Left Ventricular Ejection Fraction and Risk of Stroke and Cardiac Events in Heart Failure

Data From the Warfarin Versus Aspirin in Reduced Ejection Fraction Trial

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Background and Purpose—In heart failure (HF), left ventricular ejection fraction (LVEF) is inversely associated with mortality and cardiovascular outcomes. Its relationship with stroke is controversial, as is the effect of antithrombotic treatment. We studied the relationship of LVEF with stroke and cardiovascular events in patients with HF and the effect of different antithrombotic treatments.

Methods—In the Warfarin Versus Aspirin in Reduced Ejection Fraction (WARCEF) trial, 2305 patients with systolic HF (LVEF<35%) and sinus rhythm were randomized to warfarin or aspirin and followed for 3.5±1.8 years. Although no differences between treatments were observed on primary outcome (death, stroke, or intracerebral hemorrhage), warfarin decreased the stroke risk. The present report compares the incidence of stroke and cardiovascular events across different LVEF and treatment subgroups.

Results—Baseline LVEF was inversely and linearly associated with primary outcome, mortality and its components (sudden and cardiovascular death), and HF hospitalization, but not myocardial infarction. A relationship with stroke was only observed for LVEF of <15% (incidence rates: 2.04 versus 0.95/100 patient-years; \( P=0.009 \)), which more than doubled the adjusted stroke risk (adjusted hazard ratio, 2.125; 95% CI, 1.182–3.818; \( P=0.012 \)). In warfarin-treated patients, each 5% LVEF decrement significantly increased the stroke risk (adjusted hazard ratio, 1.346; 95% CI, 1.044–1.737; \( P=0.022 \); \( P \) value for interaction=0.04).

Conclusions—In patients with systolic HF and sinus rhythm, LVEF is inversely associated with death and its components, whereas an association with stroke exists for very low LVEF values. An interaction with warfarin treatment on stroke risk may exist.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00041938.

Key Words: aspirin □ echocardiography □ heart failure □ heart ventricles □ stroke □ warfarin

In patients with heart failure (HF), a reduced left ventricular (LV) systolic function is associated with an increase in mortality and incidence of cardiovascular events. LV ejection fraction (LVEF) is the most widely accepted indicator of LV systolic function and is associated with cardiovascular outcomes. LVEF was shown to be inversely associated with cardiovascular mortality up to an LVEF of 45%, above which level the association is lost. In the Candesartan in Heart Failure Reduction in Mortality (CHARM) trial, all-cause mortality increased by 39% for every 10% reduction in
LVEF <45%. Similar results were reported by the Digitalis Investigation Group (DIG). Some aspects of the relationship between LVEF and cardiovascular events in HF remain controversial. An association between decreased LVEF and thromboembolic events (stroke or peripheral embolism) has been alternatively suggested or refuted. Although patients with HF are often treated with antithrombotic agents (antiplatelet or systemic anticoagulation) to prevent thromboembolic complications and especially ischemic stroke, it is unclear whether lower LVEF may have a different impact on outcome depending on the antithrombotic treatment chosen.

In the Warfarin Versus Aspirin in Reduced Ejection Fraction (WARCEF) trial, 2305 patients with HF were randomized to aspirin or adjusted-dose warfarin and followed-up for an average of 3.5 years. In the main results of the trial, patients on either treatment had similar rates of death and primary outcome (death, stroke, or intracerebral hemorrhage), although patients on warfarin had significantly reduced incidence of stroke. Here, we analyze the relationship of LVEF with mortality, stroke, and cardiovascular outcomes in WARCEF and possible interactions between LVEF and antithrombotic treatment.

Materials and Methods

Study Patients
Details of the WARCEF trial enrollment were previously published. Briefly, from October 2002 through January 2010, a total of 2305 patients were enrolled in the trial (1119 in the United States and Canada and 1186 in Europe and Argentina) at 168 centers in 11 countries. Eligible patients were ≥18 years of age and had normal sinus rhythm, no contraindication to warfarin therapy, and an LVEF of ≤35% as assessed by quantitative echocardiography (or a wall-motion index of ≤1.2) or by radionuclide or contrast angiography within 3 months before randomization.

For details on eligibility criteria and study medications, please see the online-only Data Supplement. Patients were randomized to either adjusted-dose warfarin with target international normalized ratio of 2.75 (acceptable range: 2.0–3.5) or aspirin 325 mg daily in a double-blind, double-dummy design.

LVEF Determination
LVEF assessment was performed by echocardiography at the individual sites. Mean time from echocardiogram performance to enrollment was 6.5 days. All echocardiograms were reinterpreted, blinded to treatment assignment, at a core echocardiography laboratory to confirm LVEF assessment. LVEF was determined by contrast angiography, radionuclide scanning, or magnetic resonance imaging in 239 patients (10.4%).

Follow-Up and Outcome Events
Follow-up was performed monthly by telephone or in person. An in-person assessment was conducted quarterly for clinical evaluation. Primary outcome of the trial was the time to first event in a composite end point of ischemic stroke, intracerebral hemorrhage, or death. Individual outcomes were also recorded. For definitions of outcome events, please see the online-only Data Supplement.

Statistical Analysis
Baseline demographics, clinical characteristics, and various outcome events by LVEF categories were compared using ANOVA F tests for continuous variables, χ² tests for categorical variables, and log-rank tests for time-to-event outcomes. Univariable and multivariable Cox models were used to assess the effect of demographic and clinical variables on outcomes of interest.

To identify high-risk thresholds, we dichotomized LVEF at different cutoff points and assessed the association between dichotomized LVEF and each outcome first with univariable Cox models and then with adjustment for covariates. Incidence rates of outcome events stratified by optimal LVEF cutoff points were compared using Poisson regression.

Cox models were used to evaluate separately the association between LVEF and outcomes in patients treated with warfarin or aspirin and assess any interaction between LVEF level and treatment type.

For warfarin treatment, time in therapeutic range (TTR) was compared in different stroke and LVEF subgroups using Wilcoxon signed-rank test.

Results
Mean LVEF in the study cohort was 24.7±7.5. Demographics and clinical characteristics of the cohort by LVEF category are shown in Table I.

The mean follow-up time was 3.5±1.8 years, and the total follow-up time was 8225 patient-years. Survival status was known for 97.0% of the patients. A total of 34 patients (1.5%) withdrew consent, and 35 patients (1.5%) were lost to follow-up.

Overall, 622 of the 2305 patients (27.0%) had a primary outcome (531 deaths [85.4%], 84 ischemic stroke [13.5%), and 7 intracerebral hemorrhage [1.1%]), 356 patients (15.4%) had cardiovascular death, 195 patients (8.5%) had sudden death, 72 patients (3.1%) had a myocardial infarction (MI), and 451 patients (19.6%) experienced HF hospitalization.

LVEF and Outcomes
Table I also summarizes the frequency of outcome events by LVEF category. Incidence of primary outcome, death (all-cause, cardiovascular death, and sudden death), and HF hospitalization increased progressively with decreasing LVEF; no such relationship was observed for stroke and MI.

Age, male sex, heart rate, diabetes mellitus, New York Heart Association class, ischemic cardiomyopathy, previous stroke/transient ischemic attack, and serum creatinine level were significantly associated with the primary outcome. LVEF, body mass index, systolic blood pressure, and the presence of an internal defibrillator were inversely associated with this outcome (Table I in the online-only Data Supplement).

Although most of these variables were also associated with all-cause death (Table II in the online-only Data Supplement) and also with cardiovascular or sudden death and HF hospitalization, only LVEF of <15% and previous stroke/transient ischemic attack were associated with stroke (Table III in the online-only Data Supplement).

For the primary outcome and all-cause death, the LVEF cutoff point associated with the greatest increase in risk was 25%; for cardiovascular death, sudden death, and HF hospitalization it was 20% (Table IV in the online-only Data Supplement). For all 5 outcomes, all LVEF cutoff points were associated with increased risk, confirming the linearity of the association. LVEF of <15% was associated with a doubling of the risk of stroke; no other cutoff point was identified. No cutoff point of increased risk was identified for MI.

Table 2 shows the hazard ratios for each outcome after adjustment for pertinent covariates, using the cutoff points of greatest increase in risk.
Table 1. Demographics and Clinical Characteristics of the Study Cohort by LVEF Categories*

<table>
<thead>
<tr>
<th>Covariate</th>
<th>LVEF&lt;20% (n=603)</th>
<th>LVEF 21%–25% (n=559)</th>
<th>LVEF 26%–29% (n=533)</th>
<th>LVEF ≥30% (n=610)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Argentina</td>
<td>18/603 (3.0)</td>
<td>29/559 (5.2)</td>
<td>15/533 (2.8)</td>
<td>30/610 (4.9)</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>284/603 (47.1)</td>
<td>221/559 (39.5)</td>
<td>249/533 (46.7)</td>
<td>340/610 (55.7)</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>301/603 (49.9)</td>
<td>309/559 (55.3)</td>
<td>260/533 (50.5)</td>
<td>240/610 (39.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td>59.6±11.6</td>
<td>60.6±11.2</td>
<td>60.9±11.4</td>
<td>62.0±11.1</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>486/603 (80.6)</td>
<td>438/556 (78.8)</td>
<td>419/531 (78.9)</td>
<td>497/610 (81.5)</td>
<td>0.598</td>
</tr>
<tr>
<td><strong>Race or ethnic group</strong></td>
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<td></td>
<td></td>
<td></td>
<td>0.018</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>440/603 (73.0)</td>
<td>407/555 (73.3)</td>
<td>395/531 (74.4)</td>
<td>491/610 (80.5)</td>
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<tr>
<td>Non-Hispanic black</td>
<td>106/603 (17.6)</td>
<td>88/555 (15.9)</td>
<td>76/531 (14.3)</td>
<td>62/610 (10.2)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>37/603 (6.1)</td>
<td>47/555 (8.5)</td>
<td>41/531 (7.7)</td>
<td>41/610 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>20/603 (3.3)</td>
<td>13/555 (2.3)</td>
<td>19/531 (3.6)</td>
<td>16/610 (2.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td>171.6±9.2</td>
<td>171.8±9.4</td>
<td>171.4±9.1</td>
<td>171.8±9.4</td>
<td>0.841</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>85.6±20.0</td>
<td>86.0±19.5</td>
<td>86.8±19.7</td>
<td>86.2±18.7</td>
<td>0.768</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>29.0±6.3</td>
<td>29.0±5.8</td>
<td>29.4±5.9</td>
<td>29.1±5.8</td>
<td>0.666</td>
</tr>
<tr>
<td><strong>Heart rate, bpm</strong></td>
<td>74.5±12.9</td>
<td>71.3±11.9</td>
<td>71.4±11.1</td>
<td>70.5±11.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Educational level</strong></td>
<td></td>
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<td></td>
<td></td>
<td>0.574</td>
</tr>
<tr>
<td>&lt;High school</td>
<td>248/603 (41.1)</td>
<td>235/553 (42.5)</td>
<td>238/530 (44.9)</td>
<td>271/609 (44.5)</td>
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</tr>
<tr>
<td>High-school graduate or some college</td>
<td>267/603 (44.3)</td>
<td>231/531 (41.8)</td>
<td>213/530 (40.2)</td>
<td>236/609 (38.8)</td>
<td></td>
</tr>
<tr>
<td>College graduate or postgraduate</td>
<td>88/603 (14.6)</td>
<td>87/553 (15.7)</td>
<td>79/530 (14.9)</td>
<td>102/609 (16.7)</td>
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<tr>
<td><strong>Systolic blood pressure, mm Hg</strong></td>
<td>120.5±18.2</td>
<td>122.3±18.3</td>
<td>125.5±18.5</td>
<td>127.6±19.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mm Hg</strong></td>
<td>74.2±11.3</td>
<td>73.5±11.5</td>
<td>74.2±11.6</td>
<td>74.9±11.4</td>
<td>0.203</td>
</tr>
<tr>
<td><strong>NYHA classification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.135</td>
</tr>
<tr>
<td>I</td>
<td>69/599 (11.5)</td>
<td>75/553 (13.6)</td>
<td>78/529 (14.7)</td>
<td>93/609 (15.3)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>324/599 (54.1)</td>
<td>314/553 (56.8)</td>
<td>289/529 (54.6)</td>
<td>340/609 (55.8)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>195/599 (32.6)</td>
<td>154/553 (27.8)</td>
<td>158/529 (29.9)</td>
<td>173/609 (28.4)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>11/599 (1.8)</td>
<td>10/553 (1.8)</td>
<td>4/529 (0.8)</td>
<td>3/609 (0.5)</td>
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</tr>
<tr>
<td><strong>Distance covered on 6-min walk, m</strong></td>
<td>353.5±147.5</td>
<td>339.1±146.2</td>
<td>340.4±139.4</td>
<td>369.1±151.5</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Pacemaker or defibrillator</strong></td>
<td>141/603 (23.4)</td>
<td>142/551 (25.8)</td>
<td>132/531 (24.9)</td>
<td>109/610 (17.9)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Serum creatinine, mg/dL</strong></td>
<td>1.2±0.3</td>
<td>1.2±0.3</td>
<td>1.1±0.3</td>
<td>1.2±0.3</td>
<td>0.677</td>
</tr>
<tr>
<td><strong>eGFR, mL/min</strong></td>
<td>69.0±19.9</td>
<td>67.6±20.0</td>
<td>69.5±22.0</td>
<td>67.7±20.6</td>
<td>0.310</td>
</tr>
<tr>
<td><strong>Hemoglobin, g/dL</strong></td>
<td>14.1±1.6</td>
<td>14.0±1.6</td>
<td>14.0±1.5</td>
<td>14.1±1.6</td>
<td>0.731</td>
</tr>
<tr>
<td><strong>Serum sodium, mEq/L</strong></td>
<td>139.2±6.4</td>
<td>139.4±3.3</td>
<td>139.7±3.3</td>
<td>140.0±3.4</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>Medical comorbidities</strong></td>
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<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>182/603 (30.2)</td>
<td>183/551 (33.2)</td>
<td>163/531 (30.7)</td>
<td>194/609 (31.9)</td>
<td>0.699</td>
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<td>Hypertension</td>
<td>330/580 (56.9)</td>
<td>300/530 (56.6)</td>
<td>331/520 (63.7)</td>
<td>406/602 (67.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>254/603 (42.1)</td>
<td>247/550 (44.9)</td>
<td>239/531 (45.0)</td>
<td>251/609 (41.2)</td>
<td>0.453</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>263/602 (43.7)</td>
<td>276/551 (50.1)</td>
<td>273/531 (51.4)</td>
<td>300/610 (49.2)</td>
<td>0.045</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>18/603 (3.0)</td>
<td>25/551 (4.5)</td>
<td>20/531 (3.8)</td>
<td>23/610 (3.8)</td>
<td>0.588</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>55/603 (9.1)</td>
<td>58/559 (10.4)</td>
<td>70/533 (13.1)</td>
<td>78/610 (12.8)</td>
<td>0.092</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>67/603 (11.1)</td>
<td>68/551 (12.3)</td>
<td>73/531 (13.7)</td>
<td>86/610 (14.1)</td>
<td>0.393</td>
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<td>Alcohol consumption</td>
<td></td>
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<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current consumption, &gt;2 oz/d</td>
<td>141/603 (23.4)</td>
<td>113/555 (20.4)</td>
<td>130/531 (24.5)</td>
<td>188/609 (30.9)</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
The incidence of ischemic stroke, primary outcome, and death, also stratified by optimal cutoff point for each outcome, is reported in Figure 1, which also reports the rate ratio for each event. Corresponding information for other outcomes is provided in Figure I in the online-only Data Supplement.

Effect of Antithrombotic Treatment

Figure 2 shows the outcome incidence rates for ischemic stroke, primary outcome, and death by antithrombotic treatment (aspirin or warfarin), stratified by LVEF category (for other outcomes, please refer to Figure II in the online-only Data Supplement). Incidence rates were similar between aspirin- and warfarin-treated patients, as already known from the WARCEF main results.4 The deleterious effect of a lower LVEF tended to be stronger in warfarin-treated than in aspirin-treated patients for all 3 outcomes. A trend toward a significant interaction between treatment type and LVEF was noted for ischemic stroke and primary outcome. An additional analysis by 5% LVEF decrements showed a significant interaction between LVEF and treatment for ischemic stroke only, with the warfarin-treated group showing a significantly greater stroke risk per each 5% LVEF decrement (adjusted hazard ratio, 1.346; 95% CI, 1.044–1.737; P=0.022) than the aspirin-treated group (adjusted hazard ratio, 0.971; 95% CI, 0.805–1.171; P=0.757; P value for the interaction=0.04).

Because the interaction between LVEF and warfarin on stroke risk might be mediated by differences in TTR, this variable was examined in different stroke and LVEF subgroups. TTR was similar in patients with LVEF of <15% or ≥15% (56.5±28.6% versus 57.1±28.5%; P=0.971); TTR tended to be lower in patients who experienced a stroke during follow-up than in those who did not (45.9±27.9% versus 57.2±28.4%; P=0.064); this trend was stronger in patients with LVEF of <15% (36.1±24.1% versus 57.6±28.5%; P=0.074) than in patients with LVEF of ≥15% (49.0±29.0% versus 57.2±28.4%; P=0.249).

Table 1. Continued

<table>
<thead>
<tr>
<th>Covariate</th>
<th>LVEF&lt;20% (n=603)</th>
<th>LVEF 21%–25% (n=559)</th>
<th>LVEF 26%–29% (n=533)</th>
<th>LVEF≥30% (n=610)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous consumption, &gt;2 oz/d</td>
<td>148/603 (24.5)</td>
<td>141/555 (25.4)</td>
<td>105/531 (19.8)</td>
<td>112/609 (18.4)</td>
<td>0.449</td>
</tr>
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<td>Never consumed alcohol</td>
<td>314/603 (52.1)</td>
<td>301/555 (54.2)</td>
<td>296/531 (55.7)</td>
<td>309/609 (50.7)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
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<td></td>
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<td>0.001</td>
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<tr>
<td>Current smoker</td>
<td>122/602 (20.3)</td>
<td>90/555 (16.2)</td>
<td>93/531 (17.5)</td>
<td>103/608 (16.9)</td>
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</tr>
<tr>
<td>Former smoker</td>
<td>307/602 (51.0)</td>
<td>295/555 (53.2)</td>
<td>275/531 (51.8)</td>
<td>303/608 (49.8)</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>173/602 (28.7)</td>
<td>170/555 (30.6)</td>
<td>163/531 (30.7)</td>
<td>202/608 (33.2)</td>
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</tr>
<tr>
<td>Medications</td>
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<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>593/603 (98.3)</td>
<td>541/551 (98.2)</td>
<td>522/529 (98.7)</td>
<td>601/610 (98.5)</td>
<td>0.922</td>
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<tr>
<td>β-Blocker</td>
<td>538/603 (89.2)</td>
<td>489/551 (88.7)</td>
<td>490/530 (92.5)</td>
<td>545/610 (89.3)</td>
<td>0.163</td>
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<td>Aldosterone blocker</td>
<td>231/355 (65.1)</td>
<td>220/333 (66.1)</td>
<td>175/296 (59.1)</td>
<td>187/361 (51.8)</td>
<td>&lt;0.001</td>
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<tr>
<td>Nitrate</td>
<td>143/603 (23.7)</td>
<td>122/555 (22.1)</td>
<td>141/530 (26.6)</td>
<td>137/609 (22.5)</td>
<td>0.296</td>
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<tr>
<td>Calcium-channel blocker</td>
<td>38/603 (6.3)</td>
<td>51/555 (9.3)</td>
<td>48/528 (9.1)</td>
<td>66/610 (10.8)</td>
<td>0.047</td>
</tr>
<tr>
<td>Diuretic</td>
<td>519/603 (86.1)</td>
<td>446/551 (80.9)</td>
<td>421/530 (79.4)</td>
<td>469/610 (76.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Statin</td>
<td>327/418 (78.2)</td>
<td>340/408 (83.3)</td>
<td>341/397 (85.9)</td>
<td>386/455 (84.8)</td>
<td>0.017</td>
</tr>
<tr>
<td>Warfarin</td>
<td>305/603 (50.6)</td>
<td>287/559 (51.3)</td>
<td>261/533 (49.0)</td>
<td>289/610 (47.4)</td>
<td>0.532</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and TIA, transient ischemic attack.

*For continuous variables, mean±SD were reported, and P values were calculated using ANOVA F-test. For categorical variables, no/total no (%) were reported, and P values were calculated using χ² test. For time-to-event outcomes, no (Kaplan–Meier %) were reported, and P values were calculated using log-rank test.
Discussion

This study evaluates the effect of LVEF on ischemic stroke and other outcome events in HF patients with sinus rhythm and reduced LVEF treated with currently recommended HF medications and randomized to different antithrombotic treatments.

In patients with systolic HF, several hemodynamic variables have been shown to be associated with outcome, some of which easily obtainable such as systolic blood pressure, pulse pressure, and resting heart rate. However, LVEF is the most widely used clinical indicator of LV systolic function and related risk for cardiovascular events in patients with HF. The results of our study support the presence of a linear, inverse relationship between LVEF and the considered outcome events with the exception of stroke, for which a relationship was observed only for low LVEF (<15%) and of MI, for which no relationship was observed. An LVEF of <15% more than doubled the risk of stroke.

Comparison With Previous Studies

The observation of an inverse relationship between LVEF and death is in agreement with those from previous observational and more recent, large-scale studies. Among the latter, results from the CHARM trial showed LVEF to be inversely and linearly associated with all-cause mortality and with all components of cardiovascular death for LVEF values <45% over a median follow-up of 38 months. The DIG trial also reported similar results. Our study provides similar results in a more recently enrolled cohort, but notable differences exist. Our study only included patients with systolic HF, and an LVEF cutoff of 35% was indeed the one associated with increased mortality at 180 days in the recent Acute Studies of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, and a linear relationship between decreasing LVEF and risk of death was only observed below that level. Compared with the CHARM cohort, the WARCEF cohort had differences

Table 2. LVEF and Outcome Events (by Optimal Cutoff Point of Increased Risk)

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>LVEF &lt;15% vs ≥15%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2.105 (1.186–3.738)</td>
<td>0.011</td>
<td>2.125 (1.182–3.818)</td>
</tr>
<tr>
<td>LVEF &lt;25% vs ≥25%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>1.266 (1.081–1.484)</td>
<td>0.004</td>
<td>1.250 (1.063–1.469)</td>
</tr>
<tr>
<td>Death</td>
<td>1.288 (1.085–1.529)</td>
<td>0.004</td>
<td>1.252 (1.050–1.492)</td>
</tr>
<tr>
<td>LVEF &lt;20% vs ≥20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1.481 (1.189–1.845)</td>
<td>&lt;0.001</td>
<td>1.359 (1.085–1.702)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>1.593 (1.187–2.136)</td>
<td>0.002</td>
<td>1.481 (1.097–1.999)</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>1.520 (1.249–1.849)</td>
<td>&lt;0.001</td>
<td>1.395 (1.142–1.706)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BP, blood pressure; CI, confidence interval; HF, heart failure; HR, hazard ratio; ICD, intracardiac defibrillator; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association.

*Adjusted for age, sex, BMI, systolic BP, heart rate, smoking status, education, NYHA class (III, IV vs I, II), diabetes mellitus, hypertension, ischemic cardiomyopathy, previous stroke or TIA, ICD presence, serum creatinine and hemoglobin for primary outcome, death, cardiovascular death and sudden death; adjusted for age, sex, BMI, systolic BP, smoking status, NYHA class (III, IV vs I, II), diabetes mellitus, hypertension, ischemic cardiomyopathy, previous stroke or TIA, ICD presence, serum creatinine and hemoglobin for stroke; adjusted for age, sex, BMI, systolic BP, heart rate, smoking status, alcohol consumption, NYHA class (III, IV vs I, II), diabetes mellitus, hypertension, ischemic cardiomyopathy, previous stroke or TIA, ICD presence, serum creatinine, hemoglobin and sodium for HF hospitalization.

Figure 1. Outcome incidence rates for ischemic stroke, primary outcome, and death by left ventricular ejection fraction (LVEF; dichotomized at optimal cutoff points). CI indicates confidence interval.

No. events (incidence per 100 pt-yrs) Rate Ratio (95% CI) p-value

<table>
<thead>
<tr>
<th></th>
<th>Lower EF</th>
<th>higher EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF&lt;15% (n=219)</td>
<td>14 (2.04)</td>
<td>70 (0.95)</td>
</tr>
<tr>
<td>EF≥15% (n=2086)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>310 (7.39)</td>
<td>230 (5.74)</td>
</tr>
<tr>
<td>Death</td>
<td>350 (8.56)</td>
<td>2723 (6.79)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* From Poisson regression.
in the medical treatment that reflect the more recent conduct of the study. Patients in WARCEF were more often on β-blockers (>90% of patients versus ~55%), aldosterone-blockers (60% versus ~20%), and statins or other lipid-lowering medications (>80% versus ~40%). The most important difference, however, is that all patients in WARCEF received an antithrombotic medication per-protocol, which may have affected the relationship between LVEF and thromboembolic events.

Unlike CHARM, which found no association between LVEF and incidence of stroke, we observed an increased stroke risk for extremely low LVEF values (~<15%). This difference may reflect the low incidence of stroke in CHARM (slightly >1% over a mean follow-up of ~3 years). The stroke incidence in WARCEF (slightly >1% per year) is at the lower end of what traditionally reported in the HF literature (1.3%–3.5% per year),!#!# probably reflecting the updated background medical treatment and the per-protocol antithrombotic agents. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), the rate of stroke or other thromboembolic events was 1.7% per year, and lower LVEF was associated with an increased risk of thromboembolic events, with the highest risk observed in patients with LVEF of ~<20%.

The hypothesis that patients with extremely low LVEF might have greater difficulty in maintaining an adequate TTR was not confirmed in our analysis because mean TTR was nearly identical in patients with LVEF of ~<15% or ~≥15%; however, the mean TTR tended to be lower in patients with LVEF of ~<15% who experienced a stroke than in patients with LVEF of ~<15% who did not (~P=0.074). Taken together, these results suggest that, although maintaining an adequate TTR may not necessarily be more difficult in patients with extremely low LVEF, the stroke risk may increase in them when an adequate TTR is for any reason not achieved. Given the low number of incident strokes, these results should be regarded with a degree of caution; however, particular emphasis should be placed on international normalized ratio control in patients with very low LVEF and switching to another antithrombotic agent considered when international normalized ratio management proves difficult. The use of newer oral anticoagulants in patients with severely reduced LVEF and sinus rhythm, while an appealing possibility, requires appropriately designed and powered clinical trials to assess safety and efficacy of these drugs in this specific clinical setting.

Our study has strengths and limitations. Strengths are the relatively large cohort of patients with HF in sinus rhythm, the central interpretation of echocardiograms and consequent standardization of LVEF measurement, and the ability to investigate the effect of 2 antithrombotic treatments. Among the limitations, the study only included patients with systolic HF; therefore, the effect of LVEF on outcomes within

Effect of Antithrombotic Treatment

In the main results of WARCEF, patients on warfarin or aspirin treatment had similar rates of death and primary outcome, although patients on warfarin treatment had significantly reduced incidence of ischemic stroke. In the present analysis, lower LVEF tended to have a more deleterious effect in patients treated with warfarin than in patients receiving aspirin with respect to primary outcome, death, and ischemic stroke (Figure 2). The only significant interaction between LVEF and treatment was observed for stroke, where each ~5% decrease in LVEF was associated with a 35.6% increase in the adjusted risk of stroke in patients treated with warfarin (~P=0.02). Warfarin-treated patients with LVEF of ~<15% showed an increased stroke rate, whereas those with higher LVEF had low stroke incidence, actually lower than that of aspirin-treated patients. The hypothesis that patients with extremely low LVEF might have greater difficulty in maintaining an adequate TTR was not confirmed in our analysis because mean TTR was nearly identical in patients with LVEF of ~<15% or ~≥15%; however, the mean TTR tended to be lower in patients with LVEF of ~<15% who experienced a stroke than in patients with LVEF of ~<15% who did not (~P=0.074). Taken together, these results suggest that, although maintaining an adequate TTR may not necessarily be more difficult in patients with extremely low LVEF, the stroke risk may increase in them when an adequate TTR is for any reason not achieved. Given the low number of incident strokes, these results should be regarded with a degree of caution; however, particular emphasis should be placed on international normalized ratio control in patients with very low LVEF and switching to another antithrombotic agent considered when international normalized ratio management proves difficult. The use of newer oral anticoagulants in patients with severely reduced LVEF and sinus rhythm, while an appealing possibility, requires appropriately designed and powered clinical trials to assess safety and efficacy of these drugs in this specific clinical setting.

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a normal or mildly decreased LVEF could not be evaluated. The incidence of some outcomes was rather low; therefore, the related results for subgroup analyses should be considered exploratory.

Summary
In patients with systolic HF in sinus rhythm treated with currently recommended HF regimen and antithrombotic medications, LVEF is inversely associated with death and its various components, ischemic stroke, and HF hospitalization, but not MI; the association is linear for most outcomes, but an increased stroke risk is observed only for very low LVEF (<15%); an interaction between LVEF and warfarin treatment may exist on stroke risk, which deserves further investigation.

Acknowledgments
We thank Michelle Bierig, RDCC, and Rui Liu, MD, for their help with the echocardiographic measurements.

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References
Left Ventricular Ejection Fraction and Risk of Stroke and Cardiac Events in Heart Failure: Data From the Warfarin Versus Aspirin in Reduced Ejection Fraction Trial

for the WARCEF Investigators

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Left Ventricular Ejection Fraction and Risk of Stroke and Cardiovascular Events in Heart Failure: Insights from the WARCEF trial
SUPPLEMENTAL METHODS

Eligibility criteria
Patients in any New York Heart Association (NYHA) functional classes were eligible, but patients in NYHA class I could account for no more than 20% of the total number of patients undergoing randomization. Patients who had a clear indication for warfarin or aspirin were not eligible. Patients were also ineligible if they had a condition that conferred a high risk of cardiac embolism, such as atrial fibrillation, a mechanical cardiac valve, endocarditis, or an intracardiac mobile or pedunculated thrombus. Planned treatment with a beta-blocker, an angiotensin-converting–enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB), or hydralazine and nitrates, was also a reason for ineligibility, whereas current treatment with those medications was allowed.

Study Medication
Patients were randomized to adjusted dose warfarin or aspirin in a double-blind, double-dummy design in which patients who were assigned to active warfarin received warfarin and placebo aspirin, and patients assigned to active aspirin received aspirin and placebo warfarin. The statistical analysis center fabricated clinically plausible INR results for patients in the aspirin group and provided these results to the sites, along with the actual INR results for the patients in the warfarin group, so that all the patients were treated as if they were receiving active warfarin.

Definition of outcome events

Stroke was defined as a clinically relevant new lesion detected on computed tomography or MRI or, in the absence of a new lesion, clinical findings that were consistent with the occurrence of clinical stroke and that lasted for longer than 24 hours.

The diagnosis of MI based was based on two of the following: 1) Typical cardiac pain or its equivalent; 2) ECG evidence of acute MI; 3) Cardiac biomarkers indicative of acute MI.

Sudden death was defined as: 1) death witnessed and noted to occur instantaneously or within 15 minutes of observed collapse or new cardiac symptoms, without preceding circulatory failure (shock, pulmonary edema, refractory NYHA class IV CHF) or other modes of death, or 2) death unwitnessed, but known to have occurred in the absence of pre-existing circulatory failure or other modes of death within an observation period of 72 hours, or 3) patient resuscitated from cardiac arrest in the absence of pre-existing circulatory failure or other modes of death and died within 24 hours or prior to discharge if neurologic function was not restored.

Cardiovascular death included sudden death; documented ventricular tachycardia or fibrillation; documented bradyarrhythmia; MI; and circulatory failure.

Hospitalizations for heart failure during the follow-up were defined as admissions with the following features: typical symptoms; IV diuretics, vasodilator or inotropic therapy; at least 24-hour hospital stay.
**SUPPLEMENTAL TABLES**

Supplemental Table I – Association of demographic and clinical variables with primary outcome (death, stroke or intracerebral hemorrhage). Univariable and multivariable Cox models

<table>
<thead>
<tr>
<th>covariate</th>
<th>For an increase of</th>
<th>Univariable model</th>
<th>Multivariable model</th>
</tr>
</thead>
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<tr>
<td>Ejection fraction, %</td>
<td>1</td>
<td>0.982 (0.971,0.992)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age-yr</td>
<td>1</td>
<td>1.027 (1.020,1.035)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td>1.348 (1.089,1.668)</td>
<td>0.006</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>1</td>
<td>0.966 (0.952,0.980)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>1</td>
<td>0.994 (0.990,0.998)</td>
<td>0.006</td>
</tr>
<tr>
<td>Heart rate - beats/min</td>
<td>1</td>
<td>1.008 (1.001,1.014)</td>
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<td>. Current smoker</td>
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<td>1.133 (0.889,1.445)</td>
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<tr>
<td>. Former smoker</td>
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<td>1.266 (1.051,1.525)</td>
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<td>. High-school graduate or some college</td>
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<td>0.908 (0.766,1.075)</td>
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<tr>
<td>. College graduate or postgraduate</td>
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<td>0.716 (0.561,0.915)</td>
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<td>NYHA class III or IV</td>
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<td>Diabetes Mellitus</td>
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<td>1.486 (1.265,1.745)</td>
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<td>Hypertension</td>
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<td>0.991 (0.843,1.165)</td>
<td>0.912</td>
</tr>
<tr>
<td>Ischemic Cardiomyopathy</td>
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<td>1.621 (1.385,1.898)</td>
<td>&lt;0.001</td>
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<td>Univariable model</td>
<td>Multivariable model</td>
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<tr>
<td></td>
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<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>yes vs. no</td>
<td>1.402 (1.133, 1.735)</td>
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<tr>
<td>Pacemaker or defibrillator</td>
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<td>0.838 (0.685, 1.024)</td>
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<tr>
<td>creatinine - mg/dL</td>
<td>1</td>
<td>2.255 (1.830, 2.778)</td>
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<tr>
<td>hemoglobin - g/dL</td>
<td>1</td>
<td>0.873 (0.827, 0.921)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR = Hazard Ratio

CI = Confidence Interval
**Supplemental Table II** – Demographics and clinical variables associated with death from any cause in the study cohort

<table>
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<td>p-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Ejection fraction %</td>
<td>1</td>
<td>0.981 (0.969, 0.992)</td>
<td>0.001</td>
</tr>
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<td>Age-yr</td>
<td>1</td>
<td>1.030 (1.022, 1.038)</td>
<td>&lt;0.001</td>
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<td>Male sex</td>
<td>1</td>
<td>1.413 (1.118, 1.786)</td>
<td>0.004</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>1</td>
<td>0.964 (0.949, 0.980)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>1</td>
<td>0.993 (0.988, 0.998)</td>
<td>0.003</td>
</tr>
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<td>pulse - beats/min</td>
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<td>1.010 (1.003, 1.017)</td>
<td>0.006</td>
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<td>0.361</td>
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<td>Current smoker</td>
<td>1.181 (0.907, 1.537)</td>
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<tr>
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<td>Former smoker</td>
<td>1.320 (1.077, 1.618)</td>
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<td>0.033</td>
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<td>High-school graduate or some college</td>
<td>0.889 (0.741, 1.066)</td>
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<tr>
<td></td>
<td>College graduate or postgraduate</td>
<td>0.629 (0.478, 0.828)</td>
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<tr>
<td>NYHA class III or IV</td>
<td>1</td>
<td>1.642 (1.380, 1.952)</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
<td>1.508 (1.267, 1.794)</td>
<td>&lt;0.001</td>
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<tr>
<td>Hypertension</td>
<td>1</td>
<td>0.991 (0.832, 1.180)</td>
<td>0.920</td>
</tr>
<tr>
<td>Ischemic Cardiomyopathy</td>
<td>1</td>
<td>1.681 (1.417, 1.993)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>1</td>
<td>1.136 (0.886, 1.456)</td>
<td>0.315</td>
</tr>
<tr>
<td>Pacemaker or defibrillator</td>
<td>1</td>
<td>0.875 (0.706, 1.084)</td>
<td>0.223</td>
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<td>For an increase of</td>
<td>Univariable model</td>
<td>Multivariable model</td>
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<td>-------------------</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>creatinine - mg/dL</td>
<td>1</td>
<td>2.384 (1.906, 2.982)</td>
<td>&lt;0.001</td>
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<tr>
<td>hemoglobin - g/dL</td>
<td>1</td>
<td>0.850 (0.803, 0.901)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR = Hazard Ratio
CI = Confidence Interval
**Supplemental Table III** – Demographics and clinical variables associated with ischemic stroke in the study cohort

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<tr>
<th>covariate</th>
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<th>Multivariable model</th>
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<tbody>
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<td></td>
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<td></td>
<td></td>
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<td>p-value</td>
</tr>
<tr>
<td>Ejection fraction &lt;15%</td>
<td>2.105 (1.186, 3.738)</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Age-yr</td>
<td>1</td>
<td>1.008 (0.988, 1.027)</td>
<td>0.442</td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td>0.947 (0.562, 1.594)</td>
<td>0.836</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>1</td>
<td>0.979 (0.943, 1.017)</td>
<td>0.281</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>1</td>
<td>1.000 (0.988, 1.011)</td>
<td>0.968</td>
</tr>
<tr>
<td>Smoking status</td>
<td>ref: never smoked</td>
<td></td>
<td>0.992</td>
</tr>
<tr>
<td>.</td>
<td>Current smoker</td>
<td>0.975 (0.516, 1.841)</td>
<td>.</td>
</tr>
<tr>
<td>.</td>
<td>Former smoker</td>
<td>0.970 (0.596, 1.579)</td>
<td>.</td>
</tr>
<tr>
<td>NYHA class III or IV</td>
<td></td>
<td>1.125 (0.712, 1.778)</td>
<td>0.615</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td></td>
<td>1.337 (0.858, 2.082)</td>
<td>0.199</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>1.006 (0.648, 1.563)</td>
<td>0.978</td>
</tr>
<tr>
<td>Ischemic Cardiomyopathy</td>
<td></td>
<td>1.157 (0.752, 1.781)</td>
<td>0.507</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td></td>
<td>3.381 (2.139, 5.345)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pacemaker or defibrillator</td>
<td></td>
<td>0.583 (0.316, 1.075)</td>
<td>0.084</td>
</tr>
<tr>
<td>creatinine - mg/dL</td>
<td>1</td>
<td>1.657 (0.908, 3.026)</td>
<td>0.100</td>
</tr>
<tr>
<td>hemoglobin - g/dL</td>
<td>1</td>
<td>1.037 (0.891, 1.207)</td>
<td>0.638</td>
</tr>
</tbody>
</table>
Supplemental Table IV – LVEF and outcomes: cutoff points of increased risk

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted HR (95% CI)</th>
<th>p-value</th>
<th>Adjusted* HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF &lt; 15% vs. EF≥15%</td>
<td>1.395 (1.090,1.787)</td>
<td>0.008</td>
<td>1.247 (0.969, 1.606)</td>
<td>0.087</td>
</tr>
<tr>
<td>EF &lt; 20% vs. EF≥20%</td>
<td>1.274 (1.074,1.511)</td>
<td>0.006</td>
<td>1.242 (1.043, 1.480)</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>EF &lt; 25% vs. EF≥25%</strong></td>
<td><strong>1.266 (1.081,1.484)</strong></td>
<td><strong>0.004</strong></td>
<td><strong>1.250 (1.063, 1.469)</strong></td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td>EF &lt; 30% vs. EF≥30%</td>
<td>1.269 (1.047,1.538)</td>
<td>0.015</td>
<td>1.231 (1.014, 1.496)</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF &lt; 15% vs. EF≥15%</td>
<td>1.284 (0.973,1.694)</td>
<td>0.077</td>
<td>1.113 (0.838, 1.477)</td>
<td>0.460</td>
</tr>
<tr>
<td>EF &lt; 20% vs. EF≥20%</td>
<td>1.282 (1.066,1.543)</td>
<td>0.008</td>
<td>1.223 (1.012, 1.479)</td>
<td>0.037</td>
</tr>
<tr>
<td><strong>EF &lt; 25% vs. EF≥25%</strong></td>
<td><strong>1.288 (1.085,1.529)</strong></td>
<td><strong>0.004</strong></td>
<td><strong>1.252 (1.050, 1.492)</strong></td>
<td><strong>0.012</strong></td>
</tr>
<tr>
<td>EF &lt; 30% vs. EF≥30%</td>
<td>1.366 (1.104,1.690)</td>
<td>0.004</td>
<td>1.310 (1.056, 1.625)</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>CV death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF &lt; 15% vs. EF≥15%</td>
<td>1.324 (0.949,1.847)</td>
<td>0.098</td>
<td>1.102 (0.784, 1.547)</td>
<td>0.577</td>
</tr>
<tr>
<td>EF &lt; 20% vs. EF≥20%</td>
<td>1.481 (1.189,1.845)</td>
<td>&lt;0.001</td>
<td>1.359 (1.085, 1.702)</td>
<td>0.008</td>
</tr>
<tr>
<td>EF &lt; 25% vs. EF≥25%</td>
<td>1.432 (1.159,1.769)</td>
<td>0.001</td>
<td>1.337 (1.077, 1.660)</td>
<td>0.008</td>
</tr>
<tr>
<td>EF &lt; 30% vs. EF≥30%</td>
<td>1.503 (1.151,1.964)</td>
<td>0.003</td>
<td>1.387 (1.058, 1.818)</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Sudden death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF &lt; 15% vs. EF≥15%</td>
<td>1.420 (0.919,2.195)</td>
<td>0.114</td>
<td>1.257 (0.806, 1.960)</td>
<td>0.314</td>
</tr>
<tr>
<td>EF &lt; 20% vs. EF≥20%</td>
<td>1.593 (1.187,2.136)</td>
<td>0.002</td>
<td>1.481 (1.097, 1.999)</td>
<td>0.010</td>
</tr>
<tr>
<td>EF &lt; 25% vs. EF≥25%</td>
<td>1.328 (1.000,1.764)</td>
<td>0.050</td>
<td>1.273 (0.953, 1.700)</td>
<td>0.102</td>
</tr>
<tr>
<td>EF &lt; 30% vs. EF≥30%</td>
<td>1.472 (1.029,2.106)</td>
<td>0.034</td>
<td>1.395 (0.972, 2.004)</td>
<td>0.071</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF &lt; 15% vs. EF≥15%</td>
<td>2.105 (1.186,3.738)</td>
<td>0.011</td>
<td>2.125 (1.182, 3.818)</td>
<td>0.012</td>
</tr>
<tr>
<td>EF &lt; 20% vs. EF≥20%</td>
<td>1.302 (0.820,2.067)</td>
<td>0.264</td>
<td>1.388 (0.868, 2.220)</td>
<td>0.170</td>
</tr>
<tr>
<td>EF &lt; 25% vs. EF≥25%</td>
<td>1.190 (0.775,1.829)</td>
<td>0.427</td>
<td>1.238 (0.800, 1.915)</td>
<td>0.337</td>
</tr>
<tr>
<td>EF &lt; 30% vs. EF≥30%</td>
<td>0.868 (0.540,1.393)</td>
<td>0.556</td>
<td>0.879 (0.543, 1.422)</td>
<td>0.599</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF &lt; 15% vs. EF≥15%</td>
<td>0.766 (0.309,1.900)</td>
<td>0.565</td>
<td>0.753 (0.302, 1.879)</td>
<td>0.543</td>
</tr>
<tr>
<td>EF &lt; 20% vs. EF≥20%</td>
<td>1.192 (0.717,1.981)</td>
<td>0.499</td>
<td>1.243 (0.743, 2.082)</td>
<td>0.407</td>
</tr>
<tr>
<td>EF &lt; 25% vs. EF≥25%</td>
<td>1.232 (0.774,1.961)</td>
<td>0.380</td>
<td>1.305 (0.815, 2.092)</td>
<td>0.268</td>
</tr>
<tr>
<td>EF &lt; 30% vs. EF≥30%</td>
<td>1.040 (0.610,1.772)</td>
<td>0.887</td>
<td>1.083 (0.630, 1.859)</td>
<td>0.773</td>
</tr>
<tr>
<td><strong>HF hospitalization (1st event)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF &lt; 15% vs. EF≥15%</td>
<td>1.337 (0.993,1.798)</td>
<td>0.055</td>
<td>1.139 (0.841, 1.544)</td>
<td>0.400</td>
</tr>
<tr>
<td>EF &lt; 20% vs. EF≥20%</td>
<td>1.520 (1.249,1.849)</td>
<td>&lt;0.001</td>
<td>1.395 (1.142, 1.706)</td>
<td>0.001</td>
</tr>
<tr>
<td>EF &lt; 25% vs. EF≥25%</td>
<td>Unadjusted HR (95% CI)</td>
<td>Adjusted* HR (95% CI)</td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------</td>
<td>-----------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>EF &lt; 25% vs. EF≥25%</td>
<td>1.413 (1.172, 1.704)</td>
<td>1.277 (1.054, 1.546)</td>
<td>&lt;0.001</td>
<td>0.012</td>
</tr>
<tr>
<td>EF &lt; 30% vs. EF≥30%</td>
<td>1.551 (1.225, 1.964)</td>
<td>1.380 (1.086, 1.753)</td>
<td>&lt;0.001</td>
<td>0.008</td>
</tr>
</tbody>
</table>

* adjusted for age, gender, BMI, systolic BP, heart rate, smoking status, education, NYHA class (III, IV vs. I, II), diabetes, hypertension, ischemic cardiomyopathy, prior stroke or TIA, device, creatinine and hemoglobin for primary outcome, death, CV death and sudden death; adjusted for age, gender, BMI, systolic BP, smoking status, NYHA class (III, IV vs. I, II), diabetes, hypertension, ischemic cardiomyopathy, prior stroke or TIA, device, creatinine and hemoglobin for stroke, and MI; adjusted for age, gender, BMI, systolic BP, heart rate, smoking status, alcohol consumption, NYHA class (III, IV vs. I, II), diabetes, hypertension, ischemic cardiomyopathy, prior stroke or TIA, device, creatinine, hemoglobin and sodium for HF hospitalization.
Supplemental Figure I

<table>
<thead>
<tr>
<th>Event Type</th>
<th>EF&lt;20% (n=603)</th>
<th>EF≥20% (n=1702)</th>
<th>Rate Ratio (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death</td>
<td>120 (5.81)</td>
<td>236 (3.93)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sudden Death</td>
<td>69 (3.34)</td>
<td>126 (2.10)</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>HF hospitalization (1st event)</td>
<td>150 (7.26)</td>
<td>301 (5.01)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* From Poisson regression.

No LVEF cutoff of increased risk was identified for MI.
Supplemental Figure II

* From Cox models, adjusted for age, gender, BMI, systolic BP, heart rate, smoking status, education, NYHA class (III, IV vs. I, II), diabetes, hypertension, ischemic cardiomyopathy, prior stroke or TIA, ICD presence, serum creatinine and hemoglobin for CV death and sudden death; adjusted for age, gender, BMI, systolic BP, heart rate, smoking status, alcohol consumption, NYHA class (III, IV vs. I, II), diabetes, hypertension, ischemic cardiomyopathy, prior stroke or TIA, ICD presence, serum creatinine, hemoglobin and sodium for HF hospitalization.
左室駆出率と心不全患者の脳卒中および心イベントのリスク

Warfarin Versus Aspirin in Reduced Ejection Fraction (WARCEF) Trial データ

左室駆出率（LVEF）は心不全（HF）における死亡および心管の転帰と逆相関する。抗血栓治療の影響と同様、LVEFと脳卒中との関連についても議論がある。本研究では、HF患者におけるLVEFと脳卒中および心管イベントの関連性、および2種類の抗血栓薬の影響を検討した。

背景および目的：左室駆出率（LVEF）は心不全（HF）における死亡および心管の転帰と逆相関する。抗血栓治療の影響と同様、LVEFと脳卒中との関連についても議論がある。本研究では、HF患者におけるLVEFと脳卒中および心管イベントの関連性、および2種類の抗血栓薬の影響を検討した。

方法：Warfarin Versus Aspirin in Reduced Ejection Fraction (WARCEF) 試験において収縮期HF（LVEF≤35%）で洞調律の患者2,305例をワルファリン投与群またはアスピリン投与群に無作為に割り付け、3.5±1.8年間追跡調査した。主要評価項目（死亡、脳卒中、脳内出血）に関して群間差は認めなかったが、ワルファリンは脳卒中リスクを低下させた。本報告では、LVEFおよび治療法の異なるサブグループ間における脳卒中および心血管イベントの発生率を比較する。

結果：ベースラインのLVEFは、主要評価項目、死亡および死亡の内訳（突然死、心血管死）、HFによる入院に対して線形の逆相関を示したが、心筋梗塞との相関は示されなかった。脳卒中との関連はLVEF15%未満の場合にのみ認められ（発生率：2.04 vs. 0.95/100患者年, P = 0.009）。調整済みの脳卒中リスクは2倍を超えた（調整ハザード比2.125、95%信頼区間（CI）：1.182～3.818, P = 0.012）。ワルファリン投与患者ではLVEFが5%低下することに脳卒中リスクが有意に増加した（調整ハザード比1.346、95% CI：1.044～1.737, P = 0.022, P value for interaction = 0.04）。

結論：収縮期HFで洞調律の患者においてLVEFは死亡および死亡の内訳と逆相関するが、脳卒中との関連はLVEF値が著しく低い場合にのみ認められる。脳卒中リスクに対するワルファリン投与の交互作用は存在すると考えられる。

臨床試験登録情報：URL: http://www.clinicaltrials.gov。固有の識別番号：NCT00041938。