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Dabigatran compared with warfarin in patients with atrial fibrillation and symptomatic heart failure: a subgroup analysis of the RE-LY trial

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Aims We evaluated the effects of dabigatran compared with warfarin in the subgroup of patients with previous symptomatic heart failure (HF) in the RE-LY trial.

Methods and results RE-LY compared two fixed and blinded doses of dabigatran (110 and 150 mg twice daily) with open-label warfarin in 18 113 patients with AF at increased risk for stroke. Among 4904 patients with HF, annual rates of stroke or systemic embolism (SE) were 1.92% for patients on warfarin compared with 1.90% for dabigatran 110 mg [hazard ratio (HR) 0.99, 95% confidence interval (CI) 0.69–1.42] and 1.44% for dabigatran 150 mg (HR 0.75, 95% CI 0.51–1.10). Annual rates of major bleeding were 3.90% for the group on warfarin, compared with 3.26% for dabigatran 110 mg (HR 0.83, 95% CI 0.64–1.09) and 3.10% for dabigatran 150 mg (HR 0.79, 95% CI 0.60–1.03). Rates of intracranial bleeding were significantly lower for both dabigatran dosages compared with warfarin in patients with HF (dabigatran 110 mg vs. warfarin, HR 0.34, 95% CI 0.14–0.80; dabigatran 150 mg vs. warfarin, HR 0.39, 95% CI 0.17–0.89). The relative effects of dabigatran vs. warfarin on the occurrence of stroke or SE and major bleeding were consistent among those with and without HF and those with low (≤40%) or preserved (>40%) LVEF (*P* interaction not significant).

Conclusions The overall benefits of dabigatran for stroke/SE prevention, and major and intracranial bleeding, relative to warfarin in the RE-LY trial were consistent in patients with and without HF.

Keywords Atrial fibrillation • Heart failure • Dabigatran etexilate • Anticoagulation

Introduction

Atrial fibrillation (AF) and heart failure (HF) are both common and frequently co-exist.[1,2] The prevalence of AF increases with the severity of HF, ranging from 4% in patients with asymptomatic LV systolic dysfunction to 50% in NYHA class IV patients.[3] The Euro Heart Survey in AF showed that HF is present in 34% of AF patients.[2]

Atrial fibrillation is a predictor of mortality in patients with HF, and HF is a risk factor for stroke in AF.[4,5] Accordingly, anticoagulation is recommended for patients with AF and co-existing HF in the prevention of stroke or systemic embolism (SE).[6,7] Nevertheless, patients with HF present increased variability in metabolism of vitamin K antagonists (VKAs), which is reflected in a poorer international normalized ratio (INR) control[8] and possibly in the efficacy and safety profiles of VKAs.[9] Indeed, HF is a risk factor for bleeding in patients treated with VKAs.[10] However, little information is available regarding efficacy and safety of VKAs in patients with AF and HF for the prevention of thrombo-embolic events.[11]

In the Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, comparing dabigatran etexilate (henceforth designated as dabigatran) with warfarin in 18 113 patients with AF, the 150 mg dose of dabigatran twice daily reduced stroke or SE by 35% with a similar rate of major bleeding, and the 110 mg dose of dabigatran twice daily had a similar rate of stroke and SE and

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reduced major bleeding by 20%.[12,13] Both doses of dabigatran reduced intracranial bleeding substantially.

This analysis compares the effects of dabigatran 110 mg and 150 mg twice daily with warfarin on outcomes in patients with and without previous symptomatic HF. In addition, we evaluated the impact of HF on outcomes.

Methods

Details of the study design, outcome definitions, patients, and main results have been published.[12,14] In brief, patients with AF documented on ECG in the 6 months before screening and at least one risk factor for stroke [previous stroke or transient ischaemic attack (TIA); LVEF <40%; NYHA class II or higher or HF symptoms in the 6 months before screening; and age ≥75 years or age 65–74 years with diabetes mellitus, hypertension, or CAD] were randomized to receive open-label study warfarin adjusted locally to an INR of 2.0–3.0 or two fixed doses of dabigatran (110 mg and 150 mg twice a day) administered in a blinded manner. Relevant exclusions to trial participation included severe valvular heart disease, stroke in the last 14 days or severe stroke in the 6 months before screening, any condition that increased the risk of haemorrhage, creatinine clearance (CrCl) <30 mL/min, active liver disease, or pregnancy.

Study outcomes

The primary study outcome was time to first occurrence of stroke (including haemorrhagic) or SE. The main safety outcome was time to first occurrence of major bleeding defined as symptomatic bleeding in a critical area or organ, transfusion of at least 2 units of blood, or a reduction in the haemoglobin level of at least 20 g/L. Other outcomes analysed were vascular death, hospitalizations, intracranial bleeding, and total bleeding.

Heart failure

Heart failure was defined as the presence of NYHA class II or higher HF symptoms (fatigue, dyspnoea) in the 6 months before screening, in patients with a history of previous admission for congestive HF.

The LVEF could be assessed by echocardiogram, or radionuclide or contrast angiography, in the last 6 months before randomization. Information about LVEF (≤ or >40%) was available in 2889 patients with HF (58.9%) and in 6004 patients without HF (45.5%), which represent 49.1% of the whole RE-LY population.

Statistical analysis

The baseline characteristics of treatment groups with and without symptomatic HF were compared using Fisher's exact test for categorical variables and *t*-test for continuous variables. Study outcomes are presented as the total number and annual rates, and were examined by Cox regression hazard model. A sensitivity analysis was performed to evaluate the impact of the severity of HF (NYHA functional class II and III/IV), low (≤ 40%) and preserved (>40%) LVEF, different levels of baseline calculated CrCl (<50 and ≥50 mL/min), and the use of HF medications at baseline [renin–angiotensin system inhibitors (ACE inhibitors or ARBs), beta-blockers, or diuretics] on study treatment effects in patients with and without HF. Multivariable proportional hazards models were undertaken using baseline characteristics and study treatments to adjust the impact of HF on clinical outcomes. A *P*-value of <0.05 was considered statistically significant.

All analyses were performed using SAS statistical software, version 9.2 (SAS Institute, Cary, NC, USA).

Results

In the RE-LY trial, 4904 patients (27%) had a history of HF and 13 209 (73%) did not. Most patients classified as having HF were in NYHA functional class II [$n = 3645$ (74.4%)]. There were 1140 patients (23.2%) in class III and only 119 patients (2.4%) in class IV.

Patient characteristics

Baseline demographic and clinical characteristics were balanced across the three treatment groups with or without HF (*Table 1*). In the warfarin group, the median time in the therapeutic range (INR 2.0–3.0) was 63.8% for patients with HF and 68.5% for those without HF ($P < 0.001$).

Patients with HF were younger, and more likely to be male and to have a history of diabetes, heart disease, and CrCl <50 mL/min, but less likely to have a history of hypertension or previous stroke, TIA, or SE (*Table 1*). Patients with HF were more likely to be treated with ACE inhibitors, beta-blockers, and diuretics.

The prevalence of previous VKA exposure (VKA-experienced) before inclusion in the RE-LY trial was 48.5% in patients with HF and 50.0% in those without [non-significant (NS)]. At baseline, the use of antiplatelet therapy was 40.5% in patients with HF and 39.1% in those without HF (NS).

Outcomes according to treatment group

During the median treatment period of 2.0 years, the incidence of stroke or SE in patients with HF was 1.90% per year for 110 mg of dabigatran, 1.44% per year for 150 mg of dabigatran, and 1.92% per year for warfarin (*Figure 1*). Compared with warfarin, the hazard ratios (HRs) for dabigatran 110 mg [0.99; 95% confidence interval (CI) 0.69–1.42] and dabigatran 150 mg (0.75; 95% CI 0.51–1.10) were consistent with the results in the whole trial (*P*-value for interaction = NS). In patients with HF, vascular death and hospitalizations were not significantly different in either of the dabigatran groups compared with the warfarin group (*Figure 1*).

The annual rate of major bleeding in the group with HF was 3.90% in patients receiving warfarin, compared with 3.26% in patients receiving 110 mg of dabigatran (HR 0.83, 95% CI 0.64–1.09) and 3.10% in those receiving 150 mg of dabigatran (HR 0.79, 95% CI 0.60–1.03) (*Figure 1*).

In this subset of patients, intracranial bleeding occurred significantly more often with warfarin (0.65% per year) than with either the 110 mg dose of dabigatran (0.22% per year) or the 150 mg dose of dabigatran (0.26% per year). Total bleeding was significantly reduced with dabigatran 110 mg (HR 0.80, 95% CI 0.71–0.91) and dabigatran 150 mg (HR 0.85, 95% CI 0.75–0.96), when compared with warfarin.

There was no significant interaction between the treatment effect of 110 mg and 150 mg of dabigatran and the presence or absence of HF regarding the efficacy and safety outcomes (*Figure 1*).

The results regarding the primary efficacy and the main safety outcomes were consistent in patients with or without HF with low or preserved LVEF, in HF patients in NYHA functional class II and III/IV (*Figure 2*), across the levels of baseline calculated CrCl, or who received or did not receive HF medications at baseline (*Tables 2* and *3*).

Table 1 Baseline characteristics according to treatment group in the study population with and without heart failure

	With HF				Without HF				*P*-value[a]
	Dabigatran 110 mg b.i.d. (*n* = 1641)	Dabigatran 150 mg b.i.d. (*n* = 1640)	Warfarin (*n* = 1623)	All (*n* = 4904)	Dabigatran 110 mg b.i.d. (*n* = 4374)	Dabigatran 150 mg b.i.d. (*n* = 4436)	Warfarin (*n* = 4399)	All (*n* = 13 209)	
Age, years	68.5 ± 10.3	68.0 ± 10.5	68.4 ± 9.9	68.3 ± 10.2	72.5 ± 7.7	72.8 ± 7.8	72.7 ± 7.7	72.7 ± 7.7	<0.0001
Male, *n* (%)	1142 (69.6)	1061 (64.7)	1079 (66.5)	3282 (66.9)	2723 (62.3)	2779 (62.6)	2730 (62.1)	8232 (62.3)	<0.0001
Diabetes, *n* (%)	420 (25.6)	458 (27.9)	420 (25.9)	1298 (26.5)	989 (22.6)	944 (21.3)	990 (22.5)	2923 (22.1)	<0.0001
Hypertension, *n* (%)	1229 (74.9)	1230 (75.0)	1227 (75.6)	3686 (75.2)	3509 (80.2)	3565 (80.4)	3523 (80.1)	10 597 (80.2)	<0.0001
Stroke or TIA or SE, *n* (%)	270 (16.5)	306 (18.7)	262 (16.1)	838 (17.1)	1038 (23.7)	1052 (23.7)	1025 (23.3)	3115 (23.6)	<0.0001
CAD, *n* (%)	522 (31.8)	515 (31.4)	522 (32.2)	1559 (31.8)	1139 (26.0)	1195 (26.9)	1141 (25.9)	3475 (26.3)	<0.0001
Valvular heart disease, *n* (%)	448 (27.3)	422 (25.7)	413 (25.4)	1283 (26.2)	840 (19.2)	931 (21.0)	890 (20.2)	2661 (20.1)	<0.0001
LVEF ≤40%, *n* (%)[b]	427 (44.0)	429 (44.0)	402 (42.5)	1258 (43.5)	222 (11.2)	223 (11.1)	228 (11.3)	673 (11.2)	<0.0001
$CHADS_2$, mean ± SD[c]	2.6 ± 1.1	2.7 ± 1.2	2.6 ± 1.1	2.6 ± 1.1	2.0 ± 1.1	2.0 ± 1.1	2.0 ± 1.1	2.0 ± 1.1	<0.0001
ACE inhibitor, *n* (%)	939 (57.2)	962 (58.7)	908 (55.9)	2809 (57.3)	1760 (40.2)	1792 (40.4)	1762 (40.1)	5314 (40.2)	<0.0001
ARB, *n* (%)	357 (21.8)	352 (21.5)	368 (22.7)	1077 (22.0)	1091 (24.9)	1118 (25.2)	1050 (23.9)	3259 (24.7)	0.0001
Beta-blocker, *n* (%)	1118 (68.1)	1155 (70.4)	1087 (67.0)	3360 (68.5)	2671 (61.1)	2733 (61.6)	2635 (59.9)	8039 (60.9)	<0.0001
Diuretic, *n* (%)	1182 (72.0)	1189 (72.5)	1199 (73.9)	3570 (72.8)	1870 (42.8)	1930 (43.5)	1876 (42.6)	5676 (43.0)	<0.0001
Systolic BP, mmHg	127.3 ± 17.4	127.3 ± 17.4	127.5 ± 17.2	127.4 ± 17.3	132.1 ± 17.3	132.3 ± 17.4	132.5 ± 17.2	132.3 ± 17.3	<0.0001
Diastolic BP, mmHg	76.9 ± 10.9	76.4 ± 10.8	76.3 ± 10.5	76.6 ± 10.7	77.0 ± 10.5	77.3 ± 10.6	77.3 ± 10.4	77.2 ± 10.5	0.0007
Heart rate, b.p.m.	76.1 ± 15.1	76.5 ± 15.7	75.9 ± 14.9	76.1 ± 15.2	72.8 ± 14.8	72.6 ± 14.5	72.3 ± 14.4	72.6 ± 14.6	<0.0001
CrCl <50 mL/min, *n* (%)[d]	340 (20.9)	362 (22.3)	315 (19.6)	1017 (20.9)	856 (19.8)	870 (19.8)	811 (18.6)	2537 (19.4)	0.0204
NT-proBNP, pg/mL[e]	1450 ± 1399	1640 ± 2417	1568 ± 2072	1552 ± 2006	984 ± 931	940 ± 1005	964 ± 954	963 ± 964	<0.0001

BP, blood pressure; ClCr, creatinine clearance; HF, heart failure; SE, systemic embolism; TIA, transient ischaemic attack.

[a]*P* value for comparison between patients with and without HF.

[b]Data available in 2889 patients with HF (970 under dabigatran 110 mg, 974 under dabigatran 150 mg, and 945 under warfarin) and 6004 patients without HF (1978 under dabigatran 110 mg, 2004 under dabigatran 150 mg, and 2022 under warfarin).

[c]Missing data in one patient without HF.

[d]Missing data in 46 patients with HF and 116 patients without HF.

[e]Data available in 1861 patients with HF (627 under dabigatran 110 mg, 620 under dabigatran 150 mg. and 614 under warfarin) and 4332 patients without HF (1454 under dabigatran 110 mg, 1436 under dabigatran 150 mg, and 1442 under warfarin).

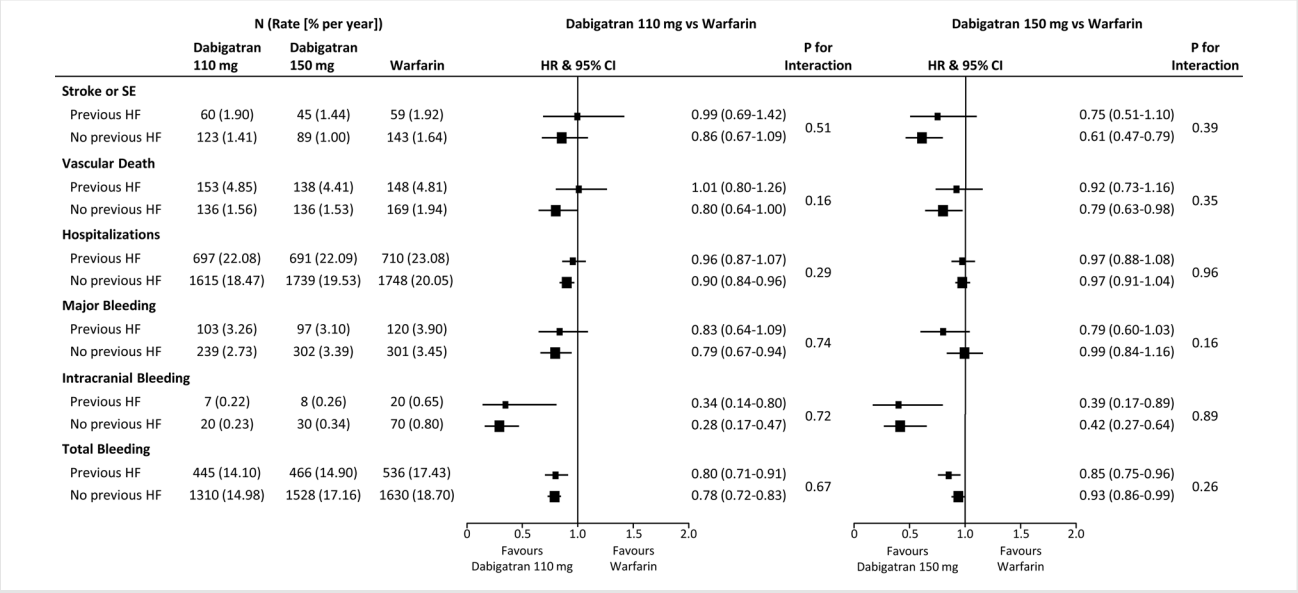

Figure 1 Total number and annual rates of outcomes, treatment effects, and interactions in patients with and without HF. CI, confidence interval; HF, heart failure; HR, hazard ratio; SE, systemic embolism.

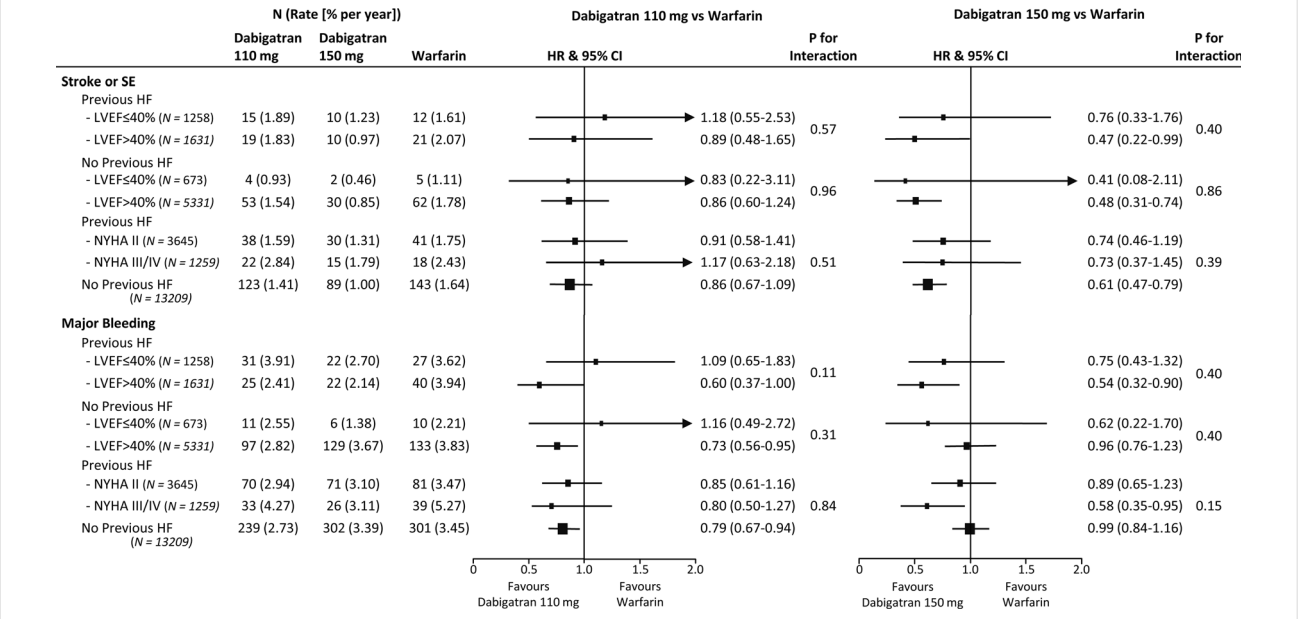

Figure 2 Total number and annual rates of stroke or systemic embolism and major bleeding, according to LVEF and NYHA, influence on treatment effects, and interactions in patients with and without HF. CI, confidence interval; HF, heart failure; HR, hazard ratio; SE, systemic embolism.

Outcomes in all patients with heart failure

Irrespective of treatment allocation, stroke or SE was numerically higher in patients with HF (1.75% per year vs. 1.35% per year in patients without HF) (*Table 4*). Vascular death (4.69% per year vs. 1.67% per year in patients without HF) was considerably higher, and hospitalizations (22.41% per year vs. 19.35% per year in patients without HF) were also more frequent in patients with HF than in those without HF. Major bleeding and intracranial haemorrhage were not different in patients with and without HF (*Table 4*).

After multivariable adjustment for baseline characteristics and study treatments, HF remained a powerful independent predictor of vascular death (adjusted HR 2.26, 95% CI 1.96–2.61) (*Table 4*). HF was also an independent determinant of all hospitalizations (adjusted HR 1.13, 95% CI 1.07–1.20) but was significantly associated

Table 2 Total number and annual rates of stroke or systemic embolism, according to renal function and heart failure medications at baseline, influence on treatment effects, and interactions in patients with and without heart failure

HF status per outcome	*n* [rate (% per year)]			Hazard ratio (95% CI)	
	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	Dabigatran 110 mg vs. warfarin	Dabigatran 150 mg vs. warfarin
With HF					
ClCr <50 mL/min ($n = 1017$)	19 (3.07)	15 (2.35)	21 (3.73)	0.82 (0.44–1.52)	0.62 (0.32–1.20)
ClCr ≥50 mL/min ($n = 3841$)	39 (1.55)	30 (1.22)	38 (1.54)	1.01 (0.65–1.58)	0.79 (0.49–1.28)
P for interaction				0.59	0.56
Without HF					
ClCr <50 mL/min ($n = 2537$)	33 (2.03)	21 (1.23)	36 (2.32)	0.87 (0.54–1.39)	0.53 (0.31–0.90)
ClCr ≥50 mL/min ($n = 10\,556$)	90 (1.28)	68 (0.95)	106 (1.50)	0.86 (0.65–1.14)	0.64 (0.47–0.87)
P for interaction				0.97	0.54
With HF					
With RAS inhibitor ($n = 3739$)	46 (1.91)	39 (1.62)	42 (1.80)	1.06 (0.70–1.61)	0.90 (0.58–1.39)
Without RAS inhibitor ($n = 1165$)	14 (1.87)	6 (0.84)	17 (2.31)	0.81 (0.40–1.65)	0.36 (0.14–0.91)
P for interaction				0.53	0.08
Without HF					
With RAS inhibitor ($n = 8244$)	67 (1.23)	65 (1.17)	83 (1.55)	0.79 (0.57–1.09)	0.75 (0.54–1.04)
Without RAS inhibitor ($n = 4965$)	56 (1.71)	24 (0.72)	60 (1.78)	0.96 (0.67–1.39)	0.40 (0.25–0.65)
P for interaction				0.42	0.03
With HF					
With beta-blocker ($n = 3360$)	43 (1.97)	29 (1.29)	45 (2.18)	0.91 (0.60–1.38)	0.59 (0.37–0.94)
Without beta-blocker ($n = 1544$)	17 (1.75)	16 (1.80)	14 (1.39)	1.25 (0.62–2.54)	1.30 (0.63–2.66)
P for interaction				0.44	0.07
Without HF					
With beta-blocker ($n = 8039$)	76 (1.42)	58 (1.05)	83 (1.58)	0.90 (0.66–1.23)	0.67 (0.48–0.93)
Without beta-blocker ($n = 5170$)	47 (1.38)	31 (0.91)	60 (1.73)	0.80 (0.54–1.17)	0.53 (0.34–0.81)
P for interaction				0.62	0.39
With HF					
With diuretic ($n = 3570$)	46 (2.01)	33 (1.47)	53 (2.33)	0.86 (0.58–1.28)	0.62 (0.40–0.96)
Without diuretic ($n = 1334$)	14 (1.60)	12 (1.36)	6 (0.74)	2.17 (0.83–5.64)	1.83 (0.69–4.89)
P for interaction				0.08	0.05
Without HF					
With diuretic ($n = 5676$)	53 (1.43)	40 (1.03)	64 (1.73)	0.82 (0.57–1.19)	0.59 (0.40–0.88)
Without diuretic ($n = 7533$)	70 (1.39)	49 (0.98)	79 (1.57)	0.89 (0.64–1.22)	0.62 (0.43–0.89)
P for interaction				0.77	0.87

CI, confidence interval; ClCr, creatinine clearance; HF, heart failure; RAS, renin–angiotensin system.

with lower risk of total bleeding (adjusted HR 0.86, 95% CI 0.81–0.92). HF was not associated with the occurrence of stroke or systemic embolism, major bleeding, or intracranial haemorrhage in multivariable analysis (*Table 4*). Notwithstanding this fact, there was a significant difference in the incidence of stroke or SE (adjusted HR 0.66, 95% CI 0.48–0.91; $P = 0.012$) and major bleeding (adjusted HR 0.75, 95% CI 0.60–0.96; $P = 0.020$) between patients with HF in NYHA class II and class III/IV (*Figure 3*).

Discussion

The current analysis showed that, among patients with a history of HF, which constituted 27% of the RE-LY study subjects, the relative effects of both doses of dabigatran compared with warfarin on clinical outcomes were consistent with the results of the main trial. This is in agreement with other RE-LY subanalyses that have replicated the relative benefits of dabigatran compared with warfarin on primary outcomes in several subgroups,[15–18] apart from the attenuated benefit in major bleeding with increasing age (110 and 150 mg dosages)[17] and the centre's mean time in the therapeutic range in the warfarin population (150 mg dosage).[16]

In our cohort of patients with HF, there was a numerically higher incidence of stroke or SE but, after multivariable adjustment, the difference was not statistically significant. The lack of increase in stroke risk with HF in our cohort is probably related to lower age, less hypertension, and less previous stroke in our cohort. HF increases the risk

Table 3 Total number and annual rates of major bleeding, according to renal function and heart failure medications at baseline, influence on treatment effects, and interactions in patients with and without heart failure

HF status per outcome	*n* [rate (% per year)]			Hazard ratio (95% CI)	
	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	Dabigatran 110 mg vs. warfarin	Dabigatran 150 mg vs. warfarin
With HF					
ClCr <50 mL/min ($n = 1017$)	43 (6.96)	40 (6.26)	38 (6.76)	1.04 (0.67–1.61)	0.93 (0.59–1.44)
ClCr ≥50 mL/min ($n = 3841$)	60 (2.39)	56 (2.28)	81 (3.28)	0.72 (0.52–1.01)	0.69 (0.49–0.97)
P for interaction				0.19	0.31
Without HF					
ClCr <50 mL/min ($n = 2537$)	79 (4.87)	89 (5.21)	78 (5.03)	0.96 (0.70–1.31)	1.05 (0.77–1.42)
ClCr ≥50 mL/min ($n = 10556$)	157 (2.24)	213 (2.99)	223 (3.15)	0.71 (0.58–0.87)	0.96 (0.79–1.15)
P for interaction				0.11	0.62
With HF					
With RAS inhibitor ($n = 3739$)	84 (3.49)	76 (3.15)	92 (3.93)	0.88 (0.66–1.19)	0.80 (0.59–1.08)
Without RAS inhibitor ($n = 1165$)	19 (2.54)	21 (2.94)	28 (3.80)	0.66 (0.37–1.19)	0.78 (0.44–1.37)
P for interaction				0.39	0.94
Without HF					
With RAS inhibitor ($n = 8244$)	149 (2.72)	203 (3.64)	186 (3.48)	0.78 (0.63–0.97)	1.05 (0.86–1.29)
Without RAS inhibitor ($n = 4965$)	90 (2.75)	99 (2.97)	115 (3.42)	0.80 (0.61–1.06)	0.88 (0.67–1.15)
P for interaction				0.88	0.28
With HF					
With beta-blocker ($n = 3360$)	72 (3.30)	73 (3.26)	78 (3.77)	0.87 (0.63–1.20)	0.87 (0.63–1.19)
Without beta-blocker ($n = 1544$)	31 (3.18)	24 (2.70)	42 (4.16)	0.76 (0.48–1.21)	0.64 (0.38–1.05)
P for interaction				0.63	0.31
Without HF					
With beta-blocker ($n = 8039$)	134 (2.51)	193 (3.51)	177 (3.37)	0.74 (0.59–0.93)	1.05 (0.86–1.29)
Without beta-blocker ($n = 5170$)	105 (3.09)	109 (3.21)	124 (3.58)	0.86 (0.67–1.12)	0.90 (0.70–1.16)
P for interaction				0.38	0.36
With HF					
With diuretic ($n = 3570$)	92 (4.03)	80 (3.56)	98 (4.32)	0.93 (0.70–1.24)	0.82 (0.61–1.10)
Without diuretic ($n = 1334$)	11 (1.26)	17 (1.93)	22 (2.73)	0.46 (0.22–0.95)	0.71 (0.38–1.34)
P for interaction				0.08	0.70
Without HF					
With diuretic ($n = 5676$)	113 (3.04)	165 (4.23)	136 (3.68)	0.83 (0.64–1.06)	1.17 (0.93–1.47)
Without diuretic ($n = 7533$)	126 (2.51)	137 (2.74)	165 (3.29)	0.76 (0.60–0.96)	0.83 (0.66–1.04)
P for interaction				0.62	0.04

CI, confidence interval; ClCr, creatinine clearance; HF, heart failure; RAS, renin–angiotensin system.

Table 4 Total number and annual rates of outcomes in the study population with and without heart failure and multivariable adjusted hazard ratios

Outcomes	With HF ($n = 4904$)	Without HF ($n = 13\,209$)	Adjusted hazard ratio (95% CI)	*P*-value
Stroke or systemic embolism	164 (1.75)	355 (1.35)	1.08 (0.89–1.31)	0.46
Vascular death	439 (4.69)	441 (1.67)	2.26 (1.96–2.61)	<0.0001
Hospitalization	2098 (22.41)	5102 (19.35)	1.13 (1.07–1.20)	<0.0001
Major bleeding	320 (3.42)	842 (3.19)	0.96 (0.83–1.10)	0.53
Intracranial bleeding	35 (0.37)	120 (0.46)	0.72 (0.49–1.06)	0.10
Total bleeding	1447 (15.46)	4468 (16.95)	0.86 (0.81–0.92)	<0.0001

CI, confidence interval; HF, heart failure.

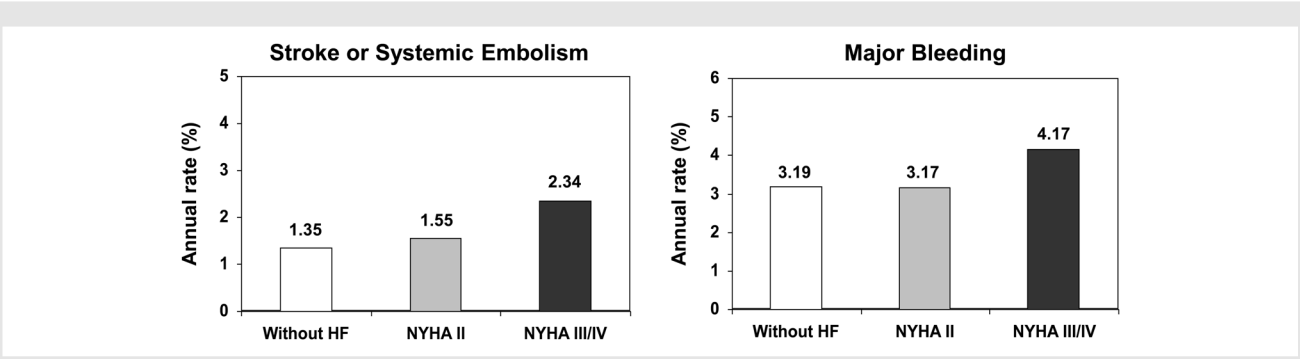

Figure 3 Annual rates of stroke or systemic embolism (SE) and major bleeding in patients without heart failure (HF) and with HF according to NYHA functional class.

of thrombo-embolic complications in patients with AF,[6] and is, together with age, hypertension, diabetes, and previous stroke, included in risk stratification using $CHADS_2$ or CHA_2DS_2-VASc scores.[19,20] The main pathophysiological features of HF leading to thrombogenesis include low blood flow and a proinflammatory state.[3,21] Current guidelines recommend the use of anticoagulation in patients with AF with co-existent HF (class I and level of evidence A),[6,7] but adherence to these recommendations in clinical practice is low.[2,22] The use of warfarin or another VKA in stroke prevention in patients with AF and HF is challenging for the clinician. Common barriers for prescription of anticoagulants, such as the need for laboratory control and the fear of haemorrhagic events, are amplified in patients with HF by the perception of increased risk associated with more co-morbidities, drug interactions, and the subsequent increased INR variability and reduced time in the therapeutic range.[2,8] Dabigatran overcomes the need for anticoagulant monitoring, and both doses provided similar benefits in the prevention of stroke or SE irrespective of the presence or absence of HF.

In a recent meta-analysis, that included data from RE-LY, ROCKET-AF, and ARISTOTLE, the reduction of stroke and SE associated with new oral anticoagulants vs. warfarin was statistically significant in patients without HF [odds ratio (OR) 0.76, 95% CI 0.67–0.87; $P < 0.0001$] and non-significant in patients with HF (OR 0.91, 95% CI 0.78–1.06; $P = 0.22$).[23] Notwithstanding this fact, the OR for stroke or SE favours the new oral anticoagulants and there is no interaction between patients with and without HF.

In our entire HF population, there was no significant increase in major and intracranial bleeding, and even a lower incidence of total bleeding, compared with patients without HF. Bleeding risk is usually increased in patients with AF and HF both in clinical practice[2] and in the more controlled setting of clinical trials.[9,10] However, lower age and lower prevalence of hypertension and previous stroke or TIA may have contributed to the observed lower risk of any bleeding in anticoagulated patients, as indicated by the HAS-BLED score.[9] This baseline demographic and clinical profile seen in our HF cohort is unusual, when compared with patients without HF of the RE-LY trial, but it is similar to the HF population included in the AF Euro Heart Survey[2] or patients with markers of HF enrolled in SPORTIF 3 and 5.[11] A misclassification of HF in patients with other causes of fatigue or dyspnoea could be an explanation, but is unlikely since source data verification of case report forms against the medical record was done throughout the trial to ensure accuracy, and baseline NT-proBNP levels were in agreement with the diagnosis of HF. A selection bias might explain those features, since hypertension (blood pressure >140/90 mmHg requiring medical treatment), age ≥75 years, and HF were inclusion criteria in our study. Accordingly, the RE-LY included 5775 patients with only one risk factor for stroke, corresponding to 3396 patients with hypertension, 1044 with age ≥75 years, and 721 with HF.[18] The presence of this exclusive feature in one group could contribute to the mismatch between patients with and without HF.

In our trial, there were no significant interactions of HF with the reduction of major bleeding by dabigatran 110 mg or the unchanged rate with dabigatran 150 mg as compared with warfarin. It is noteworthy that total bleeding was reduced by both doses of dabigatran in the HF cohort. Consistent with the overall RE-LY population and other subgroup analyses, the incidence of intracranial bleeding was markedly lower in the HF group with both doses of dabigatran, as compared with warfarin. Bleeding is an important cause of discontinuation of oral anticoagulation,[12] and physicians are less likely to prescribe a VKA after observing a bleeding complication.[24] The lower risk of bleeding with dabigatran in the HF population may be important, as it could improve compliance with guidelines for thromboprophylaxis in AF patients.

Notwithstanding the fact that HF was not an independent predictor of stroke or SE and major bleeding, there was a significant increase in the incidence of these outcomes with the growing severity in the NYHA functional class. The large proportion of patients in NYHA functional class II, compared with other cohorts,[2,25] may have attenuated the difference in main outcomes between patients with and without HF.

Heart failure with preserved EF is a major and growing public health problem, representing approximately half of the entire HF population, and LV diastolic dysfunction is thought to be the main underlying pathophysiological abnormality.[26] The occurrence of AF in these patients is associated with a risk of stroke and thromboembolism similar to that of those with reduced EF.[27] In the present study, the relative benefits of dabigatran 110 mg and 150 mg compared with warfarin in reducing stroke or SE and major bleeding were consistent in patients with low (≤40%) and preserved

(>40%) LVEF. The severity of previous HF symptoms assessed with NYHA functional class did not influence the relative risks of primary outcomes between both dosages of dabigatran and warfarin.

Among those with HF, there was no significant interaction between the levels of baseline calculated CrCl or the use of medications for HF at baseline and randomized treatments for the occurrence of stroke or SE and major bleeding. During treatment with dabigatran, since it is 80% renally excreted, CrCl should be rechecked periodically.[28] This recommendation is especially important in patients with decompensated HF, which may be associated with worsening of renal function due to neurohormonal and haemodynamic abnormalities and untoward drug effects (diuretics and vasodilators).[29]

The present study confirms the increased risk of vascular mortality associated with HF in patients with AF, as shown in other studies.[2,11] HF doubled the risk of vascular death after adjustment for confounding factors. In the RE-LY study, patients with HF compared with those without HF had substantially more LV systolic dysfunction, a marker of poor prognosis.[30] In addition, they had more permanent AF, which reinforces the concept that HF predisposes the development and maintenance of atrial arrhythmias. HF results in haemodynamic and neurohormonal alterations, as well as cellular and extracellular remodelling that promote AF.[3] HF was also independently associated with increased morbidity requiring hospitalizations. In the SOLVD registry, ~35–40% of the patients had been hospitalized at least once every year.[31] However, in our HF cohort, there was no significant effect of either dose of dabigatran vs. warfarin, on mortality or rehospitalization.

Limitations

The present study is a subgroup analysis of a large prospective randomized trial. The analysis examing the results in subgoups of patients with and without HF was pre-specified, with the results being consistent with the overall trial findings. Furthermore, combined analysis of HF and LV systolic dysfunction was not done, since >50% of patients had missing data regarding LVEF. Some demographic and clinical features in patients with HF, such as lower age and hypertension, were unusual but, given the consistency of the results in those with and without HF, and different levels of HF, the results have clinical applicability.

Conclusions

The overall results of dabigatran relative to warfarin, observed in the RE-LY trial, were essentially similar in patients with previous HF. Therefore, dabigatran is of value in patients with AF and HF.

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