Comparison of Dabigatran and Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease

The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulant Therapy)

BACKGROUND: The RE-LY trial (Randomized Evaluation of Long-Term Anticoagulant Therapy) compared dabigatran 150 and 110 mg twice daily with warfarin in 18,113 patients with atrial fibrillation. Those with prosthetic heart valves, significant mitral stenosis, and valvular heart disease (VHD) requiring intervention were excluded. Others with VHD were included.

METHODS: This is a post hoc analysis of the RE-LY trial.

RESULTS: There were 3950 patients with any VHD: 3101 had mitral regurgitation, 1179 with tricuspid regurgitation, 817 had aortic regurgitation, 471 with aortic stenosis, and 193 with mild mitral stenosis. At baseline, patients with any VHD had more heart failure, coronary disease, renal impairment, and persistent atrial fibrillation. Patients with any VHD had higher rates of major bleeds (hazard ratio [HR], 1.32; 95% confidence interval [CI], 1.16–1.5) but similar stroke or systemic embolism event rates (HR, 1.09; 95% CI, 0.88–1.33). For patients receiving dabigatran 110 mg, major bleed rates were lower than for patients taking warfarin (HR, 0.73; 95% CI, 0.56–0.95 with VHD; HR, 0.84; 95% CI, 0.71–0.99 without VHD), and major bleed rates for dabigatran 150 mg were similar to those for warfarin in patients with VHD (HR, 0.82; 95% CI, 0.64–1.06) or without VHD (HR, 0.98; 95% CI, 0.83–1.15). For dabigatran 150 mg, stroke/systemic embolic event rates were lower compared with warfarin in those with VHD (HR, 0.59; 95% CI, 0.37–0.93) and those without VHD (HR, 0.67; 95% CI, 0.52–0.86), and stroke/systemic embolic event rates were similar for warfarin and dabigatran 110 mg regardless of the presence of VHD (HR, 0.97; 95% CI, 0.65–1.45; and HR, 0.88; 95% CI, 0.70–1.10). Intracranial bleeds and death rates for dabigatran 150 and 110 mg were lower compared with warfarin independently of the presence of VHD.

CONCLUSIONS: The presence of any VHD did not influence the comparison of dabigatran with warfarin.


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Key Words: atrial fibrillation ■ stroke ■ valvular heart diseases

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Clinical Perspective

What Is New?

- The pivotal clinical trials comparing novel oral anticoagulants with warfarin defined the evaluated population as having nonvalvular atrial fibrillation; however, many patients with valve pathology were actually included in the trials, and only patients with highly specific valve disease, that is, prosthetic heart valves and severe mitral stenosis, were excluded.
- In the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulant Therapy), 3950 patients (21.8%) had valvular heart disease. Patients included were those with aortic stenosis, aortic regurgitation, mitral regurgitation, tricuspid valve disease, and mild, presumably rheumatic mitral stenosis.
- This analysis provided an opportunity to compare patients with and without any valve disease and to compare treatments.

What Are the Clinical Implications?

- In this analysis, the comparison of both doses of dabigatran for stroke and systemic embolism, major bleeding, intracranial bleeds, and mortality with warfarin was independent of the presence of valvular heart disease.
- Thus, the clinician can use the approved doses of dabigatran with confidence in patients with valve disease, excluding only those with prosthetic valve disease or patients with hemodynamic significant mitral stenosis.

Although the clinical trials that evaluated novel oral anticoagulants (NOACs) described the patients as having nonvalvular atrial fibrillation (AF), all the trials actually randomized patients with various valve pathologies,1–8 rendering the term nonvalvular AF a misnomer. The definition of nonvalvular AF was a definition of exclusion. Those excluded varied among trials, leading to inconsistencies in the definition of nonvalvular heart disease, resulting in confusion (Table 1) that may cause some clinicians to hesitate before prescribing NOACs to patients with any form of valvular heart disease (VHD). Two post hoc analyses have found that patients with a variety of valve pathologies derive benefit from their respective NOACs.9,10 ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)9 and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation: EHRA, European Heart Rhythm Association; ENGAGE-AF-TIMI 48, Effective Anticoagulation With Factor XA Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction Study 48; RE-LY, Randomized Evaluation of Long-term Anticoagulant Therapy; and ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)10 reported their respective experiences in patients with VHD. We report the outcomes of patients with VHD taking dabigatran in the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy).

The primary objective of this post hoc analysis is to compare the outcomes of dabigatran at doses of 110 mg twice daily (D110) and 150 mg twice daily (D150) with those of warfarin in patients with and without VHD. The secondary objective is to compare these results from RE-LY with the post hoc analyses from ROCKET AF and ARISTOTLE9,10 to place the accumulating information into perspective.

Table 1. Classification of Nonvalvular AF

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY2,2</td>
<td>Excluded patients with patients with prosthetic heart valves, significant mitral stenosis and valve disease requiring an intervention before study end</td>
</tr>
<tr>
<td></td>
<td>Included other valve disorders: mitral regurgitation, tricuspid regurgitation, aortic regurgitation, aortic stenosis, and mild mitral stenosis</td>
</tr>
<tr>
<td>ROCKET AF1,4,9</td>
<td>Excluded patients with hemodynamically significant mitral valve stenosis, prosthetic heart valves, and planned invasive interventions with a major risk of uncontrolled bleeding</td>
</tr>
<tr>
<td></td>
<td>Included all other valvular heart disease conditions and/or annuloplasty with or without a prosthetic ring, commissurotomy, and valvuloplasty</td>
</tr>
<tr>
<td>ARISTOTLE6,10</td>
<td>Excluded patients with clinically significant moderate or severe mitral stenosis and prosthetic heart valves</td>
</tr>
<tr>
<td></td>
<td>Included all other valvular heart disease conditions and/or moderate mitral regurgitation, aortic regurgitation, aortic stenosis, tricuspid regurgitation, and valve surgery</td>
</tr>
<tr>
<td>ENGAGE-AF-TIMI 481,4</td>
<td>Excluded patients with moderate or severe mitral stenosis, unsected atrial myxoma, and mechanical heart valve</td>
</tr>
<tr>
<td></td>
<td>Included all other valvular heart disease conditions and/or bioprosthesis heart valves and valve repair</td>
</tr>
<tr>
<td>2015 EHRA AF management guidelines11</td>
<td>Nonvalvular AF is classified as the absence of mechanical prosthetic heart valves and moderate to severe mitral stenosis (usually of rheumatic origin)</td>
</tr>
<tr>
<td>2014 AHA/ACC/HRS guidelines12</td>
<td>Nonvalvular AF is classified as the absence of rheumatic mitral stenosis and mechanical or bioprothetic heart valve or mitral valve repair</td>
</tr>
</tbody>
</table>

AHA/ACC/HRS indicates American Heart Association/American College of Cardiology/Heart Rhythm Society; AF, atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; EHRA, European Heart Rhythm Association; ENGAGE-AF-TIMI 48, Effective Anticoagulation With Factor XA Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction Study 48; RE-LY, Randomized Evaluation of Long-term Anticoagulant Therapy; and ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.
Methods

The RE-LY trial was a prospective, randomized trial investigating the effectiveness and safety of 2 doses of dabigatran in preventing stroke and systemic embolic events (SEEs) in patients with nonvalvular AF compared with warfarin. The study was funded by Boehringer Ingelheim and was coordinated by the Population Health Research Institute (Hamilton, ON, Canada). Detailed descriptions of the rationale and design of the RE-LY trial have been published previously. All patients who participated in the RE-LY trial were included in this analysis. The appropriate regulatory authorities and ethics committees approved the study. All authors vouch for the accuracy and completeness of the data. This analysis was conducted at the Cardiovascular Research Foundation in New York.

Study Definitions and End Points

Patients with a prosthetic heart valve or hemodynamically significant mitral stenosis or valve disease likely to lead to an intervention before study end were excluded from RE-LY. Patients with all other heart valve conditions were included and were classified as having VHD. In addition, we evaluated patients in 2 subcategories of VHD: patients with exclusive right-sided valve lesions and those with mild mitral stenosis. Patients with mitral stenosis were assumed to have had rheumatic valve disease. The primary efficacy end point was stroke, including hemorrhagic or an SEE. The secondary efficacy end point was total mortality. The main safety end point was major bleeding defined as bleeding with a reduction in hemoglobin of ≥20 g/L, bleeding requiring a transfusion of at least 2 units, or symptomatic bleeding in a critical area or organ, including intracranial bleeds.

Statistical Analysis

This was a post hoc analysis of all patients randomized in the RE-LY trial. All analyses were by intention to treat. Patients were initially characterized by the presence or absence of any form of VHD. Subsequently, patients with exclusive valvular right-sided lesions were identified, as were patients with mitral stenosis. For all groups, the baseline characteristics and their outcomes were compared. The outcomes of the VHD cohort included all forms of VHD and were compared with the outcomes of the non-VHD cohort. The summarized results used annualized event rates with both unadjusted and adjusted hazard ratios (HRs). The adjusted HRs were estimated from a Cox model that included propensity scores as a continuous variable. The propensity scores for VHD status were estimated from a model that included the following covariates: age, sex, race, smoking status, alcohol use, region, body mass index, AF diagnosis, AF type, previous cardioversion, previous atrioventricular node ablation, history of heart failure, diabetes mellitus, coronary

Table 2. Baseline Characteristics of Patients With and Without Any VHD, Right-Sided VHD, and Rheumatic Mitral Stenosis

<table>
<thead>
<tr>
<th></th>
<th>A, No VHD (n=14162)</th>
<th>B, VHD (n=3950)</th>
<th>C, Right-Sided VHD (n=165)</th>
<th>D, Mitral Stenosis VHD (n=193)</th>
<th>Bonferroni-Adjusted P Value, B vs A</th>
<th>Bonferroni-Adjusted P Value, C vs A</th>
<th>Bonferroni-Adjusted P Value, D vs A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent AF, n (%)</td>
<td>4448 (31.4)</td>
<td>1341 (34.0)</td>
<td>52 (31.5)</td>
<td>72 (37.5)</td>
<td>0.01</td>
<td>1.0000</td>
<td>0.26</td>
</tr>
<tr>
<td>Age, y</td>
<td>72.0 (66.0, 77.0)</td>
<td>74.0 (68.0, 79.0)</td>
<td>73.0 (67.0, 79.0)</td>
<td>66.0 (56.0, 76.0)</td>
<td>0.01</td>
<td>0.10</td>
<td>0.01</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>4991 (35.2)</td>
<td>1607 (40.7)</td>
<td>71 (43.0)</td>
<td>115 (59.6)</td>
<td>0.01</td>
<td>0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>CrCl at baseline, mL/min</td>
<td>69.0 (54.0, 87.7)</td>
<td>65.8 (51.0, 83.7)</td>
<td>67.1 (52.9, 82.0)</td>
<td>67.4 (53.5, 85.3)</td>
<td>0.01</td>
<td>0.28</td>
<td>1.00</td>
</tr>
<tr>
<td>Moderate renal impairment, n (%)</td>
<td>2480 (17.5)</td>
<td>863 (21.8)</td>
<td>33 (20.0)</td>
<td>38 (19.7)</td>
<td>0.01</td>
<td>0.81</td>
<td>1.00</td>
</tr>
<tr>
<td>History of heart failure, n (%)</td>
<td>4223 (29.8)</td>
<td>1570 (39.7)</td>
<td>58 (35.2)</td>
<td>89 (46.1)</td>
<td>0.01</td>
<td>0.27</td>
<td>0.01</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>3749 (26.5)</td>
<td>1285 (32.5)</td>
<td>51 (30.9)</td>
<td>42 (21.8)</td>
<td>0.01</td>
<td>0.40</td>
<td>0.42</td>
</tr>
<tr>
<td>History of myocardial infarction, n (%)</td>
<td>2292 (16.2)</td>
<td>713 (18.1)</td>
<td>26 (15.8)</td>
<td>20 (10.4)</td>
<td>0.02</td>
<td>1.00</td>
<td>0.09</td>
</tr>
<tr>
<td>Vitamin K antagonist experienced, n (%)</td>
<td>8516 (60.1)</td>
<td>2673 (67.7)</td>
<td>121 (73.3)</td>
<td>117 (60.6)</td>
<td>0.01</td>
<td>0.01</td>
<td>1.00</td>
</tr>
<tr>
<td>History of stroke/SEE/TIA, n (%)</td>
<td>3078 (21.7)</td>
<td>875 (22.2)</td>
<td>30 (18.2)</td>
<td>76 (39.4)</td>
<td>1.00</td>
<td>0.54</td>
<td>0.01</td>
</tr>
<tr>
<td>CHADS2 score, n (%)</td>
<td>2.0 (1.0, 3.0)</td>
<td>2.0 (1.0, 3.0)</td>
<td>2.0 (1.0, 3.0)</td>
<td>2.0 (2.0, 3.0)</td>
<td>0.01</td>
<td>1.00</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data are n (%) for categorical variables and median (quartile 1, 3) for continuous variables. AF indicates atrial fibrillation; CrCl, creatinine clearance; SEE, systemic embolic event; TIA, transient ischemic attack; and VHD, valvular heart disease.

*Ccr, 30 to <50 mL/min.
artery disease, hypertension requiring medical treatment, presence of a cardioverter-defibrillator, presence of a pacemaker, peripheral artery disease, history of myocardial infarction, history of stroke/SEE/transient ischemic attacks, and CHADS2 score.

Baseline characteristics and outcomes of patients with exclusively right-sided VHD, defined as patients with only tricuspid or pulmonary regurgitation or insufficiency, were then compared with those of patients without any form of VHD. Additionally, patients with mitral stenosis were identified, and their baseline characteristics and outcomes were compared with those of patients without any form of VHD. For both subgroups, the risk of having an event compared with patients without VHD is summarized as unadjusted HRs estimated with Cox proportional hazards models.

Subsequently, the patients who were stratified by the presence or absence of any form of VHD were further stratified into either D150 or D110 and were then compared with patients receiving warfarin. Patient outcomes were summarized by annualized event rates and HRs estimated from Cox regressions that included treatment assignment, VHD status, and an interaction between treatment and VHD status.

For all baseline comparisons, continuous variables are summarized by their median and first and third quartiles and tested with Wilcoxon rank-sum tests; categorical variables are described by their number and percent and compared by use of \( \chi^2 \) tests. When appropriate, analyses were adjusted for multiple comparisons with the Bonferroni correction. All analyses were 2 sided, and values of \( P < 0.05 \) were considered significant. Statistical analyses were conducted by the

### Table 3. Comparison of Baseline Characteristics for Patients With and Without VHD at Baseline by Treatment Group in the RE-LY Trial

<table>
<thead>
<tr>
<th>VHD</th>
<th>A, D110 (n=6014)</th>
<th>B, D150 (n=6076)</th>
<th>C, Warfarin (n=6022)</th>
<th>Bonferroni-Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A vs C</td>
<td>B vs C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>74.00 (68.00, 78.00)</td>
<td>74.00 (67.00, 79.00)</td>
<td>74.00 (68.00, 79.00)</td>
<td>0.68 1.00</td>
</tr>
<tr>
<td>No</td>
<td>72.00 (66.00, 77.00)</td>
<td>72.00 (66.00, 77.00)</td>
<td>72.00 (67.00, 77.00)</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>485 (37.5)</td>
<td>560 (41.4)</td>
<td>562 (43.1)</td>
<td>0.08 0.8</td>
</tr>
<tr>
<td>No</td>
<td>1664 (35.2)</td>
<td>1676 (35.5)</td>
<td>1651 (35.0)</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27.64 (24.45, 31.31)</td>
<td>27.73 (24.44, 31.57)</td>
<td>27.64 (24.68, 31.99)</td>
<td>0.53 1.00</td>
</tr>
<tr>
<td>No</td>
<td>28.04 (24.98, 31.66)</td>
<td>27.89 (25.00, 31.59)</td>
<td>28.03 (24.98, 31.75)</td>
<td>1.00 1.00</td>
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<tr>
<td>CrCl at baseline, mL/min</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>66.66 (50.52, 84.55)</td>
<td>65.40 (51.72, 83.11)</td>
<td>66.07 (51.05, 83.53)</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>No</td>
<td>69.35 (53.82, 87.89)</td>
<td>68.49 (53.34, 87.68)</td>
<td>69.20 (54.65, 87.52)</td>
<td>0.98 0.37</td>
</tr>
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<td>Moderate renal impairment, n (%)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>295 (23.8)</td>
<td>283 (21.6)</td>
<td>285 (22.5)</td>
<td>1.00 1.00</td>
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<tr>
<td>No</td>
<td>841 (18.6)</td>
<td>873 (19.3)</td>
<td>766 (17.0)</td>
<td>0.102 0.012</td>
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<td>History of heart failure, n (%)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>538 (41.6)</td>
<td>521 (38.5)</td>
<td>511 (39.2)</td>
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<tr>
<td>No</td>
<td>1399 (29.6)</td>
<td>1413 (29.9)</td>
<td>1411 (29.9)</td>
<td>1.00 1.00</td>
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<tr>
<td>History of diabetes mellitus, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>298 (23.1)</td>
<td>320 (23.7)</td>
<td>316 (24.2)</td>
<td>1.00 1.00</td>
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<tr>
<td>No</td>
<td>1111 (23.5)</td>
<td>1082 (22.9)</td>
<td>1094 (23.2)</td>
<td>1.00 1.00</td>
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<td>Coronary artery disease, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>426 (33.0)</td>
<td>456 (33.7)</td>
<td>403 (30.9)</td>
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<tr>
<td>No</td>
<td>1235 (26.2)</td>
<td>1254 (26.6)</td>
<td>1260 (26.7)</td>
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<td>Hypertension requiring medical treatment, n (%)</td>
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<tr>
<td>Yes</td>
<td>988 (76.5)</td>
<td>1051 (77.7)</td>
<td>1012 (77.5)</td>
<td>1.00 1.00</td>
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<tr>
<td>No</td>
<td>3750 (79.4)</td>
<td>3744 (79.3)</td>
<td>3738 (79.2)</td>
<td>1.00 1.00</td>
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<tr>
<td>History of myocardial infarction, n (%)</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>251 (19.4)</td>
<td>250 (18.5)</td>
<td>212 (16.2)</td>
<td>0.06 0.26</td>
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<tr>
<td>No</td>
<td>757 (16.0)</td>
<td>779 (16.5)</td>
<td>756 (16.0)</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>History of stroke/SEE/TIA, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>279 (21.6)</td>
<td>310 (22.9)</td>
<td>286 (21.9)</td>
<td>1.00 1.00</td>
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<tr>
<td>No</td>
<td>1029 (21.8)</td>
<td>1048 (22.2)</td>
<td>1001 (21.2)</td>
<td>1.00 0.25</td>
</tr>
<tr>
<td>CHADS² score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.00 (1.00, 3.00)</td>
<td>2.00 (1.00, 3.00)</td>
<td>2.00 (1.00, 3.00)</td>
<td>0.55 1.00</td>
</tr>
<tr>
<td>No</td>
<td>2.00 (1.00, 3.00)</td>
<td>2.00 (1.00, 3.00)</td>
<td>2.00 (1.00, 3.00)</td>
<td>1.00 1.00</td>
</tr>
</tbody>
</table>

Data are n (%) for categorical variables and median (quartile 1, 3) for continuous variables. CrCl indicates creatinine clearance; D110, dabigatran 110 mg; D150, dabigatran 150 mg; RE-LY, Randomized Evaluation of Long-term Anticoagulant Therapy; SEE, systemic embolic event; TIA, transient ischemic attack; and VHD, valvular heart disease.

*CrCl, 30 to <50 mL/min.
Baseline Characteristics

Of the 18,113 patients randomized in the RE-LY trial, 3,950 (21.8%) had VHD as defined by the study definition and as determined by the local site investigator. The majority (3,101, 17.1%) had mitral regurgitation, and 817 (4.5%) had aortic regurgitation, 471 (2.6%) had aortic stenosis, 1,179 (6.5%) had tricuspid regurgitation, and 193 (1.1%) had mild mitral stenosis. Regardless of drug assignment, patients with VHD were older, were more often female, and more often had congestive heart failure, coronary artery disease, moderate renal impairment (creatinine clearance, 30 to <50 mL/min) and higher CHADS2 scores compared with patients without VHD. They also more frequently had a history of myocardial infarction, persistent AF, and prior vitamin K antagonist use (Table 2).

For patients with exclusive right-sided valve lesions compared with patients without any VHD at baseline, the only difference was an increase in vitamin K–experienced patients with patients without VHD. They also more frequently had a history of myocardial infarction, persistent AF, and prior vitamin K antagonist use (Table 2).

Patients with mitral stenosis at baseline were younger, were more often female, and more often had a prior stroke and history of heart failure compared with patients without any VHD (Table 2).

Patients were stratified on the basis of the presence or absence of any VHD and whether they were assigned to 1 of the 2 doses of dabigatran. The baseline characteristics of the 2 dabigatran cohorts were compared with those of the warfarin cohort. The only difference was seen in patients with moderate renal impairment: Patients assigned to D150 had moderate renal impairment more often than patients assigned warfarin in the group without any VHD (Table 3).

Clinical Outcomes

Regardless of treatment assignment, the risk of stroke and SEE was not significantly different between patients with and without any VHD (HR, 1.09; 95% confidence interval [CI], 0.88–1.33; P=0.43; Figure 1 and Table 4). Patients assigned to D150 had significantly lower risk of stroke/SEE compared with patients taking warfarin in the VHD group (HR, 0.59; 95% CI, 0.37–0.93; P=0.021) and the group without VHD (HR, 0.67; 95% CI, 0.52–0.86; P=0.001; interaction P=0.63). Patients assigned to D110 had similar rates of SEE compared with patients taking warfarin among both patients with VHD (HR, 0.97; 95% CI, 0.65–1.45; P=0.9) and those without VHD (HR, 0.88; 95% CI, 0.70–1.10; P=0.3; interaction P=0.65; Figure 2).

Patients with any VHD had a greater risk of major bleeding compared with those without VHD (propensity score adjusted HR, 1.32; 95% CI, 1.16–1.50; P<0.001; Figure 1 and Table 4).

Table 4. Univariate HRs for VHD Versus No VHD

<table>
<thead>
<tr>
<th>Event Type</th>
<th>HR, VHD vs No VHD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SEE</td>
<td>1.14 (0.94–1.40)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.21 (1.07–1.37)</td>
</tr>
<tr>
<td>Major bleed</td>
<td>1.51 (1.33–1.71)</td>
</tr>
<tr>
<td>ICH</td>
<td>1.24 (0.87–1.78)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; ICH, intracranial hemorrhage; SEE, systemic embolic event; and VHD, valvular heart disease.
The risk of death was comparable between patients with VHD and without any VHD (propensity score adjusted HR, 1.09; 95% CI, 0.96–1.23; P = 0.18). Total mortality was similar in patients assigned to both doses of dabigatran and warfarin regardless of VHD status (Figure 3).

Compared with patients assigned to warfarin, patients randomized to D110 had significantly lower rates of major bleeding both with VHD (HR, 0.73; 95% CI, 0.56–0.95; P = 0.017) and without any VHD (HR, 0.84; 95% CI, 0.71–0.99; P = 0.042; interaction P = 0.38; Figure 4). Similar rates of major bleeds were seen in patients assigned to D150 compared with warfarin either with VHD (HR, 0.82; 95% CI, 0.64–1.06; P = 0.12) or without any VHD (HR, 0.98; 95% CI, 0.83–1.15; P = 0.8; interaction P = 0.25).

There was no difference in rates of intracranial hemorrhage for patients with and without VHD (HR, 1.20; 95% CI, 0.83–1.74; P = 0.3). Regardless of the presence of VHD, patients assigned to either dose of dabigatran had significantly lower risk of intracranial bleeding compared with warfarin (Figure 5).

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For patients with exclusive right-sided valve lesions, outcomes were similar to outcomes in patients without valvular disease (Figure 6).

There was no difference between patients with rheumatic mitral stenosis and patients without any form of heart valve disease in terms of outcomes (Figure 6).

**DISCUSSION**

A large number of patients with AF have VHD and therefore are often seen in routine clinical practice. Hence, it is important to emphasize that many patients with VHD were included in RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE-AF (Effective Anticoagulation With Factor XA Next Generation in Atrial Fibrillation; Table 1). To compare and place these pivotal trials into perspective, RE-LY had 3950 (21.8%) patients with VHD, which included mitral regurgitation (3101 patients), aortic regurgitation (817), aortic stenosis (471), tricuspid regurgitation (1179), and mild mitral stenosis (193). In ROCKET AF, 2003 patients (14.1%) had VHD, referred to as significant valvular disease, which included mitral regurgitation (1756), aortic regurgitation (486), aortic stenosis (215), and other valve conditions (11). In the ARISTOTLE...
trial, 4808 patients (26.4%) had VHD, which included moderate mitral regurgitation (3526), mitral stenosis (131), aortic regurgitation (887), aortic stenosis (384), tricuspid regurgitation (2124), and valve surgery (251).

The definition of nonvalvular AF in each trial, which importantly led to the approval of their respective NOAC, was based on the exclusion of certain valve conditions, which were different in each trial (Table 1). The distinction between prosthetic valves and mechanical valves is important. Prosthetic valves included bioprosthetic valves but excluded mechanical valves (Table 1).

In the 3 trials for which post hoc analyses of patients with VHD have been conducted, the baseline characteristics of patients with VHD reflected a higher cardiovascular risk than those of patients without VHD. To compare, in the RE-LY trial, patients with any VHD had more heart failure (P<0.001), renal impairment (P<0.001), and persistent AF (P<0.002) and higher CHADS2 score (2.3 versus 2.1; P<0.001). In ROCKET AF, patients with VHD were older (P<0.0001) and had more heart failure (P<0.0001), coronary disease/myocardial infarction (P<0.0001), and persistent AF (P<0.05) but had similar CHADS2 (3.5 versus 3.5; P=0.98) and HAS-BLED (2.8 versus 2.8; P=0.18) scores. In ARISTOTLE, patients with VHD were older (P<0.0001); had more previous myocardial infarction (P<0.0001), heart failure (P<0.0001), and renal impairment (P<0.0001); had more persistent or permanent AF (P<0.0001); and had a higher mean CHADS2 score (2.2 versus 2.1; P<0.001). Accordingly, in ARISTOTLE, Kaplan-Meier estimates of rates of strokes and SEEs were 3.2% versus 2.4% in patients with and without VHD, and in ROCKET AF, rates of strokes and SEEs per 100 patient-years were 2.23 versus 2.09. We acknowledge that although the trend would probably hold if the same type of estimates were obtained for each study, a direct comparison of Kaplan-Meier estimates with annualized event rates can be questioned.

RE-LY and ARISTOTLE patients derived similar benefit from their respective NOAC (dabigatran and apixaban) compared with warfarin without any interaction with VHD status (Figures 2–5). However, in the ROCKET AF trial, there was a significant interaction between rivaroxaban and VHD in terms of the risk of major bleeding (P=0.01).

In RE-LY, D110 was associated with significantly less major bleeding compared with warfarin, whereas D150 had a rate of major bleeding similar to that of warfarin in both VHD and non-VHD patients (Figure 4). In ROCKET AF, patients with VHD taking rivaroxaban had more major bleeds compared with those taking warfarin (Figure 4). In ARISTOTLE, apixaban treatment was associated with less major bleeding compared with warfarin regardless of VHD status (Figure 4).

The rate of intracranial hemorrhage in each trial was lower among patients randomized to dabigatran, rivaroxaban, or apixaban compared with warfarin regardless of the presence of VHD (Figure 5).

The evidence for the value of NOACs in patients with VHD as defined in the 3 studies is very strong. Accordingly, in the current European guidelines, NOAC therapy is indicated in all forms of valvular disease, including valve repair, severe aortic stenosis, bioprosthetic valves, mitral valve repair, percutaneous transluminal aortic valvuloplasty, and transcatheter aortic valve replacement, with the exception of mechanical heart valves and moderate to severe mitral stenosis. The most recent American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines recommend oral anticoagulation (options include warfarin, dabigatran, rivaroxaban, or apixaban) for patients with nonvalvular AF (as defined in Table 1) with a CHA2DS2-VASc score of ≥2 (Class 1). The guidelines recommend that patients with mechanical heart valves should be managed only with warfarin (Class 1).

In the RE-LY trial, 165 patients had right-sided valve lesions as their exclusive valve lesion, and 192 patients had mitral stenosis presumed to be rheumatic. For the former, the numbers were small but the differences were minor: more anticoagulation use at baseline and higher bleeding rates during the course of the trial. Interestingly, the former had the characteristics of a rheumatic heart disease population: younger, female, with heart failure...
and a history of transient ischemic attack and stroke, supporting our assumption that the patients with mitral valve stenosis had suffered from rheumatic heart disease.

**Limitations**

This is a retrospective analysis of patients with and without VHD enrolled in the RE-LY trial. Case report forms used in the study were not prospectively designed to support an analysis of VHD cause and severity. Although all the pivotal trials used warfarin as the comparator, the mean time in therapeutic range for the 3 trials varied from 55% in ROCK-ET AF to 62% for ARISTOTLE and 64% for RE-LY, emphasizing the limitations of comparisons when indirect. Despite these limitations, the results were remarkably consistent.

**Conclusions**

The pivotal trials comparing NOACs and warfarin characterized the included patients as having nonvalvular AF when in fact many patients with all forms of valvular disease were studied. In RE-LY, approximately one fifth of the patients with nonvalvular AF were classified as having VHD. The presence of VHD did not influence comparison of dabigranat at either dose with warfarin in terms of stroke or systemic embolism, major bleed, death, or intracranial hemorrhage.

**SOURCES OF FUNDING**

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**DISCLOSURES**

Dr Ezekowitz has served as a consultant for AstraZeneca, Eisai, Pozen Inc, Boehringer Ingelheim, ARYx Therapeutics, Pfizer, Sanofi, Bristol-Myers Squibb, Portola, Daiichi Sankyo, Medtronic, Merck, Johnson & Johnson, Gilead, Janssen Scientific Affairs, and Armetheon. He has received grants from Boehringer Ingelheim, Bayer, Daiichi Sankyo, Pfizer, and Bristol-Myers Squibb. Drs Noack, Bruckmann, and Reilly are employees of Boehringer Ingelheim. Dr Clements was formerly employed by Boehringer Ingelheim GmbH & Co, KG, Germany. Dr Connolly has received research grant money from Boehringer Ingelheim, Sanofi-Aventis, Portola, and Bristol-Myers Squibb; has served on a speakers bureau for Boehringer Ingelheim, Sanofi-Aventis, Portola, and Merck. Dr Yusuf has received research grant money/honoraria from Boehringer Ingelheim; Sanofi-Aventis, Portola, and Pfizer; and Bristol-Myers Squibb; received honoraria from Boehringer Ingelheim, AstraZeneca; GlaxoSmithKline, Eli Lilly, Schering-Plow, and Bristol-Myers Squibb; and has served as consultant for Boehringer Ingelheim, Regado Biosciences, Athera Biosciences, AstraZeneca, GlaxoSmithKline, Eli Lilly, Schering-Plow, and Bristol-Myers Squibb. The other authors report no conflicts.

**REFERENCES**


Comparison of Dabigatran and Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulant Therapy)

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Carolyn: Welcome to Circulation on the Run, your weekly podcast summary and backstage pass to the journal and its editors. I'm Dr. Carolyn Lam, Associate Editor from the National Heart Center and Duke National University of Singapore.

In just a moment, we are going to be discussing the feature paper on results of the RE-LY trial in patients with valvular heart disease. Yes, you heard me right, this means dabigatran versus warfarin in patients with atrial fibrillation and valvular heart disease. You need to listen to this discussion with first author Dr. Michael Ezekowitz, but first here is a summary of this week's issue.

In the first study, Dr. Norby and colleagues from the School of Public Heath University of Minnesota assessed trajectories of cardiovascular risk factors and the incidence of atrial fibrillation over 25 years in the ARIC study or the Atherosclerosis Risk in Communities Study. They first assessed the trajectories of cardiovascular risk factors in more than 2,400 individuals with incident atrial fibrillation and more than 6,400 matched controls. Next, they determined the association of those risk factor trajectories with the incidence of new atrial fibrillation among more than 10,500 individuals free of atrial fibrillation at baseline.

The main finding was that stroke, myocardial infarction and heart failure risk increase steeply during the time close to diagnosis of atrial fibrillation. All cardiovascular risk factors were elevated in atrial fibrillation cases compared to controls more than 15 years prior to the diagnosis. A trajectory analysis showed not only the presence of the risk factors such hypertension and obesity, but also their duration which was more informative in determining the risk of atrial fibrillation compared to a one time clinical measurement.

Finally, they identified diverse and distinct trajectories for the risk factors findings that carry implications for the different roles of different risk factors in the pathogenesis of atrial fibrillation. The findings of this very significant study also highlight the need to establish preventive strategies that address risk factors decades before atrial fibrillation diagnosis.

The next study is by first author Dr. van der Valk and corresponding author Dr. Strauss from the Academic Medical Center in Amsterdam. These authors aimed to better understand the underlying mechanisms responsible for atherogenicity of lipoprotein a or LPa. The authors achieved this aim by a combination of three approaches. First, in vivo magnetic resonance imaging using 18F-FDG PET/CT and SPECT to measure atherosclerotic burden, arterial wall inflammation and monocyte trafficking to the arterial wall. Secondly, ex vivo analysis of monocytes using facts analysis, inflammatory stimulation assays and trans endothelial migration assays. Third, in vitro studies on monocytes using an in vitro model for trained immunity.

Their main findings were that, firstly, individuals with elevated LPa had increased arterial wall inflammation in vivo. Secondly, that monocytes from these individual remain in a long lasting activated state ex vivo, and finally, that LPa elicited a pro-
inflammatory response in healthy monocytes in vitro, an effect that was markedly attenuated by removing or inactivating oxidized phospholipids on LPa.

In summary, this study nicely shows that LPa induces monocyte trafficking to the arterial wall and mediates pro-inflammatory responses through its oxidized phospholipid content. The clinical implications are therefore, that oxidation's specific epitope targeted therapy using for example specific antibodies as single gene antibodies may bear clinical potential to modulate the arthrogenic impact of LPa.

The final study is from first author Dr. Mazen, and corresponding author Dr. Ouzounian from Toronto General Hospital and University of Toronto in Ontario, Canada. These authors sought to compare the long term outcomes of patients undergoing the Ross procedure compared to mechanical aortic valve replacement in a propensity match cohort study of 208 pairs followed for a mean of 14 years.

They found long term survival and freedom from re-intervention were comparable between the Ross procedure and mechanical aortic valve replacement. Of note however, the Ross procedure was associated with improved freedom from cardiac and valve related mortality, as well as a significant reduction in the incidence of stroke and major bleeding. This paper provides important evidence that supports continued used of the Ross procedure in properly selected young adult patients in specialized centers.

What this means is having experienced surgical teams dedicated to mastering the technique and committed to carefully following up the patients for possible late complications. This and more is discussed in a provocative editorial by Dr. Schaff from Mayo Clinic Rochester, Minnesota who provocatively entitled his editorial 'The Ross Procedure: Is it the Preferred Procedure or Double, Double Toil and Trouble?'

Those were all summaries, now for our featured paper.

I am so excited to be joined from all over the world to discuss the featured paper today, and that is on the comparison of dabigatran versus warfarin in patients with atrial fibrillation and valvular heart disease. To discuss this first we have, first and corresponding author, Dr. Michael Ezekowitz from the Sidney Kimmel Medical College at Thomas Jefferson University and Lankenau Medical Center in Philadelphia, as well as from the Cardiovascular Research Foundation in New York. Welcome Michael.

Michael: Thank you very much.

Carolyn: Michael, you're calling from South Africa aren't you?

Michael: I am indeed.

Carolyn: That's wonderful. We're very honored to have Dr. Shinya Goto Sensei, Associate Editor of Circulation from Tokai University Japan. Hello Shinya.
Shinya: Hello Carolyn, thank you very much for your invitation to such an excited podcast. I enjoy podcast every week.

Carolyn: I love this and it is extremely exciting and the most global discussion that we have had so far, with calling in Japan and Singapore and South Africa. Indeed it's because we're discussing a very important problem globally. Michael first, when we talk about the RE-LY trial and the NOAC trials, we're always associating them with non-valvular atrial fibrillation, and yet your topic is discussing valvular heart disease from RE-LY. Can you please start by clarifying that?

Michael: I think the reason we wrote this paper is that there is a misunderstanding of the patient populations that was studied in all the NOAC trials because they were characterized as having non-valvular atrial fibrillation. That's only partially true because in all the trials, patients with mechanical heart valve and hemodynamically significant mitral stenosis were excluded, and yet there were many patients with valvular disease that were included. In the RE-LY trial which is the focus of this particular paper, 25% of the patients had some form of valvular disease that were recruited into the study. So the term non-valvular is misleading.

Carolyn: That is such an important clarification, and it's an issue that I see a lot in Singapore. Frankly, lots of patients with atrial fibrillation have some valve disease even if you exclude prosthetic valves, significant mitral stenosis or valvular heart disease requiring intervention. We're very clear not that this is the patient population you're referring to. Shinya, I want to bring you into this. I see lots of these patients, how about you?

Shinya: The same. Majority of patients have valvular heart disease, small mitral regurgitation is very common. We are excluding only clinically overt mitral stenosis and basically mechanical heart valve in all the newest trials. As Michael pointed out, it is very important to correct misunderstanding. Non-valvular atrial fibrillation, we used in the clinical trial is all atrial fibrillation except clinical overt mitral stenosis and prosthetic for mechanical heart valve.

Carolyn: Exactly. A great foundation for us to get our understand right before we discuss the findings. Michael, could you please give us the top line result and tell us what do the results mean for your own clinical practice?

Michael: Basically, it means that the patients with valvular heart disease that were included in the trial, and these included patients with mitral regurgitation with was the most common lesion, mixed aortic valve disease, tricuspid regurgitation, and also it turned out that there were 192 patients that had mild mitral stenosis. Those with mitral stenosis were presumed to be rheumatic in ideology, and they did have a profile of having rheumatic heart disease, that there were more females, they were younger, there was a high incidence of heart failure and a high incidence of TIA and stroke.

The bottom line here is whether the patients had mild mitral stenosis or the other forms of valvular disease that I just mentioned, that they benefited in an identical
fashion from the 150 milligram BID dose of dabigatran and the one 110 milligram BID
dose of dabigatran as those patients without any valvular disease. The bottom line is
that clinicians can use dabigatran with equal confidence in these patients with
valvular disease as in patients without valvular disease.

Carolyn: Thank you Michael, that was very reassuring and something that is very clinically
important. Shinya, I'm going to ask a different question. First, maybe your take on the
findings, and secondly, what was it like handling this paper across the globe as the
Associate Editor Managing this?

Shinya: That is a very important point. The past as Michael pointed out, this paper is very
important to remind the clinician of non-valvular atrial fibrillation is not really non-
valvular atrial fibrillation, and there is no difference between valvular atrial fibrillation
except mitral stenosis and prosthetic valve. The result is similar to non-valvular atrial
fibrillation in regard to the effect of dabigatran or by warfarin. That is the one point I
have to assure. As a part, it is very important. We are now including many patients
not limited in that North America, Europe. We are participating a huge number of
patients from Asia. The results is applicable to the global level. We are now leading in
that global evidence-based world and RE-LY is one of the good example for the global
trial testing the hypothesis with [inaudible 00:13:58] over warfarin.

Michael made a very good summary of that, not only limited to RE-LY, he talked
about as our trial like ARISTOTLE and the ROCKET trial. All of the NOAC trial include
patient who is valvular heard disease, and the exclusion criteria is a little bit different.
Michael beautifully summarized that difference in the table, in his paper. There is a
strong intention to publish this paper integration from all the editorial of old member.
This is a very nice paper.

Michael: He's been very kind, that's very nice. That's true. In fact, the results in RE-LY were
compared in an indirect fashion with the other trials, ROCKET and ARISTOTLE, through
have published similar papers on patients with and without valvular heart disease.
Just in summary, the bottom line is that this finding in RE-LY is highly reproducible in
the other two trials so this is an important finding that is reproducible and true of the
three novel agents that had looked at this in detail.

The other point that was raised is that there were differences in the exclusion criteria
in these trials, but at the end of the day, the Europeans and the Americans in terms of
guidelines, had fairly similar recommendation. For instance in the United States, it
was felt that all patients with valvular disease could be anti-coagulated with the novel
agent unless they had rheumatic mitral stenosis, mechanical or bioprosthetic heart
valves, or patients that had undergone a prior mitral valve repair. The emphasis was
that all other patients could be included.

The Europeans differed slightly and that they agreed that mechanical prosthetic valve
and moderate to severe mitral stenosis should be excluded, but they were somewhat
more global in recommending inclusions of all other valvular conditions. There is a
slight difference then between the European and the American recommendations and guidelines.

Carolyn: On that note of looking across the world at the guidelines and what these results mean, it really leaves me to congratulate you Michael on such an excellent paper, and Shinya for just managing this paper so well.

Michael: Thank you.

Shinya: Thank you very much for your invitation. Bye-bye.

Carolyn: You've been listening to Circulation on the Run. Thank you for joining us today.
유의한 승모판협착을 제외한 판막질환이 동반된 심방세동 환자에서 다비가트란은 와파린을 대체할 수 있다
: RE-LY 연구 사후분석 결과

최 기 준 교수 서울아산병원 심장내과

초록

배경
RE-LY(Randomized Evaluation of Long-term Anticoagulation Therapy) 연구에서는 18,113명의 심방세동 환자를 대상으로, 다비가트란 150mg 및 110mg 1일 2회 복용과 와파린의 효과를 비교 분석하였다. 연구대상에서 금속인공판막(prosthetic heart valve), 유의한 승모판협착, 시술을 요하는 판막질환 (valvular heart disease) 환자들은 제외하였으며, 그 외 나머지 판막질환 환자들은 포함하였다.

방법
본 연구는 RE-LY 연구의 사후분석(post hoc analysis) 연구이다.

결과
본 연구는 RE-LY 연구에 포함된 3,950명의 판막질환 환자들을 대상으로 분석하였으며, 이 중에는 승모판판막질환 3,101명, 삼차판판막질환 1,179명, 대동맥판판막질환 817명, 대동맥판협착 471명 그리고 경도의 승모판협착 환자 193명이 포함되었다. 기저분석에서 판막질환 환자들은 심부전, 관상동맥질환, 신기능 저하, 자속성 심방세동의 빈도가 비판막질환 환자들에 비해 높았다. 그리고 주요 출혈의 발생률은 높았으나(HR, 1.32; 95% CI, 1.16-1.5), 뇌경색이나 전신색소증의 빈도는 비슷하였다(HR, 1.09; 95% CI, 0.88-1.33).
다비가트란 110mg 복용군의 주요출혈 발생은 와파린군에 비해 적었고(판막절환: HR, 0.73; 95% CI, 0.56-0.95; 비판막질환: HR, 0.84; 95% CI, 0.71-0.99), 다비가트란 150mg 복용군의 주요출혈 발생은 와파린군과 비슷하였다(판막절환: HR, 0.82; 95% CI, 0.64-1.06; 비판막질환: HR, 0.98; 95% CI, 0.83-1.15). 다비가트란 150mg 복용군은 판막질환(HR, 0.59; 95% CI, 0.37-0.93) 또는 비판막질환 환자(HR, 0.67; 95% CI, 0.52-0.86) 모두에서 뇌경색이나 전신색소증의 빈도가 와파린군에 비해 적었다. 반면, 다비가트란 110mg 복용군에서의 뇌경색이나 전신색소증의 빈도는 판막질환 환자와 관계없이 와파린군과 비슷하였고(판막절환: HR, 0.97; 95% CI, 0.65-1.45; 비판막질환: HR, 0.88; 95% CI, 0.70-1.10).
두개나 출혈이나 사망률은 판막질환 환자와 관계없이 다비가트란 150mg 복용군과 110mg 복용군 모두에서 와파린에 비해 낮았다.

결론
심방세동 환자에서 유의한 승모판협착 외의 판막질환 환자는 다비가트란과 와파린의 치료효과 비교에 영향을 미치지 않았다.
Comparison of Dabigatran and Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease

The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulant Therapy)

BACKGROUND: The RE-LY trial (Randomized Evaluation of Long-Term Anticoagulant Therapy) compared dabigatran 150 and 110 mg twice daily with warfarin in 18113 patients with atrial fibrillation. Those with prosthetic heart valves, significant mitral stenosis, and valvular heart disease (VHD) requiring intervention were excluded. Others with VHD were included.

METHODS: This is a post hoc analysis of the RE-LY trial.

RESULTS: There were 3950 patients with any VHD: 3101 had mitral regurgitation, 1179 with tricuspid regurgitation, 817 had aortic regurgitation, 471 with aortic stenosis, and 193 with mild mitral stenosis. At baseline, patients with any VHD had more heart failure, coronary disease, renal impairment, and persistent atrial fibrillation. Patients with any VHD had higher rates of major bleeds (hazard ratio [HR], 1.32; 95% confidence interval [CI], 1.16–1.5) but similar stroke or systemic embolism event rates (HR, 1.09; 95% CI, 0.88–1.33). For patients receiving dabigatran 110 mg, major bleed rates were lower than for patients taking warfarin (HR, 0.73; 95% CI, 0.56–0.95 with VHD; HR, 0.84; 95% CI, 0.71–0.99 without VHD), and major bleed rates for dabigatran 150 mg were similar to those for warfarin in patients with VHD (HR, 0.82; 95% CI, 0.64–1.06) or without VHD (HR, 0.98; 95% CI, 0.83–1.15). For dabigatran 150 mg, stroke/systemic embolic event rates were lower compared with warfarin in those with VHD (HR, 0.59; 95% CI, 0.37–0.93) and those without VHD (HR, 0.67; 95% CI, 0.52–0.86), and stroke/systemic embolic event rates were similar for warfarin and dabigatran 110 mg regardless of the presence of VHD (HR, 0.97; 95% CI, 0.65–1.45; and HR, 0.88; 95% CI, 0.70–1.10). Intracranial bleeds and death rates for dabigatran 150 and 110 mg were lower compared with warfarin independently of the presence of VHD.

CONCLUSIONS: The presence of any VHD did not influence the comparison of dabigatran with warfarin.

Clinical Perspective

What Is New?

- The pivotal clinical trials comparing novel oral anticoagulants with warfarin defined the evaluated population as having nonvalvular atrial fibrillation; however, many patients with valve pathology were actually included in the trials, and only patients with highly specific valve disease, that is, prosthetic heart valves and severe mitral stenosis, were excluded.
- In the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulant Therapy), 3950 patients (21.8%) had valvular heart disease. Patients included were those with aortic stenosis, aortic regurgitation, mitral regurgitation, tricuspid valve disease, and mild, presumably rheumatic mitral stenosis.
- This analysis provided an opportunity to compare patients with and without any valve disease and to compare treatments.

What Are the Clinical Implications?

- In this analysis, the comparison of both doses of dabigatran for stroke and systemic embolism, major bleeding, intracranial bleeds, and mortality with warfarin was independent of the presence of valvular heart disease.
- Thus, the clinician can use the approved doses of dabigatran with confidence in patients with valve disease, excluding only those with prosthetic valve disease or patients with hemodynamic significant mitral stenosis.

Table 1. Classification of Nonvalvular AF

<table>
<thead>
<tr>
<th>Study</th>
<th>Excluded Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY1,2</td>
<td>Patients with patients with prosthetic heart valves, significant mitral stenosis and valve disease requiring an intervention before study end</td>
</tr>
<tr>
<td></td>
<td>Included other valve disorders: mitral regurgitation, tricuspid regurgitation, aortic regurgitation, aortic stenosis, and mild mitral stenosis</td>
</tr>
<tr>
<td>ROCKET AF3,4,9</td>
<td>Excluded patients with hemodynamically significant mitral valve stenosis, prosthetic heart valves, and planned invasive interventions with a major risk of uncontrolled bleeding</td>
</tr>
<tr>
<td></td>
<td>Included all other valvular heart disease conditions and/or annuloplasty with or without a prosthetic ring, commissurotomy, and valvuloplasty</td>
</tr>
<tr>
<td>ARISTOTLE5,6,10</td>
<td>Excluded patients with clinically significant moderate or severe mitral stenosis and prosthetic heart valves</td>
</tr>
<tr>
<td></td>
<td>Included all other valvular heart disease conditions and/or moderate mitral regurgitation, aortic regurgitation, aortic stenosis, tricuspid regurgitation, and valve surgery</td>
</tr>
<tr>
<td>ENGAGE-AF-TIMI 487,8</td>
<td>Excluded patients with moderate or severe mitral stenosis, unresected atrial myxoma, and mechanical heart valve</td>
</tr>
<tr>
<td></td>
<td>Included all other valvular heart disease conditions and/or bioprosthesis heart valves and valve repair</td>
</tr>
<tr>
<td>2015 EHRA AF management guidelines11</td>
<td>Nonvalvular AF is classified as the absence of mechanical prosthetic heart valves and moderate to severe mitral stenosis (usually of rheumatic origin)</td>
</tr>
<tr>
<td>2014 AHA/ACC/HRS guidelines12</td>
<td>Nonvalvular AF is classified as the absence of rheumatic mitral stenosis and mechanical or bioprosthetic heart valve or mitral valve repair</td>
</tr>
</tbody>
</table>

Although the clinical trials that evaluated novel oral anticoagulants (NOACs) described the patients as having nonvalvular atrial fibrillation (AF), all the trials actually randomized patients with various valve pathologies, rendering the term nonvalvular AF a misnomer. The definition of nonvalvular AF was a definition of exclusion. Those excluded varied among trials, leading to inconsistencies in the definition of nonvalvular heart disease, resulting in confusion (Table 1) that may cause some clinicians to hesitate before prescribing NOACs to patients with any form of valvular heart disease (VHD). Two post hoc analyses have found that patients with a variety of valve pathologies derive benefit from their respective NOACs. ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) reported their respective experiences in patients with VHD. We report the outcomes of patients with VHD taking dabigatran in the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy).

The primary objective of this post hoc analysis is to compare the outcomes of dabigatran at doses of 110 mg twice daily (D110) and 150 mg twice daily (D150) with those of warfarin in patients with and without VHD. The secondary objective is to compare these results from RE-LY with the post hoc analyses from ROCKET AF and ARISTOTLE to place the accumulating information into perspective.

AHA/ACC/HRS indicates American Heart Association/American College of Cardiology/Heart Rhythm Society; AF, atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; EHRA, European Heart Rhythm Association; ENGAGE-AF-TIMI 48, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction Study 48; RE-LY, Randomized Evaluation of Long-term Anticoagulant Therapy; and ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.
METHODS
The RE-LY trial was a prospective, randomized trial investigating the effectiveness and safety of 2 doses of dabigatran in preventing stroke and systemic embolic events (SEE)s in patients with nonvalvular AF compared with warfarin. The study was funded by Boehringer Ingelheim and was coordinated by the Population Health Research Institute (Hamilton, ON, Canada). Detailed descriptions of the rationale and design of the RE-LY trial have been published previously. All patients who participated in the RE-LY trial were included in this analysis. The appropriate regulatory authorities and ethics committees approved the study. All authors vouch for the accuracy and completeness of the data. This analysis was conducted at the Cardiovascular Research Foundation in New York.

Study Definitions and End Points
Patients with a prosthetic heart valve or hemodynamically significant mitral stenosis or valve disease likely to lead to an intervention before study end were excluded from RE-LY. Patients with all other heart valve conditions were included and were classified as having VHD. In addition, we evaluated patients in 2 subcategories of VHD: patients with exclusive right-sided valve lesions and those with mild mitral stenosis. Patients with mitral stenosis were assumed to have had rheumatic valve disease. The primary efficacy end point was stroke, including hemorrhagic or an SEE. The secondary efficacy end point was total mortality. The main safety end point was major bleeding defined as bleeding with a reduction in hemoglobin of ≥20 g/L, bleeding requiring a transfusion of at least 2 units, or symptomatic bleeding in a critical area or organ, including intracranial bleeds.

Statistical Analysis
This was a post hoc analysis of all patients randomized in the RE-LY trial. All analyses were by intention to treat. Patients were initially characterized by the presence or absence of any form of VHD. Subsequently, patients with exclusive valvular right-sided lesions were identified, as were patients with mitral stenosis. For all groups, the baseline characteristics and their outcomes were compared. The outcomes of the VHD cohort included all forms of VHD and were compared with the outcomes of the non-VHD cohort. The summarized results used annualized event rates with both unadjusted and adjusted hazard ratios (HRs). The adjusted HRs were estimated from a Cox model that included propensity scores as a continuous variable. The propensity scores for VHD status were estimated from a model that included the following covariates: age, sex, race, smoking status, alcohol use, region, body mass index, AF diagnosis, AF type, previous cardioversion, previous atrioventricular node ablation, history of heart failure, diabetes mellitus, coronary

Table 2. Baseline Characteristics of Patients With and Without Any VHD, Right-Sided VHD, and Rheumatic Mitral Stenosis

<table>
<thead>
<tr>
<th></th>
<th>A, No VHD (n=14,162)</th>
<th>B, VHD (n=3,950)</th>
<th>C, Right-Sided VHD (n=165)</th>
<th>D, Mitral Stenosis VHD (n=193)</th>
<th>Bonferroni-Adjusted ( P ) Value, B vs A</th>
<th>Bonferroni-Adjusted ( P ) Value, C vs A</th>
<th>Bonferroni-Adjusted ( P ) Value, D vs A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent AF, n (%)</td>
<td>4448 (31.4)</td>
<td>1341 (34.0)</td>
<td>52 (31.5)</td>
<td>72 (37.5)</td>
<td>0.01</td>
<td>1.00</td>
<td>0.26</td>
</tr>
<tr>
<td>Age, y</td>
<td>72.0 (66.0, 77.0)</td>
<td>74.0 (68.0, 79.0)</td>
<td>73.0 (67.0, 79.0)</td>
<td>66.0 (56.0, 76.0)</td>
<td>0.01</td>
<td>0.10</td>
<td>0.01</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>4991 (35.2)</td>
<td>1607 (40.7)</td>
<td>71 (43.0)</td>
<td>115 (59.6)</td>
<td>0.01</td>
<td>0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>CrCl at baseline, ml/min</td>
<td>69.0 (54.0, 87.7)</td>
<td>65.8 (51.0, 83.7)</td>
<td>67.1 (52.9, 82.0)</td>
<td>67.4 (53.5, 85.3)</td>
<td>0.01</td>
<td>0.28</td>
<td>1.00</td>
</tr>
<tr>
<td>Moderate renal impairment, n (%)</td>
<td>2480 (17.5)</td>
<td>863 (21.8)</td>
<td>33 (20.0)</td>
<td>38 (19.7)</td>
<td>0.01</td>
<td>0.81</td>
<td>1.00</td>
</tr>
<tr>
<td>History of heart failure, n (%)</td>
<td>4223 (29.8)</td>
<td>1570 (39.7)</td>
<td>58 (35.2)</td>
<td>89 (46.1)</td>
<td>0.01</td>
<td>0.27</td>
<td>0.01</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>3749 (26.5)</td>
<td>1285 (32.5)</td>
<td>51 (30.9)</td>
<td>42 (21.8)</td>
<td>0.01</td>
<td>0.40</td>
<td>0.42</td>
</tr>
<tr>
<td>History of myocardial infarction, n (%)</td>
<td>2292 (16.2)</td>
<td>713 (18.1)</td>
<td>26 (15.8)</td>
<td>20 (10.4)</td>
<td>0.02</td>
<td>1.00</td>
<td>0.09</td>
</tr>
<tr>
<td>Vitamin K antagonist experienced, n (%)</td>
<td>8516 (60.1)</td>
<td>2673 (67.7)</td>
<td>121 (73.3)</td>
<td>117 (60.6)</td>
<td>0.01</td>
<td>0.01</td>
<td>1.00</td>
</tr>
<tr>
<td>History of stroke/SEE/TIA, n (%)</td>
<td>3078 (21.7)</td>
<td>875 (22.2)</td>
<td>30 (18.2)</td>
<td>76 (39.4)</td>
<td>1.00</td>
<td>0.54</td>
<td>0.01</td>
</tr>
<tr>
<td>CHADS2 score, n (%)</td>
<td>2.0 (1.0, 3.0)</td>
<td>2.0 (1.0, 3.0)</td>
<td>2.0 (1.0, 3.0)</td>
<td>2.0 (2.0, 3.0)</td>
<td>0.01</td>
<td>1.00</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data are n (%) for categorical variables and median (quartile 1, 3) for continuous variables. AF indicates atrial fibrillation; CrCl, creatinine clearance; SEE, systemic embolic event; TIA, transient ischemic attack; and VHD, valvular heart disease.

*CrCl, 30 to <50 mL/min.
artery disease, hypertension requiring medical treatment, presence of a cardioverter-defibrillator, presence of a pacemaker, peripheral artery disease, history of myocardial infarction, history of stroke/SEE/transient ischemic attacks, and CHADS2 score.

Baseline characteristics and outcomes of patients with exclusively right-sided VHD, defined as patients with only tricuspid or pulmonary regurgitation or insufficiency, were then compared with those of patients without any form of VHD. Additionally, patients with mitral stenosis were identified, and their baseline characteristics and outcomes were compared with those of patients without any form of VHD. For both subgroups, the risk of having an event compared with patients without VHD is summarized as unadjusted HRs estimated with Cox proportional hazards models.

Subsequently, the patients who were stratified by the presence or absence of any form of VHD were further stratified into either D150 or D110 and were then compared with patients receiving warfarin. Patient outcomes were summarized by annualized event rates and HRs estimated from Cox regressions that included treatment assignment, VHD status, and an interaction between treatment and VHD status.

For all baseline comparisons, continuous variables are summarized by their median and first and third quartiles and tested with Wilcoxon rank-sum tests; categorical variables are described by their number and percent and compared by use of \( \chi^2 \) tests. When appropriate, analyses were adjusted for multiple comparisons with the Bonferroni correction. All analyses were 2 sided, and values of \( P<0.05 \) were considered significant. Statistical analyses were conducted by the

<table>
<thead>
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<th>Bonferroni-Adjusted</th>
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<tbody>
<tr>
<td>( P ) Value</td>
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</tbody>
</table>

| Data are n (%) for categorical variables and median (quartile 1, 3) for continuous variables. CrCl indicates creatinine clearance; D110, dabigatran 110 mg; D150, dabigatran 150 mg; RE-LY, Randomized Evaluation of Long-term Anticoagulant Therapy; SEE, systemic embolic event; TIA, transient ischemic attack; and VHD, valvular heart disease. |
RESULTS

Baseline Characteristics

Of the 18,113 patients randomized in the RE-LY trial, 3,950 (21.8%) had VHD as defined by the study definition and as determined by the local site investigator. The majority (3,101, 17.1%) had mitral regurgitation, and 817 (4.5%) had aortic regurgitation, 471 (2.6%) had aortic stenosis, 1,179 (6.5%) had tricuspid regurgitation, and 193 (1.1%) had mild mitral stenosis. Regardless of drug assignment, patients with VHD were older, were more often female, and more often had congestive heart failure, coronary artery disease, moderate renal impairment (creatinine clearance, 30 to <50 mL/min) and higher CHADS2 scores compared with patients without VHD. They also more frequently had a history of myocardial infarction, persistent AF, and prior vitamin K antagonist use (Table 2).

For patients with exclusive right-sided valve lesions compared with patients without any VHD at baseline, the only difference was an increase in vitamin K–experienced patients among patients with right-sided VHD (Table 2).

Patients with mitral stenosis at baseline were younger, were more often female, and more often had a prior stroke and history of heart failure compared with patients without any VHD (Table 2).

Patients were stratified on the basis of the presence or absence of any VHD and whether they were assigned to 1 of the 2 doses of dabigatran. The baseline characteristics of the 2 dabigatran cohorts were compared with those of the warfarin cohort. The only difference was seen in patients with moderate renal impairment: Patients assigned to D150 had moderate renal impairment more often than patients assigned warfarin in the group without any VHD (Table 3).

Clinical Outcomes

Regardless of treatment assignment, the risk of stroke and SEE was not significantly different between patients with and without any VHD (HR, 1.09; 95% confidence interval [CI], 0.88–1.33; P=0.43; Figure 1 and Table 4). Patients assigned to D150 had significantly lower risk of stroke/SEE compared with patients taking warfarin in the VHD group (HR, 0.59; 95% CI, 0.37–0.93; P=0.021) and the group without VHD (HR, 0.67; 95% CI, 0.52–0.86; P=0.001; interaction P=0.63). Patients assigned to D110 had similar rates of SEE compared with patients taking warfarin among both patients with VHD (HR, 0.97; 95% CI, 0.65–1.45; P=0.9) and those without VHD (HR, 0.88; 95% CI, 0.70–1.10; P=0.3; interaction P=0.65; Figure 2).

Patients with any VHD had a greater risk of major bleeding compared with those without VHD (propensity score adjusted HR, 1.32; 95% CI, 1.16–1.50; P<0.001; Figure 1 and Table 4).

<table>
<thead>
<tr>
<th>Table 4. Univariate HRs for VHD Versus No VHD</th>
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<tbody>
<tr>
<td><strong>HR, VHD vs No VHD (95% CI)</strong></td>
</tr>
<tr>
<td>Stroke/SEE</td>
</tr>
<tr>
<td>1.14 (0.94–1.40)</td>
</tr>
<tr>
<td>All-cause mortality</td>
</tr>
<tr>
<td>1.21 (1.07–1.37)</td>
</tr>
<tr>
<td>Major bleed</td>
</tr>
<tr>
<td>1.51 (1.33–1.71)</td>
</tr>
<tr>
<td>ICH</td>
</tr>
<tr>
<td>1.24 (0.87–1.78)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; and SEE, systemic embolic event.
The risk of death was comparable between patients with VHD and without any VHD (propensity score adjusted HR, 1.09; 95% CI, 0.96–1.23; \( P = 0.18 \)). Total mortality was similar in patients assigned to both doses of dabigatran and warfarin regardless of VHD status (Figure 3).

Compared with patients assigned to warfarin, patients randomized to D110 had significantly lower rates of major bleeding both with VHD (HR, 0.73; 95% CI, 0.56–0.95; \( P = 0.017 \)) and without any VHD (HR, 0.84; 95% CI, 0.71–0.99; \( P = 0.042 \); interaction \( P = 0.38 \); Figure 4). Similar rates of major bleeds were seen in patients assigned to D150 compared with warfarin either with VHD (HR, 0.82; 95% CI, 0.64–1.06; \( P = 0.12 \)) or without any VHD (HR, 0.98; 95% CI, 0.83–1.15; \( P = 0.8 \); interaction \( P = 0.25 \)).

There was no difference in rates of intracranial hemorrhage for patients with and without VHD (HR, 1.20; 95% CI, 0.83–1.74; \( P = 0.3 \)). Regardless of the presence of VHD, patients assigned to either dose of dabigatran had significantly lower risk of intracranial bleeding compared with warfarin (Figure 5).

**Figure 2.** Comparison of stroke and systemic embolic events on both dabigatran doses (RE-LY [Randomized Evaluation of Long-Term Anticoagulant Therapy]), rivaroxaban (ROCKET AF [Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation]), and apixaban (ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation]) vs warfarin in patients with or without valvular heart disease (VHD).

CI indicates confidence interval; and NOAC, novel oral anticoagulant.
For patients with exclusive right-sided valve lesions, outcomes were similar to outcomes in patients without valvular disease (Figure 6).

There was no difference between patients with rheumatic mitral stenosis and patients without any form of heart valve disease in terms of outcomes (Figure 6).

**DISCUSSION**

A large number of patients with AF have VHD and therefore are often seen in routine clinical practice. Hence, it is important to emphasize that many patients with VHD were included in RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE-AF (Effective Anticoagulation With Factor XA Next Generation in Atrial Fibrillation; Table 1). To compare and place these pivotal trials into perspective, RE-LY had 3950 (21.8%) patients with VHD, which included mitral regurgitation (3101 patients), aortic regurgitation (817), aortic stenosis (471), tricuspid regurgitation (1179), and mild mitral stenosis (193). In ROCKET AF, 2003 patients (14.1%) had VHD, referred to as significant valvular disease, which included mitral regurgitation (1756), aortic regurgitation (486), aortic stenosis (215), and other valve conditions (11). In the ARISTOTLE
The definition of nonvalvular AF in each trial, which importantly led to the approval of their respective NOAC, was based on the exclusion of certain valve conditions, which were different in each trial (Table 1). The distinction between prosthetic valves and mechanical valves is important. Prosthetic valves included bioprosthetic valves but excluded mechanical valves (Table 1).

In the 3 trials for which post hoc analyses of patients with VHD have been conducted, the baseline characteristics of patients with VHD reflected a higher cardiovascular risk than those of patients without VHD. To compare, in the RE-LY trial, patients with any VHD had more heart failure (P<0.001), coronary disease (P<0.001), renal impairment (P<0.001), and persistent AF (P<0.002) and higher CHADS2 score (2.3 versus 2.1; P<0.001). In ROCKET AF, patients with VHD were older (P<0.0001) and had more heart failure (P<0.0001), coronary disease/myocardial infarction (P<0.0001), and persistent AF (P<0.05) but had similar CHADS2 (3.5 versus 3.5; P=0.98) and HAS-BLED (2.8 versus 2.8; P=0.18) scores. In ARISTOTLE, patients with VHD were older (P<0.0001); had more previous myocardial infarction (P<0.0001), heart failure (P<0.0001), and renal impairment (P<0.0001); had more persistent or permanent AF (P<0.0001); and had a higher mean CHADS2 score (2.2 versus 2.1; P<0.001). Accordingly, in ARISTOTLE, Kaplan-Meier estimates of rates of strokes and SEEs were 3.2% versus 2.4% in patients with and without VHD, and in ROCKET AF, rates of strokes and SEEs per 100 patient-years were 2.23 versus 2.09. We acknowledge that although the trend would probably hold if the same type of estimates were obtained for each study, a direct comparison of Kaplan-Meier estimates with standardized event rates can be questioned.

RE-LY and ARISTOTLE patients derived similar benefit from their respective NOAC (dabigatran and apixaban) compared with warfarin without any interaction with VHD status (Figures 2–5). However, in the ROCKET AF trial, there was a significant interaction between rivaroxaban and VHD in terms of the risk of major bleeding (P<0.01).

In RE-LY, D110 was associated with significantly less major bleeding compared with warfarin, whereas D150 had a rate of major bleeding similar to that of warfarin in both VHD and non-VHD patients (Figure 4). In ROCKET AF, patients with VHD taking rivaroxaban had more major bleeds compared with those taking warfarin (Figure 4). In ARISTOTLE, apixaban treatment was associated with less major bleeding compared with warfarin regardless of VHD status (Figure 4).

The rate of intracranial hemorrhage in each trial was lower among patients randomized to dabigatran, rivaroxaban, or apixaban compared with warfarin regardless of the presence of VHD (Figure 5).

The evidence for the value of NOACs in patients with VHD as defined in the 3 studies is very strong. Accordingly, in the current European guidelines, NOAC therapy is indicated in all forms of valvular disease, including valve repair, severe aortic stenosis, bioprosthetic valves, mitral valve repair, percutaneous transluminal aortic valvuloplasty, and transcatheter aortic valve replacement, with the exception of mechanical heart valves and moderate to severe mitral stenosis. The most recent American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines recommend oral anticoagulation (options include warfarin, dabigatran, rivaroxaban, or apixaban) for patients with nonvalvular AF (as defined in Table 1) with a CHA2DS2-VASc score of ≥2 (Class 1). The guidelines recommend that patients with mechanical heart valves should be managed only with warfarin (Class 1).

In the RE-LY trial, 165 patients had right-sided valve lesions as their exclusive valve lesion, and 192 patients had mitral stenosis presumed to be rheumatic. For the former, the numbers were small but the differences were minor; more anticoagulation use at baseline and higher bleeding rates during the course of the trial. Interestingly, the former had the characteristics of a rheumatic heart disease population: younger, female, with heart failure.
and a history of transient ischemic attack and stroke, supporting our assumption that the patients with mitral valve stenosis had suffered from rheumatic heart disease.

Limitations
This is a retrospective analysis of patients with and without VHD enrolled in the RE-LY trial. Case report forms used in the study were not prospectively designed to support an analysis of VHD cause and severity. Although all the pivotal trials used warfarin as the comparator, the mean time in therapeutic range for the 3 trials varied from 55% in ROCKET AF to 62% for ARISTOTLE and 64% for RE-LY, emphasizing the limitations of comparisons when indirect. Despite these limitations, the results were remarkably consistent.

Conclusions
The pivotal trials comparing NOACs and warfarin characterized the included patients as having nonvalvular AF when in fact many patients with all forms of valvular disease were studied. In RE-LY, approximately one fifth of the patients with nonvalvular AF were classified as having VHD. The presence of VHD did not influence comparison of dabigatran at either dose with warfarin in terms of stroke or systemic embolism, major bleed, death, or intracranial hemorrhage.

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FOOTNOTES
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