related to general medical conditions, concomitant medication, AF-specific factors, and risk factors for both stroke and bleeding were liberally included.

Subsequent analyses were performed using the matched cohort. Survival analyses were based on the time to first event. Event-free survival was graphically depicted using the Kaplan–Meier method. In addition, the Cox proportional hazard regression analysis was applied to examine whether treatment (dabigatran vs. acenocoumarol) was associated with the occurrence of the primary effectiveness and safety outcomes. To account for the potential lack of independence in patients within matched pairs, robust sandwich estimation of Lin and Wei was applied.

The primary effectiveness outcome analysis was adjusted for the CHA₂DS₂-VASc score.¹¹ The primary safety outcome analysis was adjusted for the HAS-BLED score.¹² In this, stroke and bleeding risk were controlled for using the established composite rather than the separate components of the two risk scores. In addition, other covariates univariately associated ($P < 0.10$) with the endpoint of interest were considered for multivariable analysis. Both CHA₂DS₂-VASc and HAS-BLED scores were included as categorized variables, as linearity for these composite variables over categories was not confirmed. We examined the proportionality hazard assumption by checking if the correlation coefficient between survival time and the scaled Schoenfeld residuals was significantly different from zero.

To address a potential healthy-user bias introduced by including 'VKA to dabigatran switching' patients in the dabigatran group, we performed a sensitivity analysis on the primary effectiveness and safety endpoint using the matched pairs of patients that were anticoagulation naïve at the time of initiation of dabigatran and acenocoumarol. For this, the propensity score matching procedure was repeated in all anticoagulation-naïve patients from the original cohort.

All analyses were performed using commercially available software (Statistical Analysis Software, version 9.4, SAS Institute, Cary, NC), and a two-tailed *P*-value of < 0.05 was considered statistically significant.

Results

Characteristics of the patients

A total of 920 patients were enrolled, including 442 patients with dabigatran and 478 patients with acenocoumarol. Propensity score matching resulted in 766 matched patients (383 in both groups). Mean follow-up duration was 1.5 ± 0.56 year. Mean follow-up duration was 1.3 ± 0.54 year in the dabigatran group and 1.8 ± 0.46 year in the acenocoumarol group. As presented in Table 1, after matching, a balanced study cohort was achieved with only limited differences between the treatment groups. There still was a small absolute difference in the CHA₂DS₂-VASc score (3.2 vs. 3.0 in dabigatran vs. acenocoumarol, respectively) mainly due to a difference in age (70.6 vs. 72.3 years, respectively). Furthermore, beta-blockers were more frequently used in patients treated with acenocoumarol and verapamil more frequently used in patients treated with dabigatran. With regard to the HAS-BLED score, matching resulted in comparable scores in dabigatran vs. acenocoumarol (mean HAS-BLED score 1.4 vs. 1.4).

In the dabigatran group, 231 patients received dabigatran 150 mg b.i.d. and 152 patients received the reduced dose of dabigatran 110 mg b.i.d. Of all dabigatran patients, 23.0% previously received long-term VKA therapy for at least 2 months.

Primary study outcomes

The mean calculated stroke risk at baseline per year as derived from the CHA₂DS₂-VASc score was 3.5% per year in the dabigatran group vs. 3.7% per year in the acenocoumarol group. The actual incidence rate of stroke or systemic embolism was 0.8% per year [95% confidence interval (CI): 0.2–2.0] vs. 1.0% per year (95% CI: 0.4–2.1), respectively (Table 2, Figure 1). This lower but non-significant risk in dabigatran vs. acenocoumarol was confirmed in multivariable analysis resulting in an adjusted hazard ratio (HR) of 0.72 (95% CI 0.20–2.63, $P = 0.61$) for dabigatran vs. acenocoumarol. In the multivariable model, also the a priori stroke risk as assessed by the CHA₂DS₂-VASc score was included. No other baseline variables reached the level of $P < 0.10$ set for inclusion in the multivariable model (Table 3).

The calculated bleeding risk at baseline per year, according to the HAS-BLED score, was 1.7% per year both groups. The actual incidence rate of major bleeding was 2.1% per year (95% CI: 1.0–3.8) in the dabigatran vs. 4.3% per year (95% CI: 2.9–6.2) in acenocoumarol (Table 2, Figure 2). This strongly reduced risk of major bleeding in dabigatran vs. acenocoumarol was confirmed in multivariable analysis resulting in an adjusted HR of 0.45 (95% CI: 0.22–0.93, $P = 0.031$) for dabigatran vs. acenocoumarol. In the multivariable model, also the a priori bleeding risk as assessed by the HAD-BLED score was included. No other baseline variables reached the level of $P < 0.10$ set for inclusion in the multivariable model (Table 3).

Secondary outcomes

As presented in Table 4, no significant differences were observed in the secondary effectiveness endpoints. In patients treated with dabigatran, a non-significant but slightly higher rate of myocardial infarction was observed (1.0 vs. 0.6%/year in dabigatran vs. acenocoumarol, respectively), whereas in patients treated with

Table 1 Baseline characteristics of the patients.^a

Characteristic	All (N = 766)	Dabigatran (N = 383)	Acenocoumarol (N = 383)	P-value
Age (year)	71.5 ± 9.1	70.6 ± 8.9	72.3 ± 9.3	0.007
Weight (kg)	84.4 ± 17.7	84.3 ± 17.1	84.5 ± 18.4	0.94
Systolic blood pressure (mmHg)	148 ± 23	148 ± 22	147 ± 25	0.27
Diastolic blood pressure (mmHg)	84 ± 13	85 ± 13	84 ± 14	0.24
Male sex, n (%)	401 (52.4)	205 (53.5)	196 (51.2)	0.56
Paroxysmal AF, n (%)	459 (59.9)	231 (60.3)	228 (59.5)	0.10
Persistent AF, n (%)	192 (25.1)	86 (22.5)	106 (27.7)	
Permanent AF, n (%)	115 (15.0)	66 (17.2)	49 (12.8)	
CHA ₂ DS ₂ -VASc score ^b	3.1 ± 1.4	3.0 ± 1.4	3.2 ± 1.3	0.008
1, n (%)	91 (11.9)	57 (14.9)	34 (8.9)	0.021
2, n (%)	189 (24.7)	102 (26.6)	87 (22.7)	
3–4, n (%)	371 (48.4)	171 (44.7)	200 (52.2)	
5–6, n (%)	104 (13.6)	46 (12.0)	58 (15.1)	
7–9, n (%)	11 (1.4)	7 (1.8)	4 (1.0)	
CHADS ₂ score ^b	1.7 ± 1.1	1.6 ± 1.2	1.7 ± 1.1	0.008
0–1, n (%)	388 (50.7)	216 (56.4)	172 (44.9)	0.003
2, n (%)	223 (29.1)	92 (24.0)	131 (34.2)	
3–6, n (%)	155 (20.2)	75 (19.6)	80 (20.9)	
HAS-BLED score ^b	1.4 ± 0.9	1.4 ± 0.9	1.4 ± 0.9	0.84
0–1, n (%)	438 (57.2)	210 (54.8)	228 (59.5)	0.25
2–3, n (%)	315 (41.1)	168 (43.9)	147 (38.4)	
4–5, n (%)	13 (1.7)	5 (1.3)	8 (2.1)	
Previous stroke, TIA or systemic embolism, n (%)	141 (14.9)	54 (14.1)	60 (15.7)	0.61
Prior myocardial infarction, n (%)	62 (8.1)	30 (7.8)	32 (8.4)	0.89
Prior bleeding, n (%)	55 (7.2)	27 (7.1)	28 (7.3)	1.00
Heart failure or reduced left ventricular ejection fraction, n (%)	120 (15.7)	57 (14.9)	63 (16.5)	0.62
Diabetes mellitus, n (%)	128 (16.7)	61 (15.9)	67 (17.5)	0.63
Hypertension, n (%)	494 (64.5)	246 (64.2)	248 (64.8)	0.94
Abnormal renal function (creatinine clearance <30), n (%)	7 (1.0)	0 (0.0)	7 (1.9)	0.015
Creatinine (µmol/L)	84.7 ± 38.6	82.6 ± 19.5	86.7 ± 50.4	0.89
Creatinine clearance (mL/min)	73.2 ± 18.8	73.7 ± 17.0	72.7 ± 20.3	0.53
Abnormal liver function (ASAT, ALAT of LD >2 times upper limit of normal), n (%)	13 (1.8)	7 (2.0)	6 (1.6)	0.78
Alcohol use (≥8 units/week), n (%)	85 (11.1)	37 (9.7)	48 (12.5)	0.25
Concomitant medication, n (%)				
Antiplatelet therapy				
Single	27 (3.5)	14 (3.7)	13 (3.4)	1.00
Dual	2 (0.3)	1 (0.3)	1 (0.3)	
Angiotensin-receptor blocker or ACE inhibitor	482 (62.9)	243 (63.5)	239 (62.4)	0.82
Beta-blocker	520 (67.9)	248 (64.8)	272 (71.0)	0.075
Amiodarone	7 (0.9)	5 (1.3)	2 (0.5)	0.45
Statin	292 (38.1)	152 (39.7)	140 (36.6)	0.41
Proton pump inhibitor	217 (28.3)	104 (27.2)	113 (29.5)	0.52
H ₂ -receptor antagonist	4 (0.5)	2 (0.5)	2 (0.5)	1.00
Verapamil	102 (13.3)	62 (16.2)	40 (10.4)	0.025
Non-steroidal anti-inflammatory drugs	16 (2.1)	7 (1.8)	9 (2.4)	0.80
Previous use of vitamin K antagonist for >2 months, n (%)	88 (11.5)	88 (23.0)	–	

^aPlus–minus values are means ± standard deviation.^bThe CHADS₂ score is a measure of the risk of stroke in which congestive heart failure, hypertension, an age of ≥75 years, and diabetes mellitus are each assigned 1 point and previous stroke or TIA is assigned 2 points. The CHA₂DS₂-VASc score is a measure of risk of stroke in which congestive heart failure, hypertension, an age of 65–74, diabetes mellitus, vascular disease, and female sex are each assigned 1 point and previous stroke, TIA or systemic embolism, and age ≥75 are assigned 2 points. The HAS-BLED score is a measure of the risk of bleeding in which hypertension, abnormal renal function, abnormal liver function, previous stroke, prior bleeding, labile INRs, an age of >65, antiplatelet therapy or NSAIDs use, and alcohol use are assigned each 1 point.

Table 2 Rates of primary effectiveness and safety outcomes.

	Dabigatran	Acenocoumarol
Primary effectiveness outcome		
Calculated stroke risk ^a (%/year)	3.5	3.7
Stroke or systemic embolism, %/year (95% CI)	0.8 (0.2–2.1)	1.0 (0.4–2.1)
Primary safety outcome		
Calculated bleeding risk ^b (%/year)	1.7	1.7
Major bleeding, %/year (95% CI)	2.1 (1.0–3.8)	4.3 (2.9–6.2)

^aCalculated stroke risk according to the CHA₂DS₂-VASc score.

^bCalculated bleeding risk according to the HAS-BLED score.

95% CI indicates 95% confidence interval.

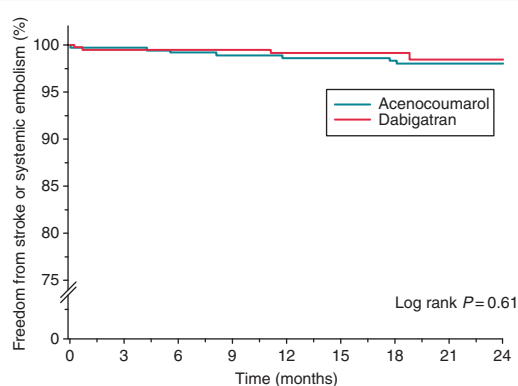


Figure 1 The Kaplan–Meier survival curve of dabigatran vs. acenocoumarol for stroke or systemic embolism.

acenocoumarol rates of stroke (0.6 vs. 0.9%/year in dabigatran vs. acenocoumarol, respectively) and death from vascular cause (0 vs. 0.6%/year in dabigatran vs. acenocoumarol, respectively) were slightly higher.

Rate of total bleeding (major or minor) was significantly lower in patients receiving dabigatran compared with those who received acenocoumarol (8.4 vs. 14.2%/year, $P = 0.003$). For minor bleeds only, rates were 6.4 vs. 10.0%/year in dabigatran and acenocoumarol, respectively ($P = 0.032$). Also for the separate components of the primary safety endpoint of major bleeding, rates were all lower in the dabigatran group, compared with the acenocoumarol group.

Sensitivity analysis: anticoagulation-naïve dabigatran vs. acenocoumarol

After propensity score matching using only patients in whom dabigatran was initiated without previous use of a VKA, the matching

procedure resulted in 333 pairs of patients that were all naïve to anticoagulation. Again, matching resulted in a balanced cohort of 666 patients (data not shown). The sensitivity analysis showed a similar non-significant result with regard to the effectiveness of dabigatran vs. acenocoumarol in preventing stroke. In this subset of patients, incidence rate of stroke or systemic embolism was 0.7%/year (95% CI: 0.2–2.1) in dabigatran vs. 0.7%/year (95% CI: 0.2–1.7) in acenocoumarol (HR = 1.2, 95% CI: 0.3–5.2, $P = 0.83$, for dabigatran vs. acenocoumarol).

With regard to the primary safety endpoint, a similar significantly reduced bleeding risk in the dabigatran patients vs. acenocoumarol was observed [incidence rates 1.9 (95% CI: 0.8–3.8) and 4.6 (95% CI: 3.0–6.7), HR = 0.39, 95% CI: 0.18–0.86, $P = 0.019$, for dabigatran vs. acenocoumarol].

Furthermore, there was no relation between the dose of dabigatran and outcome. None of the patients who switched from a VKA to dabigatran suffered from a stroke or systemic embolism, or major bleeding in the first week following change of anticoagulation therapy.

Time in therapeutic range

In the patients treated with acenocoumarol, the TTR according to the Rosendaal method¹⁴ was assessed using available INR data. The therapeutic range was defined as INR 2.0–3.5, as this range is routinely applied in the Netherlands. With a mean TTR of 78.0% (9.4% below and 12.6% above this range), overall level of anticoagulation was good. A poor level of anticoagulation, i.e. TTR < 45%, was only observed in 5.5% of patients. When considering a narrower range of INR between 2.0 and 3.0 TTR reduced to 55.0% (9.4% below and 35.6% above this range). The individual INR at the time of event was not related to the occurrence of stroke or major bleeding. Furthermore, there was no significant relation between the individual TTR and outcome.

Discussion

To date, two large database studies in Denmark and the USA examined the real-world experience of dabigatran compared with warfarin, and one study examined NOACs (mainly dabigatran) based on examination of individual patient records in Sweden.^{15–17} All these studies confirmed the results from the RE-LY study in which dabigatran 150 mg b.i.d. demonstrated improved efficacy and non-inferior safety as compared with warfarin.⁵ In Figure 3, it is shown that the present study demonstrated the lowest stroke rates compared with the other studies, presumably due to a relatively healthy AF population. This is illustrated by an average CHADS₂ score of 1.7 in the present study vs. 2.1 in the RE-LY study. The dabigatran patients in the present study also demonstrate a low bleeding rate. In contrast, despite the same definition of major bleeds, bleeding rate in the acenocoumarol patients was amongst the highest scores. Furthermore, in our study, bleeding rate in the dabigatran patients was in line with that what was predicted from the HAS-BLED score, whereas bleeding rate in the acenocoumarol patients was much higher than expected from the HAS-BLED score. In part, this may be explained by a different target INR range than previously used in the trials with warfarin. Traditionally, in the Netherlands, the Thrombosis Service aims at an INR between 2.0 and 3.5, while

Table 3 Results from multivariate analysis

	Crude			Adjusted		
	HR	95% CI	P-value	HR	95% CI	P-value
Stroke or systemic embolism						
Dabigatran treatment	0.73	0.21–2.55	0.62	0.72	0.20–2.63	0.61
CHA ₂ DS ₂ -VASC score ^a						
1–4	–	–	0.067	–	–	0.066
5–6	2.69	0.71–10.3		2.64	0.69–10.1	
6–9	9.14	1.13–74.1		9.59	1.13–81.7	
Major bleeding						
Dabigatran treatment	0.44	0.21–0.93	0.032	0.45	0.22–0.93	0.031
HAS-BLED score ^b						
0–1	–	–	0.028	–	–	0.031
2	0.94	0.46–1.96		0.98	0.48–2.02	
3–4	2.78	1.24–6.23		2.79	1.24–6.26	

^aThe CHA₂DS₂-VASC score was categorized into three score classes, as linearity was not established.

^bThe HAS-BLED score was categorized into three score classes, as linearity was not established (of note, 4 was the maximum score observed).

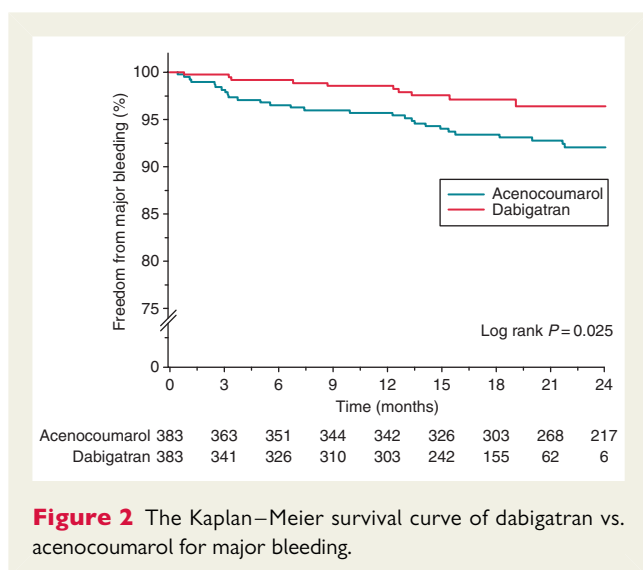


Figure 2 The Kaplan–Meier survival curve of dabigatran vs. acenocoumarol for major bleeding.

the RE-LY study followed the international guidelines with an advised INR level between 2.0 and 3.0 for stroke prevention in AF.² Furthermore, acenocoumarol has a shorter half-life than warfarin. Higher INRs are thereby more easy to counteract, but it may also result in more labile INR values, especially towards the higher end of the therapeutic range. Indeed, aiming for an INR of 2.0–3.5 resulted in a TTR of 78.0%, but the TTR between 2.0 and 3.0 was only 55.0%. This is much lower than the TTR on warfarin in the RE-LY study (64%).⁵ Using the stricter target INR between 2.0 and 3.0 could result in a higher TTR in patients on acenocoumarol and may lead to a lower rate of events. On the other hand, it has been described that only a TTR of <45% was associated with poor outcome in patients treated with acenocoumarol.¹⁸ In our study, poor TTR was observed in only a very limited number of patients possibly explaining the absence of an association between

individual TTR and the occurrence of a stroke or bleeding. This is in line with previous reports showing that TTR is a poor predictor of clinical outcomes.¹⁹ Furthermore, no association was observed with the INR values at the time of event.

Although the majority of the dabigatran patients in our study received dabigatran in a dose of 150 mg b.i.d., we found non-inferior effectiveness rates and superior safety rates of dabigatran, compared with acenocoumarol. This observation is in contrast to the RE-LY trial, where superior effectiveness rates and non-inferior safety rates were found for dabigatran dosed at 150 mg b.i.d., when compared with warfarin. On one hand, this may be due to the higher bleeding rates on acenocoumarol than expected. On the other hand, our low reported bleeding rate of dabigatran may be a reflection of the application of prescribing recommendations and guidelines, whereby the 150 mg dose dabigatran was not administered in elderly patients (age ≥80 years), in patients at high bleeding risk, using concomitant interacting drugs (e.g. verapamil) or in patients with a moderate renal impairment (CrCl 30–49 mL/min). In these patients, the adjusted dose of dabigatran 110 mg was recommended.⁹

One of the most dramatic complications of oral anticoagulation therapy is intracranial bleeding, especially haemorrhagic stroke. In our study, none of the patients with dabigatran got an intracranial bleeding, compared with 0.3%/year in patients with acenocoumarol, without a reduction in the effectiveness against ischaemic stroke. Although the sample size of the study has insufficient power to analyse this difference, it is in line with the results from the randomized trials comparing the different NOACs with warfarin, in which intracranial bleeding rates were also lower in patients using the NOACs.^{5–8} Also all other crude rates of bleeding, including gastrointestinal bleeding, were lower with dabigatran, compared with acenocoumarol (Table 4).

In a sensitivity analysis, we compared the primary effectiveness and safety outcomes of anticoagulation-naïve dabigatran with acenocoumarol. We show that also in anticoagulation-naïve patients, dabigatran was associated with significant less major bleeding events when

Table 4 Secondary effectiveness and safety outcomes, according to treatment group.^a

Event	Dabigatran (N = 383)		Acenocoumarol (N = 383)		Dabigatran vs. acenocoumarol P-value*
	No. of patients	%/year	No. of patients	%/year	
Secondary effectiveness outcomes					
Stroke or systemic embolism	4	0.8	7	1.0	0.61
Stroke	3	0.6	6	0.9	0.50
Ischaemic stroke	2	0.4	3	0.4	0.77
TIA	1	0.2	3	0.4	0.52
Systemic embolism	1	0.2	1	0.1	0.73
Myocardial infarction	5	1.0	4	0.6	0.35
Pulmonary embolism	0	0.0	0	0.0	–
Death from vascular cause	0	0.0	4	0.6	NE
Death from any cause	10	2.0	11	1.6	0.83
Secondary safety outcomes					
Major bleeding	10	2.1	28	4.3	0.031
Life-threatening	1	0.2	6	0.9	0.17
Gastrointestinal ^b	1	0.2	5	0.7	0.24
Perioperative ^b	8	1.6	15	2.3	0.42
Minor bleeding	30	6.4	62	10.0	0.032
Major or minor bleeding	39	8.4	84	14.2	0.003
Intracranial bleeding	0	0.0	2	0.3	NE

^aData are shown for all patients who had at least one event. All calculations were based on the time to the first event.

^bSome gastrointestinal and perioperative bleedings were life-threatening and are included in both categories.

NE; not estimable due to zero counts and/or small numbers.

*P-values derived from the univariate Cox regression analysis.

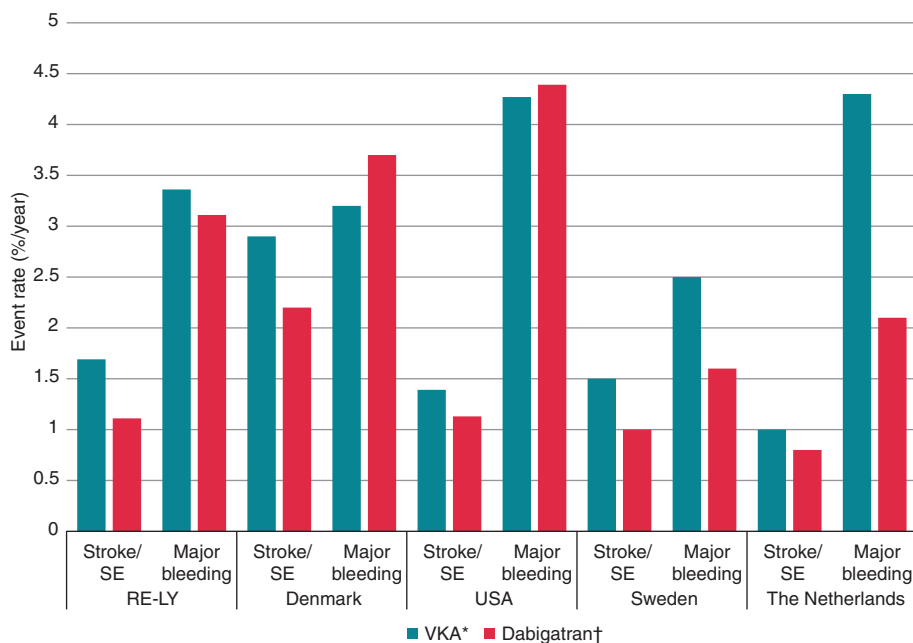


Figure 3 Effectiveness and safety outcomes of ‘real-world’ registries investigating stroke prevention in AF by dabigatran vs. vitamin K antagonists in relation to the randomized RE-LY trial. *VKA: warfarin in all studies, except for the Netherlands; acenocoumarol. †Dabigatran in a dose of 150 mg b.i.d. in all studies, except for the USA (150 or 75 mg b.i.d.); and the Netherlands (all doses).

compared with acenocoumarol. Furthermore, we found no significant difference in safety between the anticoagulation-naïve dabigatran patients and the patients who initiated dabigatran after long-term VKA therapy. In short, previous use of anticoagulation therapy does not seem to have an influence on our primary results. The protocol which we used for switching VKA therapy to dabigatran appeared to be safe.

Because in randomized trials all NOACs provide an improved efficacy/safety ratio, and are more convenient to use when compared with warfarin, they are recommended as broadly preferable to VKAs in the 2012 updated ESC guideline for the management of AF. However, concerns have been raised about presumed excess of bleeding events on dabigatran.²⁰ In our 'real-world' investigation, we found no evidence for an excess of bleeding events among patients treated with dabigatran. In fact, patients treated with dabigatran experienced less than half the rate of major bleedings per year as patients treated with acenocoumarol (HR = 0.45, 95% CI: 0.22–0.93, $P = 0.031$). Our conclusions are in line with the randomized trials and other registries, also showing an improved effectiveness/safety ratio of dabigatran.

Study limitations

Because this was a retrospective study, significant differences existed between study groups. According to the ESC guideline,⁹ from 2012 on, we preferably prescribed NOACs, unless patients had a poor renal function or were at very old age. In these cases, a VKA was prescribed. This might have led to a selection bias, whereby the acenocoumarol group is probably more fragile compared with the dabigatran patients. To address this issue, we performed propensity score matching to achieve a more balanced cohort, based on estimated probabilities for receiving dabigatran/acenocoumarol. Although selection bias cannot be fully excluded, our treatment groups were highly comparable after matching. With respect to poor renal function in our study population only seven patients had an abnormal renal function (Table 1). Furthermore, we included the CHA₂DS₂-VASC and HAS-BLED scores in our Cox regression model to correct for any remaining confounding due to differences in a priori risk status. Follow-up duration was significantly different between the two patient groups; therefore, events were described in per cent per year. The Cox regression model used for comparing the two treatment groups adjusts for differences in follow-up duration by using the time till first event.

Furthermore, this was a single-centre investigation, and the sample size was too small to study the secondary outcomes with sufficient power. Data were retrieved from our institution's electronic patient records. Events that occurred in other hospitals or at home might be missing, but this is true for both treatment groups. Finally, we had no special service to ensure compliance. On the other hand, this may resemble real-life NOAC use in general. In our clinic, every new patient with AF is informed about the risk of stroke and thromboembolism and is advised to adhere to the prescribed anticoagulation regimen.

Conclusion

The present study compared effectiveness and safety outcomes of dabigatran and acenocoumarol in patients with non-valvular AF. We

showed that dabigatran was associated with significantly lower rates of major bleeding with a comparable rate of stroke or systemic embolism compared with acenocoumarol. We therefore conclude that dabigatran in daily clinical practice in patients with AF appears to be as effective, but significantly safer than acenocoumarol.

Funding

Funding to pay the Open Access publication charges for this article was provided by Boehringer Ingelheim BV, The Netherlands.

Conflict of interest: I.C.V.G. reports receiving personal fees from Boehringer Ingelheim, Pfizer BMS, and Bayer and grant support from Boehringer Ingelheim and Bayer. R.G.T. reports receiving personal fees from Boehringer Ingelheim, Pfizer BMS, and Bayer and grant support from Boehringer Ingelheim and Pfizer BMS.

References

- Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener H et al. Outcome parameters for trials in atrial fibrillation: recommendations from a consensus conference organized by the German Atrial Fibrillation Competence Network and the European Heart Rhythm Association. *Europace* 2009;**11**:771–817.
- Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 2010;**12**:1360–420.
- Lip GY, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E et al. Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. *Europace* 2011;**13**:723–46.
- Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013;**15**:625–51.
- Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–51.
- Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–91.
- Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–104.
- Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–92.
- Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;**14**:1385–413.
- Verhoef TI, Redekop WK, Daly AK, van Schie RM, de Boer A, Maitland-van der Zee AH. Pharmacogenetic-guided dosing of coumarin anticoagulants: algorithms for warfarin, acenocoumarol and phenprocoumon. *Br J Clin Pharmacol* 2014;**77**:626–41.
- Lip GYH, Nieuwlaar R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;**137**:263–72.
- Pisters R, Lane DA, Nieuwlaar R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;**138**:1093–100.
- Lip GYH, Frison L, Halperin JL, Lane DA. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke* 2010;**41**:2731–8.
- Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993;**69**:236–9.
- Larsen TB, Rasmussen LH, Skjøth F, Due KM, Callréus T, Rosenzweig M et al. Efficacy and safety of dabigatran etexilate and warfarin in real-world patients with atrial fibrillation: a prospective nationwide cohort study. *J Am Coll Cardiol* 2013;**61**:2264–73.

16. Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M *et al*. Cardiovascular, bleeding, and mortality risks in elderly medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation* 2015; **131**:157–64.
17. Labaf A, Carlwe M, Svensson PJ. Efficacy and safety of novel oral anticoagulants in clinical practice; a report from three centers in Sweden. *Thrombosis J* 2014; **12**:29.
18. Veeger NJ, Piersma-Wichers M, Tijssen JG, Hillige HL, van der Meer J. Individual time within target range in patients treated with vitamin K antagonists: main determinant of quality of anticoagulation and predictor of clinical outcome. A retrospective study of 2300 consecutive patients with venous thromboembolism. *Br J Haematol* 2005; **128**:513–9.
19. Lind M, Fahlen M, Kosiborod M, Eliasson B, Oden A. Variability of INR and its relationship with mortality, stroke, bleeding and hospitalisations in patients with atrial fibrillation. *Thromb Res* 2012; **129**:32–5.
20. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ETTL. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. *Gastroenterology* 2013; **145**:105–12.e15.

EP CASE EXPRESS

doi:10.1093/europace/euw001

Online publish-ahead-of-print 8 February 2016

A useful irrigated tip to cannulate distal coronary sinus

J. Fedida, C. Lepiece, and S. Knecht

A 69-year-old man was referred to our centre for an ablation procedure of symptomatic ventricular ectopics with left bundle branch block morphology, inferior axis, and transition in lead V2 suggesting a left ventricle outflow tract origin.

Using a 3D Carto[®] mapping system and an irrigated-tip ablation catheter (Thermocool[®] SF, Biosense[®]), pace-mapping from the left ventricular outflow tract rose to 88% of correlation in the left coronary cusp. An attempt was then made to cannulate the distal coronary sinus (CS) with a long sheath to stabilize the catheter but was impossible distally from the lateral mitral annulus despite multiple attempts (Panel A). A high-flow saline perfusion, 60 mL/min at room temperature during an arbitrary period of 2 min, was administered via the ablation catheter in the distal CS. Advancing further the ablation catheter was then successfully carried out (Panel A). At this location, in front of the left coronary cusp, pace-mapping showed a correlation of 98.5% (Panel B).

Distal CS cannulation may be challenging mainly because of the presence of a Vieussens valve or a small distal vein. However, the origin of a focus can be epicardial and only reachable via the very distal CS. High-flow irrigation may help its cannulation probably by increasing CS volume allowing dilatation and therefore accessibility for the catheter.

The full-length version of this report can be viewed at: <http://www.escardio.org/Guidelines-&-Education/E-learning/Clinical-cases/Electrophysiology/EP-Case-Reports>.

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