Efficacy and Safety of Rivaroxaban in Patients With Heart Failure and Nonvalvular Atrial Fibrillation

Insights From ROCKET AF

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Background—In Rivaroxaban Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), rivaroxaban was noninferior to warfarin for the prevention of stroke and systemic embolic events and significantly reduced intracranial bleeding in patients with nonvalvular atrial fibrillation. We explore the safety and efficacy of rivaroxaban in patients with heart failure (HF).

Methods and Results—A total of 9033 (63.7%) patients had HF. The primary efficacy analysis was rates of stroke or systemic embolism (per 100 patient-years) by intention to treat. The safety outcomes were major or nonmajor clinically relevant bleeding and hemorrhagic stroke during treatment. Patients with HF were younger (72 versus 74 years), more likely to have persistent atrial fibrillation (83.0% versus 77.6%), and had higher mean CHADS2 scores (3.7 versus 3.1). The efficacy of rivaroxaban compared with warfarin was similar in patients with HF (1.90 versus 2.09) and without HF (2.10 versus 2.54; P-interaction=0.62). The risk of major or nonmajor clinically relevant bleeding with rivaroxaban was similar to warfarin in patients with HF (14.22 versus 14.02) and without HF (16.12 versus 15.35; P-interaction=0.99). A reduction in hemorrhagic stroke was observed with rivaroxaban in patients with HF as in the overall trial (adjusted hazard ratio, 0.38; 95% confidence interval, 0.19–0.76; P-interaction=0.067). Among patients with HF, the efficacy of rivaroxaban was similar, irrespective of ejection fraction <40 or ≥40% (P-interaction=0.38), New York Heart Association class I-II versus III-IV (P-interaction=0.68), HF preserved or reduced ejection fraction (P-interaction=0.35), or CHADS2 score 2 versus ≥3 (P-interaction=0.48).

Conclusions—Treatment-related outcomes were similar in patients with and without HF and across HF subgroups. These findings support the use of rivaroxaban as an alternative to warfarin in patients with atrial fibrillation and HF.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00403767.

(Circ Heart Fail. 2013;6:740-747.)

Key Words: anticoagulants ■ arrhythmias, cardiac ■ heart failure

The prevalence of both heart failure (HF) and atrial fibrillation (AF) is increasing in the general population. AF occurs in 12% to 41% of patients with HF, and its prevalence correlates with HF severity. Multiple studies and thromboembolic risk prediction scores, such as CHADS2, have reported that a clinical history of HF is an independent risk factor for thromboembolic events in patients with nonvalvular AF. Vitamin K antagonists (VKAs) are recommended by both AF and HF guidelines to reduce thromboembolic risk in patients with both conditions.

Among patients with AF who are anticoagulated with VKAs, time in the therapeutic range (TTR) is an important determinant of stroke prevention and bleeding risk. HF is a recognized risk for reduced TTR, and patients receiving VKAs may be predisposed to reduced efficacy and increased bleeding. Rivaroxaban, an oral factor Xa inhibitor, has a predictable pharmacokinetic profile and dual clearance pathways, renal and hepatic. Therefore, rivaroxaban represents a theoretically attractive alternative to VKAs in patients with HF and AF. In the Rivaroxaban Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke

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and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial, rivaroxaban was noninferior to warfarin for the prevention of embolic events in patients with moderate- to high-risk AF, with nonvalvular AF; and it significantly reduced the risk of intracranial hemorrhage.24 A total of 62.5% of randomized patients in this trial had a history of HF or a low ejection fraction (EF); whereas 32.0% of RE-LY and 35.4% in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial participants had HF.25,26 This provided a unique opportunity to explore the efficacy and safety of rivaroxaban in a large cohort of patients with AF with HF and examine whether treatment effects were consistent across important HF subgroups such as functional class, EF, and CHADS2 score.

Methods

The methods and results of the ROCKET AF trial have been described.27 briefly, it was an international, multicenter, double-blind, double-dummy randomized noninferiority trial that compared rivaroxaban 20 mg daily (or 15 mg daily in patients with creatinine clearance 30–49 mL/min) with adjusted-dose warfarin (target international normalized ratio, 2.5; range, 2.0–3.0) in patients with nonvalvular AF. Patients with electrocardiographic documentation of AF with a moderate to high risk of stroke were eligible for enrollment. Moderate to high stroke risk was defined as a history of stroke, transient ischemic attack, or systemic embolism, or $\geq 2$ CHADS2 risk factors: clinical HF or a left ventricular EF $<40\%$, hypertension, age $\geq 75$ years, or diabetes mellitus.6 The number of patients with only 2 CHADS2 risk factors was capped at 10% for each region. Key exclusion criteria included patients with prosthetic heart valves, hemodynamically significant mitral stenosis, creatinine clearance $<30$ mL/min, a recent embolic event, and those at increased risk of bleeding.28 The Institutional Review Boards at each participating site approved the protocol, and all patients provided written consent.

Definition of HF and Subgroups

Patients with HF, and important covariates, were identified from individual case report forms, which were completed by site investigators. HF was defined a priori as a history of HF or a left ventricular EF $<40\%$ (measured by any imaging modality). Although the original ROCKET AF study classified patients with an EF $<35\%$ as having HF, in this analysis the EF was changed to $<40\%$, so that the results would be in line with the EF definition of systolic HF used in many randomized trials. The primary analysis compared patients assigned to the rivaroxaban and warfarin therapy. Prespecified secondary subgroup analyses examined the comparative efficacy in patients classified by EF ($\geq 40\%$), New York Heart Association (NYHA) class, HF with preserved and reduced EF, CHADS2 score, CHADS2-VASc score, and device (implantable cardioverter defibrillator [ICD] or biventricular-ICD).

Outcomes

The primary efficacy outcome was stroke (ischemic or hemorrhagic) or noncentral nervous system embolism. The secondary efficacy outcomes included all-cause death, myocardial infarction, and the composite (and individual components) of stroke, systemic embolism, or vascular death. The intention-to-treat study population was used for all efficacy outcomes. However, all 93 patients were excluded from 1 study site with violations in Good Clinical Practice guidelines.25 Efficacy end points were measured until the time of site notification of study termination. The primary safety end point was major or non-major clinically relevant (NMCR) bleeding. The secondary safety end points were intracranial hemorrhage and hemorrhagic stroke. Safety end points were analyzed using the safety population (patients who were randomized and received $\geq 1$ dose of the study drug). A per-protocol sensitivity analysis used the subset of patients from the safety population who had no protocol violations. For safety and per-protocol analyses, end points were measured during treatment with study drug (first dose until 2 days after the last dose). All events were adjudicated by an independent clinical events committee blinded to treatment assignment and using predefined end point definitions.29

Statistical Analysis

Categorical data are summarized as counts (percentages), and differences were tested with the Pearson $\chi^2$ test; continuous variables are summarized as medians (25th percentile–75th percentile), and differences were tested with the Wilcoxon rank-sum test. Outcomes are presented as events per 100 patient-years. Cox proportional hazards models were used to assess the association with risk of outcomes for (1) patients with versus patients without HF; (2) rivaroxaban versus warfarin within subgroups defined by HF; and (3) rivaroxaban versus warfarin within subgroups of patients with HF defined by EF, NYHA class, and CHADS2 score. Models for (2) and (3) included terms for the interaction between randomized treatment and the subgroup of interest. All models included covariates identified as predictive of outcomes by modeling in the full ROCKET AF cohort. For efficacy end points, these included age, sex, body mass index, region (Latin America), previous stroke or transient ischemic attack, previous myocardial infarction, peripheral arterial disease, carotid occlusive vascular disease, hypertension, chronic obstructive pulmonary disease, diabetes mellitus, paroxysmal AF, left ventricular EF, heart rate, diastolic blood pressure, creatinine clearance at baseline (calculated using the Cockroft–Gault formula), and abstinence from alcohol use. In the safety analysis, the following variables were entered into the model: age, sex, region (Eastern Europe), previous stroke or transient ischemic attack, gastrointestinal bleed, chronic obstructive pulmonary disease, diastolic blood pressure, creatinine clearance at baseline (calculated using the Cockroft–Gault formula), anemia, platelets, albumin, previous aspirin use, and previous use of a VKA or thienopyridine. An additional per-protocol sensitivity analysis examined the primary efficacy end point, major or NMCR bleeding, and hemorrhagic stroke in the per-protocol population; these models were performed in the same manner as above. Risk relationships are presented as adjusted hazard ratios (HR) with 95% confidence intervals (CI) derived from the adjusted Cox models. The TTR in patients treated with warfarin was calculated using the Rosendaal method.29 A level of significance of $P<0.05$ was prespecified. All analyses were performed with SAS version 9.2 (SAS Institute, Inc, Cary, NC).

Results

In the ROCKET AF trial, 9033 (63.7%) participants were classified as having HF at the time of randomization, based on a history of clinical HF or a left ventricular EF $<40\%$. Table 1 presents baseline characteristics according to treatment randomization and history of HF. Among participants with HF, 4530 (50.1%) were randomized to rivaroxaban and 4503 (49.9%) to warfarin. Rivaroxaban and warfarin-treated participants with HF had similar persistent AF rates (83.6% versus 82.3%), EF $<40\%$ (33.3% versus 34.5%), previous VKA use (58.7% versus 58.2%), concurrent aspirin use (30.3% versus 31.7%), and mean CHADS2 scores (both 3.7). Differences in baseline clinical variables among patients with and without HF are presented in Appendix I in the online-only Data Supplement. Among participants randomized to warfarin therapy, the mean TTR was 53% in participants with HF and 59% in those without HF (Appendix II in the online-only Data Supplement).

Outcomes in Patients With and Without Heart Failure

Overall rates of stroke or systemic embolization per 100 patient-years were similar in patients with and without HF (1.99 versus 2.32; adjusted HR, 0.94; 95% CI, 0.78–1.13; $P=0.51$; Table 2). HF patients had a higher risk of the composite of stroke, systemic embolization, or vascular death (5.00 versus 3.50; adjusted HR, 1.28; 95% CI, 1.11–1.47; $P=0.0006$), all-cause death (5.26 versus 3.37; adjusted HR, 1.34; 95% CI, 1.17–1.55; $P<0.0001$), and vascular death (3.53 versus 1.75; adjusted HR, 1.65; 95% CI, 1.37–1.98;
P<0.0001). Safety end points were similar between patients with and without HF. Results were similar in the per-protocol treatment population (Appendix III in the online-only Data Supplement).

### Outcomes by Heart Failure and Treatment Assignment

Table 3 and Figure 1 show the efficacy and safety outcomes in patients with and without HF by treatment assignment. The

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### Table 1. Baseline Characteristics for All Patients in the Intention-to-Treat Population Classified by History of HF and Treatment Randomization

<table>
<thead>
<tr>
<th>Variables</th>
<th>Heart Failure</th>
<th>Warfarin</th>
<th>No Heart Failure</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (25th–75th), y</td>
<td>72 (65–78)</td>
<td>72 (64–78)</td>
<td>74 (66–79)</td>
<td>74 (67–78)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1773 (39.1)</td>
<td>1760 (39.1)</td>
<td>1029 (40.3)</td>
<td>1043 (40.3)</td>
</tr>
<tr>
<td>Body mass index, median (25th–75th), kg/m²</td>
<td>28.7 (25.4–32.8)</td>
<td>28.6 (25.5–32.4)</td>
<td>27.6 (24.7–31.0)</td>
<td>27.2 (24.5–30.7)</td>
</tr>
</tbody>
</table>

### Atrial fibrillation variables

- **Persistent**
  - Rivaroxaban: 3789 (83.6)
  - Warfarin: 3708 (82.3)
  - Rivaroxaban: 1965 (77.0)
  - Warfarin: 2023 (78.2)

- **Paroxysmal**
  - Rivaroxaban: 698 (15.4)
  - Warfarin: 733 (16.3)
  - Rivaroxaban: 533 (20.9)
  - Warfarin: 526 (20.3)

- **New onset**
  - Rivaroxaban: 43 (0.9)
  - Warfarin: 62 (1.4)
  - Rivaroxaban: 53 (2.1)
  - Warfarin: 38 (1.5)

- **Previous stroke or TIA, n (%)**
  - Rivaroxaban: 1954 (42.9)
  - Warfarin: 1914 (42.2)
  - Rivaroxaban: 1800 (70.0)
  - Warfarin: 1800 (69.2)

- **Previous non-CNS embolism, n (%)**
  - Rivaroxaban: 169 (3.7)
  - Warfarin: 178 (4.0)
  - Rivaroxaban: 110 (4.3)
  - Warfarin: 99 (3.8)

- **Carotid occlusive disease, n (%)**
  - Rivaroxaban: 180 (4.0)
  - Warfarin: 176 (3.9)
  - Rivaroxaban: 123 (4.8)
  - Warfarin: 123 (4.8)

- **CHADS2 score, mean (SD)**
  - Rivaroxaban: 3.7 (0.9)
  - Warfarin: 3.7 (0.9)
  - Rivaroxaban: 3.2 (0.9)
  - Warfarin: 3.1 (0.8)

- **CHA2DS2-VASc score, mean (SD)**
  - Rivaroxaban: 5.1 (1.3)
  - Warfarin: 5.1 (1.4)
  - Rivaroxaban: 4.5 (1.2)
  - Warfarin: 4.5 (1.2)

### Heart failure variables

- **Ejection fraction <40%, n (%)**
  - Rivaroxaban: 1043 (33.3)
  - Warfarin: 1102 (34.5)
  - No Heart Failure: 0 (0.0)
  - Warfarin: 0 (0.0)

- **NYHA class, n (%)**
  - I: 606 (13.7)
  - II: 2502 (56.4)
  - III: 1255 (28.3)
  - IV: 74 (1.7)

- **ICD or BiV-ICD, n (%)**
  - Rivaroxaban: 148 (3.6)
  - Warfarin: 150 (3.7)
  - No Heart Failure: 10 (0.4)
  - Warfarin: 6 (0.3)

### Other baseline comorbidities, n (%)

- **Hypertension**
  - Rivaroxaban: 4202 (92.8)
  - Warfarin: 4200 (93.3)
  - No Heart Failure: 2187 (85.7)
  - Warfarin: 2235 (86.4)

- **Diabetes mellitus**
  - Rivaroxaban: 1916 (42.3)
  - Warfarin: 1912 (42.5)
  - No Heart Failure: 935 (36.7)
  - Warfarin: 884 (34.2)

- **Myocardial infarction**
  - Rivaroxaban: 942 (20.8)
  - Warfarin: 1011 (22.5)
  - No Heart Failure: 231 (9.1)
  - Warfarin: 262 (10.1)

- **Coronary artery bypass**
  - Rivaroxaban: 350 (7.7)
  - Warfarin: 382 (8.5)
  - No Heart Failure: 153 (6.0)
  - Warfarin: 144 (5.6)

- **Peripheral vascular disease**
  - Rivaroxaban: 292 (6.4)
  - Warfarin: 313 (7.0)
  - No Heart Failure: 106 (4.2)
  - Warfarin: 121 (4.7)

- **Chronic obstructive pulmonary disease**
  - Rivaroxaban: 557 (12.3)
  - Warfarin: 565 (12.5)
  - No Heart Failure: 190 (7.4)
  - Warfarin: 169 (6.5)

### Presenting characteristics, median (25th–75th)

- **Heart rate, beats/min**
  - Rivaroxaban: 77 (65–88)
  - Warfarin: 77 (65–87)
  - No Heart Failure: 74 (65–84)
  - Warfarin: 75 (65–84)

- **Systolic blood pressure, mmHg**
  - Rivaroxaban: 130 (120–140)
  - Warfarin: 130 (120–140)
  - No Heart Failure: 130 (120–140)
  - Warfarin: 130 (120–140)

- **Creatinine clearance,* mL/min**
  - Rivaroxaban: 68 (52–89)
  - Warfarin: 68 (52–88)
  - No Heart Failure: 67 (53–86)
  - Warfarin: 67 (53–84)

### Previous and concurrent medications, n (%)

- **Previous VKA use**
  - Rivaroxaban: 2658 (58.7)
  - Warfarin: 2621 (58.2)
  - No Heart Failure: 1755 (68.8)
  - Warfarin: 1819 (70.3)

- **Previous ASA use**
  - Rivaroxaban: 1864 (41.1)
  - Warfarin: 1901 (42.2)
  - No Heart Failure: 850 (33.3)
  - Warfarin: 846 (32.7)

- **Concurrent ASA use**
  - Rivaroxaban: 1373 (30.3)
  - Warfarin: 1428 (31.7)
  - No Heart Failure: 657 (25.8)
  - Warfarin: 640 (24.7)

- **β-Blocker**
  - Rivaroxaban: 3113 (68.7)
  - Warfarin: 3174 (70.5)
  - No Heart Failure: 1448 (56.8)
  - Warfarin: 1449 (56.0)

- **Digitalis**
  - Rivaroxaban: 2023 (44.7)
  - Warfarin: 2037 (45.2)
  - No Heart Failure: 699 (27.4)
  - Warfarin: 701 (27.1)

- **Angiotensin-converting enzyme inhibitors**
  - Rivaroxaban: 2792 (61.6)
  - Warfarin: 2707 (60.1)
  - No Heart Failure: 1059 (41.5)
  - Warfarin: 1100 (42.5)

- **Diuretics**
  - Rivaroxaban: 3235 (71.4)
  - Warfarin: 3169 (70.4)
  - No Heart Failure: 1006 (39.4)
  - Warfarin: 1031 (39.9)

ASA indicates acetylsalicylic acid; BiV-ICD, biventricular-implantable cardioverter defibrillator; CNS, central nervous system; HF, heart failure; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

*Creatinine clearance was calculated using the Cockcroft–Gault formula.
primary efficacy outcomes in rivaroxaban- and warfarin-treated patients were similar in patients with HF (1.90 versus 2.09; adjusted HR, 0.91; 95% CI, 0.74–1.13) and without HF (2.10 versus 2.54; adjusted HR, 0.84; 95% CI, 0.65–1.09; P=0.62 for interaction; Figure 2). No differences in treatment effect were detected between patients with and without HF for any of the secondary efficacy outcomes (P>0.5 for interaction for all). Additionally, no differences in treatment effect were observed in the primary safety outcome of major or NMCR bleeding. A lower risk of hemorrhagic stroke was observed with rivaroxaban therapy in HF patients (0.16 versus 0.43; adjusted HR, 0.38; 95% CI, 0.19–0.76), but not in patients without HF (0.43 versus 0.47; adjusted HR, 0.91; 95% CI, 0.48–1.73), although the interaction between HF and treatment was not significant (P=0.067). In the per-protocol sensitivity analysis, similar results were observed compared with the intention-to-treat analyses for primary efficacy outcome, major or NMCR bleeding, or hemorrhagic stroke (Appendix IV in the online-only Data Supplement).

**HF Subgroups**

The primary efficacy and safety outcomes in the HF subgroups are presented in Table 4. Point estimates for efficacy favored rivaroxaban therapy in most subgroups, and no difference was detected in the efficacy of rivaroxaban in patients classified by left ventricular EF ≤40% or >40% (P=0.38 for interaction), NYHA class I-II versus III-IV (P=0.68 for interaction), HF with preserved or reduced EF (P=0.35 for interaction), device therapy (P=0.11 for interaction), CHADS2 score 2 versus ≥3 (P=0.48 for interaction).

**Table 2. Efficacy and Safety End Points in Patients With and Without Heart Failure**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Heart Failure*</th>
<th>No Heart Failure*</th>
<th>Heart Failure vs No Heart Failure, HR (95% CI)t</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or systemic embolization</td>
<td>1.99 (343)</td>
<td>2.32 (232)</td>
<td>0.94 (0.78–1.13)</td>
<td>0.51</td>
</tr>
<tr>
<td>Stroke, systemic embolization, or vascular death</td>
<td>5.00 (835)</td>
<td>3.50 (346)</td>
<td>1.28 (1.11–1.47)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.84 (317)</td>
<td>2.16 (217)</td>
<td>0.95 (0.78–1.15)</td>
<td>0.57</td>
</tr>
<tr>
<td>Systemic embolization</td>
<td>0.17 (30)</td>
<td>0.17 (17)</td>
<td>0.93 (0.48–1.82)</td>
<td>0.84</td>
</tr>
<tr>
<td>All-cause death</td>
<td>5.26 (879)</td>
<td>3.37 (335)</td>
<td>1.34 (1.17–1.55)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vascular death</td>
<td>3.53 (600)</td>
<td>1.75 (176)</td>
<td>1.65 (1.37–1.98)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.15 (200)</td>
<td>0.71 (72)</td>
<td>1.20 (0.89–1.63)</td>
<td>0.23</td>
</tr>
<tr>
<td>Safety outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major or NMCR bleeding</td>
<td>14.12 (1766)</td>
<td>15.73 (1158)</td>
<td>1.00 (0.92–1.08)</td>
<td>0.99</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.29 (41)</td>
<td>0.45 (38)</td>
<td>0.73 (0.45–1.20)</td>
<td>0.22</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.53 (74)</td>
<td>0.77 (65)</td>
<td>0.84 (0.58–1.22)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; and NMCR, nonmajor clinically relevant bleeding.

*Reported as events per 100 patient-years (total events).

†Adjusted efficacy outcomes.

‡P value for interaction of heart failure and treatment.

**Table 3. Efficacy and Safety End Points by Treatment and Heart Failure**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Heart Failure</th>
<th>No Heart Failure</th>
<th>P Value for Interaction‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy outcomes</td>
<td>Rivaroxaban*</td>
<td>Warfarin*</td>
<td>Rivaroxaban vs Warfarin, HR (95% CI)t</td>
</tr>
<tr>
<td>Stroke or systemic embolization</td>
<td>(n=4530)</td>
<td>(n=4503)</td>
<td>1.90 (164)</td>
</tr>
<tr>
<td>Stroke, systemic embolization, or vascular death</td>
<td>4.88 (409)</td>
<td>5.11 (426)</td>
<td>0.97 (0.85–1.11)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.78 (154)</td>
<td>1.89 (163)</td>
<td>0.94 (0.76–1.17)</td>
</tr>
<tr>
<td>Systemic embolization</td>
<td>0.15 (13)</td>
<td>0.19 (17)</td>
<td>0.78 (0.38–1.61)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>5.05 (423)</td>
<td>5.46 (456)</td>
<td>0.93 (0.82–1.07)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>3.44 (292)</td>
<td>3.63 (308)</td>
<td>0.96 (0.82–1.13)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.09 (95)</td>
<td>1.21 (105)</td>
<td>0.94 (0.71–1.24)</td>
</tr>
<tr>
<td>Safety outcomes</td>
<td>Rivaroxaban*</td>
<td>Warfarin*</td>
<td>Rivaroxaban vs Warfarin, HR (95% CI)t</td>
</tr>
<tr>
<td>Major or NMCR bleeding</td>
<td>(n=4550)</td>
<td>(n=4527)</td>
<td>14.22 (888)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.16 (11)</td>
<td>0.43 (30)</td>
<td>0.38 (0.19–0.76)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.40 (28)</td>
<td>0.65 (46)</td>
<td>0.63 (0.40–1.02)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; and NMCR, nonmajor clinically relevant bleeding.

*Reported as events per 100 patient-years (total events).

†Adjusted efficacy outcomes.

‡P value for interaction of heart failure and treatment.
interaction), or CHA2DS2-VASc Score ($P=0.19$ for interaction).

No differences in treatment effect for major or NMCR bleeding were detected between NYHA class ($P=0.19$ for interaction), HF with preserved or reduced EF ($P=0.23$ for interaction), CHADS2 score ($P=0.15$ for interaction), or CHA2DS2-VASc Score ($P=0.19$ for interaction) subgroups, and a borderline $P$ value for interaction was observed in the left ventricular EF subgroups ($\text{EF} \geq 40\%$: HR, 1.00; 95% CI, 0.88–1.13; $\text{EF} < 40\%$: HR, 1.15; 95% CI, 0.96–1.36; $P=0.051$ for interaction). Rivaroxaban was associated with a higher risk of major or NMCR bleeding among 297 study participants with an ICD or biventricular-ICD (HR, 2.00; 95% CI, 1.31–3.05; $P=0.0015$ for interaction). The median times in therapeutic range for warfarin-treated participants across all HF subgroups are presented in Appendix II in the online-only Data Supplement.

**Discussion**

In this study, which represents a large cohort of AF patients with HF, 3 important findings emerge. First, adjusted rates of stroke or systemic embolism and bleeding were similar between patients

![Figure 1](http://example.com/image1.png)  
**Figure 1.** Efficacy and safety end points by treatment and heart failure (HF), showing relative efficacy and safety of rivaroxaban vs warfarin across all end points among patients with heart failure. CI indicates confidence interval.

![Figure 2](http://example.com/image2.png)  
**Figure 2.** Cumulative rate of stroke or systemic embolism in patients with heart failure (HF) and treatment, showing no difference in the primary efficacy outcome among rivaroxaban and warfarin-treated patients with and without heart failure ($P=0.62$ for interaction).
with and without HF. Second, the treatment effect of rivaroxaban was similar in patients with and without HF, suggesting the efficacy and safety of rivaroxaban extend to the patient population with HF with AF. Third, comparable treatment effects of rivaroxaban were observed across important HF subgroups, such as systolic function, functional class, and CHADS2 score.

In patients with AF, guidelines define HF (moderate to severe left ventricular systolic dysfunction or recent decompensated HF requiring hospitalization irrespective of EF) as an independent risk factor for thromboembolism.3,8,11,14,30,31 After adjusting for baseline differences, but not treatment randomization, we observed that patients with HF had a similar risk of stroke or systemic embolism, myocardial infarction, and bleeding but a higher observed risk of all-cause death and vascular death than patients without HF. Although HF was not independently associated with an increased risk of stroke or systemic embolism, we hypothesize that the lack of an observed difference may be attributable to the high thromboembolic risk of the ROCKET AF study participants; wherein the mean CHADS2 in this trial was 3.5 (compared with the RE-LY and ARISTOTLE trials, which had a mean CHADS2 scores of 2.1), and a large proportion of the study population could be categorized as having HF at the time of randomization.

With the rising prevalence of both HF and AF, it is likely that an increasing number of patients will require thromboembolic prophylaxis.1,2 VKAs are recommended in patients with AF and HF; however, the narrow therapeutic range, need for monitoring, and multiple food and drug interactions make their use challenging for physicians and patients.10,14 Warfarin therapy has been reported to decrease thromboembolic events in patients with HF and increase the risk of bleeding.32 A recent meta-analysis reported that warfarin-treated patients have mean TTRs of only 55%.33 In anticoagulated AF patients, TTR is an important determinant of both the clinical benefit and bleeding risk of warfarin.15–17 Our results are consistent with studies by Rose et al,18 which reported that HF is an independent risk factor for lower TTR and, with the Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) and the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial analyses have shown, that HF is an independent predictor of bleeding in patients anticoagulated for AF.19,20 In this analysis, the primary efficacy and safety treatment effects were similar between patients with and without HF. Although it is not clear whether optimal warfarin management would change these results, the effect of rivaroxaban did not differ across quartiles of TTR in the overall trial population.26 Additionally, a previous meta-analysis of all novel oral anticoagulants versus warfarin trials reported no significant difference in the primary trial end points in patients with HF; although details in all efficacy and safety end points were lacking.14 These findings suggest that the reported efficacy of rivaroxaban therapy extends to patients with HF and

### Table 4. Treatment Comparisons for Efficacy and Safety End Points Among Heart Failure Subgroups

<table>
<thead>
<tr>
<th>Heart Failure Subgroup</th>
<th>Stroke or Non-CNS Embolism</th>
<th>Major or Nonmajor Clinically Relevant Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ITT, n</td>
<td>Rivaroxaban*</td>
</tr>
<tr>
<td><strong>Ejection fraction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥40%</td>
<td>4893</td>
<td>2.00 (93)</td>
</tr>
<tr>
<td>&lt;40%</td>
<td>2497</td>
<td>1.34 (33)</td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>6205</td>
<td>1.90 (111)</td>
</tr>
<tr>
<td>II or IV</td>
<td>2645</td>
<td>1.88 (49)</td>
</tr>
<tr>
<td><strong>HF classification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFpEF§</td>
<td>4893</td>
<td>2.00 (93)</td>
</tr>
<tr>
<td>HF EFII</td>
<td>2315</td>
<td>1.27 (29)</td>
</tr>
<tr>
<td><strong>Device therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No device</td>
<td>7899</td>
<td>1.96 (147)</td>
</tr>
<tr>
<td>ICD or BiV-ICD</td>
<td>298</td>
<td>0.33 (1)</td>
</tr>
<tr>
<td><strong>CHA2DS2-VASc score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>610</td>
<td>1.30 (10)</td>
</tr>
<tr>
<td>≥3</td>
<td>8423</td>
<td>1.96 (154)</td>
</tr>
<tr>
<td>≥4</td>
<td>3150</td>
<td>1.27 (40)</td>
</tr>
<tr>
<td>≥5</td>
<td>5883</td>
<td>2.26 (124)</td>
</tr>
</tbody>
</table>

| Interaction‡          |        |              |          |                                  |                        |              |          |        |                                  |                        |

**BV-ICD** indicates biventricular-implantable cardioverter defibrillator; CI, confidence interval; HF, heart failure; HFpEF, heart failure preserved ejection fraction; HF EFII, heart failure reduced ejection fraction; HR, hazard ratio; ICD, implantable cardioverter defibrillator; ITT, intention to treat; and NYHA, New York Heart Association.

*Reported as events per 100 patient-years (total events).
†Adjusted efficacy outcomes.
‡P value for interaction of subgroup and treatment.
§Defined as a history of heart failure at randomization with an EF ≥40%.
||Defined as a history of heart failure at randomization with an EF <40%.
AF, and that rivaroxaban is a reasonable therapeutic alternative to warfarin in this growing clinical population.

Most studies that have evaluated thromboembolic risk factors in AF have defined HF based on clinical history or symptoms and have not accounted for differences in left ventricular function or clinical symptoms. The association between HF and thromboembolic risk has not been consistent across all studies, and it is unclear whether differences between HF subgroups could potentially account for these reported discrepancies in all studies.9,11,35–37 Analyses by 2 groups reported that the severity of left ventricular systolic dysfunction was associated with an increased risk of stroke, although an analysis of >2400 patients from AFFIRM found no significant association.32,38,39 Given that it remains unclear how EF and severity of HF symptoms modify thromboembolic risk, we explored treatment effects across important HF and thromboembolic risk subgroups. The lack of an observed interaction between the primary efficacy outcome and EF, HF with preserved versus reduced systolic function, functional class, or CHADS2 score suggests that the benefit of rivaroxaban over warfarin extends to patients with HF with AF irrespective of the definition of HF, severity of symptoms, or thromboembolic risk. A higher bleeding risk on rivaroxaban was observed among a small group of patients with ICDs or biventricular-ICDs at the time of randomization. The clinical significance of this finding is unclear.

Limitations
This analysis has several limitations that merit consideration. First, the TTR was lower than reported in some studies, but similar to that of large-scale registry and observational programs.30,40,41 The efficacy of rivaroxaban was favorable across international normalized ratio control groups in the overall trial population.25 Second, ROCKET AF predominantly enrolled patients at moderate to high embolic risk, consequently >93% of patients in this analysis had a CHADS2 score ≥2. Thus, it is unclear how well these results can be extended to patients with HF and an otherwise low embolic risk.

Conclusions
In a large international population of patients with HF and AF, the adjusted rates of stroke or systemic embolization and bleeding were similar between patients with and without HF, and no treatment-related differences were detected. Moreover, no difference in the efficacy of rivaroxaban was observed across important clinical or thromboembolic risk HF subgroups. In a clinical environment where the prevalence of both HF and AF are increasing, these data suggest that rivaroxaban is an efficacious and safe alternative to VKAs in the population with HF and AF.

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Disclosures
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14. Dries D, Exner D, Gersh B, Domanski M, Wachlawik M, Stevenson L. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and

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Efficacy and Safety of Rivaroxaban in Patients With Heart Failure and Nonvalvular Atrial Fibrillation: Insights From ROCKET AF

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Data Supplement (unedited) at:

http://circheartfailure.ahajournals.org/content/suppl/2013/05/29/CIRCHEARTFAILURE.113.000212.DC1

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### Appendix 1: Baseline characteristics for all patients in the intention to treat population classified by history of heart failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n=14171)</th>
<th>Patients with Heart Failure (n=9033)</th>
<th>Patients without Heart Failure (n=5138)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (25th, 75th), years</td>
<td>73 (65, 78)</td>
<td>72 (65, 78)</td>
<td>74 (66, 79)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>5605 (39.6%)</td>
<td>3533 (39.1%)</td>
<td>2072 (40.3%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Body Mass Index, median (25th, 75th), kg/m²</td>
<td>28.2 (25.1, 32.0)</td>
<td>28.7 (25.5, 32.5)</td>
<td>27.4 (24.6, 30.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Geographic region, n (%)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia/Pacific</td>
<td>2109 (14.8%)</td>
<td>966 (10.6%)</td>
<td>1143 (22.1%)</td>
<td></td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>5500 (38.6%)</td>
<td>4453 (49.0%)</td>
<td>1047 (20.2%)</td>
<td></td>
</tr>
<tr>
<td>Western Europe</td>
<td>2096 (14.7%)</td>
<td>1058 (11.6%)</td>
<td>1038 (20.1%)</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>2681 (18.8%)</td>
<td>1447 (15.9%)</td>
<td>1234 (23.9%)</td>
<td></td>
</tr>
<tr>
<td>Latin America</td>
<td>1878 (13.2%)</td>
<td>1167 (12.8%)</td>
<td>711 (13.7%)</td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation Variables</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial Fibrillation type, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Persistent</td>
<td>11485 (81.0%)</td>
<td>7497 (83.0%)</td>
<td>3988 (77.6%)</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>2490 (17.6%)</td>
<td>1431 (15.8%)</td>
<td>1059 (20.6%)</td>
<td></td>
</tr>
<tr>
<td>New Onset</td>
<td>196 (1.4%)</td>
<td>105 (1.2%)</td>
<td>91 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>Previous Stroke or TIA, n(%)</td>
<td>7468 (52.4%)</td>
<td>3868 (42.6%)</td>
<td>3600 (69.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous Non-CNS Embolism, n (%)</td>
<td>551 (3.9%)</td>
<td>347 (3.8%)</td>
<td>204 (4.0%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Carotid Occlusive Disease, n (%)</td>
<td>589 (4.2%)</td>
<td>356 (3.9%)</td>
<td>233 (4.5%)</td>
<td>0.089</td>
</tr>
<tr>
<td>CHADS2 Score, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>1</td>
<td>3 (&lt;0.1%)</td>
<td>0 (0.0%)</td>
<td>3 (0.1%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1859 (13.0%)</td>
<td>610 (6.7%)</td>
<td>1249 (24.1%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6216 (43.6%)</td>
<td>3966 (43.6%)</td>
<td>2250 (43.5%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4091 (28.7%)</td>
<td>2719 (29.9%)</td>
<td>1372 (26.5%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1813 (12.7%)</td>
<td>1514 (16.7%)</td>
<td>299 (5.8%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>282 (2.0%)</td>
<td>282 (3.1%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>CHADS2 Score, mean (SD)</td>
<td>3.5 (0.9)</td>
<td>3.7 (0.9)</td>
<td>3.1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc score, mean (SD)</td>
<td>4.9 (1.3)</td>
<td>4.5 (1.2)</td>
<td>5.1 (1.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart Failure Variables</td>
<td></td>
<td>Excluded</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection Fraction &lt;40%, n (%)</td>
<td>2145 (23.6%)</td>
<td>2145 (33.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA Class</td>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1192 (13.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>5013 (56.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>2511 (28.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>134 (1.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| ICD or BiV-ICD, n(%) | 314 (2.5%) | 298 (3.6%) | 16 (0.3%) | <0.0001 |

**Other Baseline Comorbidities, n (%)**

- Hypertension: 12824 (90.5%) | 8402 (93.0%) | 4422 (86.1%) | <0.0001
- Diabetes Mellitus: 5647 (39.8%) | 3828 (42.4%) | 1819 (35.4%) | <0.0001
- Myocardial Infarction: 2446 (17.3%) | 1953 (21.6%) | 493 (9.6%) | <0.0001
- Coronary Artery Bypass: 1029 (7.3%) | 732 (8.1%) | 297 (5.8%) | <0.0001
- Peripheral Vascular Disease: 832 (5.9%) | 605 (6.7%) | 227 (4.4%) | <0.0001
- Chronic Obstructive Pulmonary Disease: 1481 (10.5%) | 1122 (12.4%) | 359 (7.0%) | <0.0001

**Presenting Characteristics, median (25th, 75th)**

- Heart Rate, beats/min: 76 (67, 86) | 77 (68, 86) | 74 (65, 84) | <0.0001
- Systolic Blood Pressure, mmHg: 130 (120, 140) | 130 (120, 140) | 130 (120, 140) | 0.014
- Diastolic Blood Pressure, mmHg: 80 (70, 85) | 80 (70, 86) | 80 (70, 85) | 0.012
- Creatinine Clearance*, ml/min: 67 (52, 87) | 68 (52, 89) | 67 (53, 85) | <0.0001

**Previous and Concurrent medications, n (%)**

- Prior VKA Use: 8853 (62.5%) | 5279 (58.4%) | 3574 (69.6%) | <0.0001
- Prior ASA Use: 5461 (38.5%) | 3765 (41.7%) | 1696 (33.0%) | <0.0001
- Concurrent ASA Use: 4098 (28.9%) | 2801 (31.0%) | 1297 (25.2%) | <0.0001
- Beta-Blocker: 9184 (64.8%) | 6287 (69.6%) | 2897 (56.4%) | <0.0001
- Digitalis: 5460 (38.5%) | 4060 (44.9%) | 1400 (27.2%) | <0.0001
- Angiotensin Converting Enzyme Inhibitors: 7658 (54.0%) | 5499 (60.9%) | 2159 (42.0%) | <0.0001
- Diuretics: 8441 (59.6%) | 6404 (70.9%) | 2037 (39.6%) | <0.0001

*Creatinine Clearance was calculated using the Cockcroft–Gault formula

Abbreviations: BiV-ICD, Biventricular Implantable Cardioverter Defibrillator; NYHA, New York Heart Association; ICD, Implantable Cardioverter Defibrillator; VKA, vitamin K antagonist
### Appendix 2: Time in therapeutic range among warfarin treated patients.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Time in Therapeutic Range mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients without heart failure on warfarin</td>
<td>2554</td>
<td>59.1 (20.6)</td>
</tr>
<tr>
<td>All heart failure patients on warfarin</td>
<td>4429</td>
<td>52.9 (21.3)</td>
</tr>
<tr>
<td>HF subgroups:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 40%</td>
<td>2396</td>
<td>53.7 (20.8)</td>
</tr>
<tr>
<td>&lt; 40%</td>
<td>1244</td>
<td>52.7 (22.2)</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>3045</td>
<td>54.4 (21.1)</td>
</tr>
<tr>
<td>III or IV</td>
<td>1295</td>
<td>49.3 (21.2)</td>
</tr>
<tr>
<td>Device Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Device</td>
<td>3872</td>
<td>52.0 (21.5)</td>
</tr>
<tr>
<td>ICD or BiV-ICD</td>
<td>146</td>
<td>61.1 (16.9)</td>
</tr>
<tr>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt; Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>300</td>
<td>53.8 (19.9)</td>
</tr>
<tr>
<td>≥3</td>
<td>4129</td>
<td>52.9 (21.4)</td>
</tr>
</tbody>
</table>

Abbreviations: BiV-ICD, biventricular-implantable cardioverter defibrillator; ICD, implantable cardioverter defibrillator; SD, standard deviation
**Appendix 3**: Efficacy and safety endpoints in patients with and without heart failure (per-protocol study population)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Heart Failure *</th>
<th>No Heart Failure *</th>
<th>Heart Failure vs No Heart failure HR (95% CI)¹</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or Systemic Embolization</td>
<td>1.81 (251)</td>
<td>2.14 (178)</td>
<td>0.89 (0.72, 1.11)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Safety Outcomes</strong></td>
<td>(n=8966)</td>
<td>(n=5088)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major or NMCR bleeding</td>
<td>14.13 (1740)</td>
<td>15.80 (1142)</td>
<td>0.99 (0.92, 1.08)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.29 (40)</td>
<td>0.46 (38)</td>
<td>0.72 (0.44, 1.18)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Reported as events per 100 patient-years (total events); ¹ Adjusted efficacy outcomes
Appendix 4: Treatment comparisons for efficacy and safety endpoints in patients with and without heart failure (per-protocol study population)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Heart Failure</th>
<th>No Heart Failure</th>
<th>p-value for interaction¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban²</td>
<td>Warfarin²</td>
<td>Rivaroxaban vs. Warfarin HR (95% CI) ²</td>
</tr>
<tr>
<td>Efficacy Outcomes</td>
<td>(n=4487)</td>
<td>(n=4479)</td>
<td>(n=2521)</td>
</tr>
<tr>
<td>Stroke or Systemic Embolization</td>
<td>1.56 (107)</td>
<td>2.07 (144)</td>
<td>0.75 (0.58, 0.96)</td>
</tr>
<tr>
<td>Safety Outcomes</td>
<td>(n=4457)</td>
<td>(n=4451)</td>
<td>(n=2501)</td>
</tr>
<tr>
<td>Major or NMCR bleeding</td>
<td>14.28 (876)</td>
<td>13.99 (864)</td>
<td>1.06 (0.96, 1.16)</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.16 (11)</td>
<td>0.42 (29)</td>
<td>0.40 (0.20, 0.80)</td>
</tr>
</tbody>
</table>

*Reported as events per 100 patient-years (total events); † Adjusted efficacy outcomes
‡ p value for interaction of heart failure and treatment

Abbreviations: NMCR, Non-major clinically relevant bleeding