Myocardial Ischemic Events in Patients With Atrial Fibrillation Treated With Dabigatran or Warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) Trial

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Background—There is a modest risk of myocardial infarction (MI) and myocardial ischemic events in patients with atrial fibrillation.

Methods and Results—Data from the RE-LY study (Randomized Evaluation of Long-Term Anticoagulation Therapy) were used to report rates of MI, unstable angina, cardiac arrest, and cardiac death and the prespecified net clinical benefit and treatment effects of dabigatran versus warfarin. MI occurred at annual rates of 0.82% and 0.81% with dabigatran 110 or 150 mg BID compared with 0.64% with warfarin (hazard ratio [HR] 1.29, 95% confidence interval [CI] 0.96–1.75, P=0.09 for dabigatran 110 mg; HR 1.27, 95% CI 0.94–1.71, P=0.12 for dabigatran 150 mg). Annual rates of a composite of MI, unstable angina, cardiac arrest, and cardiac death were 3.16% per year with dabigatran 110 mg, 3.33% per year with dabigatran 150 mg, and 3.41% per year with warfarin (HR versus warfarin 0.93, 95% CI 0.80–1.06, P=0.28 for dabigatran 110 mg and HR 0.98, 95% CI 0.85–1.12, P=0.77 for dabigatran 150 mg). Events prespecified as “net clinical benefit” (all strokes, systemic embolism, MI, pulmonary embolism, major bleeding, and all-cause death) occurred at a rate of 7.34% per year with dabigatran 110 mg, 7.11% per year with dabigatran 150 mg, and 7.91% per year with warfarin (HR 0.92, 95% CI 0.84–1.01, P=0.09 for dabigatran 110 mg and HR 0.90, 95% CI 0.82–0.99, P=0.02 for dabigatran 150 mg). The relative effects of dabigatran versus warfarin on myocardial ischemic events were consistent in patients with or without a baseline history of MI or coronary artery disease.

Conclusions—There was a nonsignificant increase in MI with dabigatran compared with warfarin, but other myocardial ischemic events were not increased. Treatment effects of dabigatran were consistent in patients at higher and lower risk of myocardial ischemic events.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT 00262600.
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Key Words: atrial fibrillation ■ stroke ■ myocardial infarction ■ coronary artery disease ■ dabigatran

Vitamin K antagonists have long been the mainstay of stroke prevention therapy in atrial fibrillation (AF); however, vitamin K antagonist therapy is difficult to use because of its narrow therapeutic window, the need for coagulation monitoring, and its interactions with diets and medications.1 Dabigatran etexilate is a novel, potent, competitive, and reversible direct thrombin inhibitor that recently has been compared with warfarin for prevention of thromboembolic events in 18 113 patients with nonvalvular AF (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY trial]).2–4 At a dose of 110 mg twice daily, dabigatran had similar efficacy as warfarin in preventing stroke and systemic embolism but lower rates of major hemorrhage.3 At a dose of 150 mg twice daily, dabigatran was associated with lower rates of stroke and systemic embolism than warfarin but similar rates of major hemorrhage.3 However, there were numerically more nonfatal clinical myocardial infarctions (MIs) in dabigatran patients than in warfarin patients.3,4 The number of MIs (both clinical and silent) was relatively few (compared with stroke), and thus, the trial had low power to detect differences in this outcome, and the results may be exaggerated or diluted by chance. However, a recent meta-

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analysis of randomized noninferiority trials concluded that dabigatran was associated with an increased risk of MI or acute coronary syndrome.5

Clinical Perspective on p 676

To better understand the effects of dabigatran on myocardial ischemic events relative to warfarin, the present report presents detailed analyses of MIs and other clinical events typically related to myocardial ischemia and the relative effects of dabigatran and warfarin, both overall and in patients at higher risk of myocardial ischemia, such as those with prior coronary disease.

Methods

Patients and Study Conduct

Details of the RE-LY study protocol and its main results have been reported previously.2–4 In brief, RE-LY was a randomized trial designed to compare 2 fixed doses of dabigatran (110 or 150 mg BID), each administered in a blinded manner, with open-label use of warfarin in patients with AF who were at increased risk for stroke. Patients with documented AF were eligible if they had at least 1 of the following characteristics: Previous stroke or transient ischemic attack, left ventricular ejection fraction <0.40, New York Heart Association class 2 or higher heart failure symptoms within 6 months of screening, and an age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease (CAD). A total of 18,113 patients were randomly assigned to 1 of the treatment arms and followed up for a median of 2 years. The primary study outcome of the RE-LY trial was stroke or systemic embolism, and the primary safety end point was major hemorrhage.

Definition of MI

Clinical MI was defined as the presence of at least 2 of the following 3 criteria: (1) Typical prolonged severe chest pain or related symptoms or signs (eg, ST changes or T-wave inversion in the ECG) suggestive of MI; (2) elevation of troponin or creatine kinase-MB to more than the upper level of normal, or if creatine kinase-MB was elevated at baseline, reevaluation to more than 50% increase above the previous level; and (3) development of significant Q waves in at least 2 adjacent ECG leads. In patients after percutaneous coronary intervention (within 24 hours) or after coronary bypass surgery (within 72 hours), elevation of troponin or creatine kinase-MB to more than 3 or 5 times the upper limit of normal, respectively, or if creatine kinase-MB was elevated at baseline, reevaluation to more than 3 or 5 times the upper limit of normal, respectively, or a more than 50% increase above the previous level, and/or development of significant Q waves in at least 2 adjacent ECG leads was required.

Silent MI was defined as new asymptomatic ECG changes with significant new Q waves (≥40 ms in 2 related leads).2 The first report of RE-LY included only clinical MI, because data on silent MI had not been centrally reported or adjudicated. After database lock and during the review process of the Food and Drug Administration, an analysis of silent MI was performed by assessment of all reports of routine ECGs in which a new significant Q wave was observed. All original ECGs from such patients were reviewed by 2 blinded adjudicators, and 28 cases of silent MI were diagnosed.4

Definition of Other Myocardial Ischemic Events

The outcomes of unstable angina and cardiac arrest were collected as adverse or serious adverse events. All deaths were classified as either cardiac, noncardiac vascular, or nonvascular. Cardiac deaths included sudden/arrhythmic, pump failure, and post-MI deaths.

Other Events

Coronary artery bypass graft surgery was collected as a cause of hospitalization. Percutaneous coronary intervention was collected either as a cause of hospitalization or associated with a report of MI.

Net clinical benefit was a protocol-prespecified outcome that included stroke, systemic embolism, pulmonary embolism, MI, death, or major hemorrhage.

Statistical Analysis

We examined the effects of dabigatran 110 mg BID, dabigatran 150 mg BID, and warfarin on the occurrence of clinical and silent MI; the composite of MI and other clinical events typically related to myocardial ischemia, including unstable angina, cardiac arrest, and cardiac death; a composite of MI, unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, cardiac arrest, or cardiac death; the latter composite with the addition of stroke or systemic embolism; and the prespecified net clinical benefit. Cox regression was used to calculate hazard ratios (HRs), confidence intervals (CIs), and probability values. Kaplan-Meier curves were constructed for each of the 3 treatment groups for the outcome of MI. We also determined the risk of other study outcomes and composite outcomes for the subgroup of patients with CAD or previous MI at baseline, who were considered to be at particularly high risk for developing new MI. The net clinical benefit (prospectively defined in the RE-LY trial as the composite of stroke, systemic embolism, pulmonary embolism, all-cause death, MI, and major hemorrhage) was calculated in this subgroup and compared with that of patients without a history of MI or CAD.

All analyses were based on the intention-to-treat principle and were performed with SAS software version 9.1 (SAS Institute Inc, Cary, NC). In addition, an on-treatment analysis was performed as a sensitivity analysis. A 2-sided probability value of less than 0.05 was considered statistically significant.

Results

Impact of Treatments on Myocardial Ischemic Events

In the dabigatran 110- and 150-mg arms, there were 98 and 97 MIs at annual rates of 0.82% per year and 0.81% per year, respectively, compared with the warfarin arm, in which there were 75 MIs (0.64% per year; Table 1). The HR was 1.29 (95% CI 0.96–1.75, P = 0.09) for dabigatran 110 mg versus warfarin and 1.27 (95% CI 0.94–1.71, P = 0.12) for dabigatran 150 mg versus warfarin. Figure 1 shows the cumulative Kaplan-Meier incidence curves for new MIs in the 3 treatment arms. When both dabigatran doses together were compared with warfarin, results were similar to those obtained by the 2 separate comparisons (Table 1).

To capture a broader spectrum of myocardial ischemic events (many of which may be caused by plaque rupture with superimposed coronary thrombosis), a composite outcome was analyzed that included MI, unstable angina, cardiac arrest, and cardiac death. The annual rates of this composite were 3.16% per year with dabigatran 110 mg, 3.33% per year with dabigatran 150 mg, and 3.41% per year in the warfarin group. The HRs versus warfarin were 0.93 (95% CI 0.80–1.06, P = 0.28) for dabigatran 110 mg and 0.98 (95% CI 0.85–1.12, P = 0.77) for dabigatran 150 mg. When revascularization events were also included, again no significant differences emerged among the 3 treatment groups (Table 1).

A broader composite that included these events and both stroke and systemic embolic events occurred at annual rates of 4.76% per year with dabigatran 110 mg, 4.47% per year with dabigatran 150 mg, and 5.10% per year with warfarin. The HRs versus warfarin were 0.93 (95% CI 0.83–1.05, P = 0.24) for dabigatran 110 mg and 0.88 (95% CI 0.78–0.98, P = 0.03) for dabigatran 150 mg (Table 1; Figure 1).
Events prespecified in the net clinical benefit analysis occurred at annual rates of 7.34% per year with dabigatran 110 mg, 7.11% per year with dabigatran 150 mg, and 7.91% per year with warfarin. The HRs versus warfarin were 0.92 (95% CI 0.84–1.01, \( P = 0.09 \)) for dabigatran 110 mg and 0.90 (95% CI 0.82–0.99, \( P = 0.02 \)) for dabigatran 150 mg (Table 1; Figure 1). As a sensitivity analysis, an on-treatment analysis of cardiac events during RE-LY was

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg BID (n=6015)</th>
<th>Dabigatran 150 mg BID (n=6076)</th>
<th>Warfarin (n=6022)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate per 100 Person-Years</td>
<td>Rate per 100 Person-Years</td>
<td>Rate per 100 Person-Years</td>
</tr>
<tr>
<td>Total MI</td>
<td>98 (0.82 ± 0.04)</td>
<td>97 (0.81 ± 0.04)</td>
<td>75 (0.64 ± 0.04)</td>
</tr>
<tr>
<td>Clinical MI</td>
<td>87 (0.73 ± 0.04)</td>
<td>89 (0.74 ± 0.04)</td>
<td>66 (0.56 ± 0.04)</td>
</tr>
<tr>
<td>Silent MI</td>
<td>11 (0.09 ± 0.01)</td>
<td>8 (0.07 ± 0.01)</td>
<td>9 (0.08 ± 0.01)</td>
</tr>
<tr>
<td>Fatal MI (death within 30 d)</td>
<td>16 (0.13 ± 0.02)</td>
<td>13 (0.11 ± 0.02)</td>
<td>12 (0.10 ± 0.02)</td>
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</table>

Other myocardial events

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<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg BID (n=6015)</th>
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<tbody>
<tr>
<td></td>
<td>Rate per 100 Person-Years</td>
<td>Rate per 100 Person-Years</td>
<td>Rate per 100 Person-Years</td>
</tr>
<tr>
<td>MI, UA, cardiac arrest, or cardiac death</td>
<td>376 (3.16 ± 0.13)</td>
<td>401 (3.33 ± 0.13)</td>
<td>402 (3.41 ± 0.13)</td>
</tr>
<tr>
<td>PCI or CABG surgery</td>
<td>48 (0.40 ± 0.04)</td>
<td>44 (0.37 ± 0.04)</td>
<td>46 (0.39 ± 0.04)</td>
</tr>
<tr>
<td>MI, UA, CABG, PCI, cardiac arrest, or cardiac death</td>
<td>402 (3.38 ± 0.21)</td>
<td>425 (3.53 ± 0.21)</td>
<td>424 (3.60 ± 0.21)</td>
</tr>
<tr>
<td>MI, UA, CABG, PCI, cardiac arrest, cardiac death</td>
<td>567 (4.76 ± 0.47)</td>
<td>538 (4.47 ± 0.47)</td>
<td>601 (5.10 ± 0.47)</td>
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</table>

Net clinical benefit

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg BID (n=6015)</th>
<th>Dabigatran 150 mg BID (n=6076)</th>
<th>Warfarin (n=6022)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate per 100 Person-Years</td>
<td>Rate per 100 Person-Years</td>
<td>Rate per 100 Person-Years</td>
</tr>
<tr>
<td>MI, UA, CABG, PCI, cardiac arrest, cardiac death</td>
<td>973 (7.34 ± 0.71)</td>
<td>855 (7.11 ± 0.71)</td>
<td>933 (7.91 ± 0.71)</td>
</tr>
</tbody>
</table>

RE-LY indicates Randomized Evaluation of Long-Term Anticoagulation Therapy; BID, twice daily; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; UA, unstable angina; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; and SEE, systemic embolic event.

Net clinical benefit was defined as a composite of stroke, MI, cardiovascular death, pulmonary embolism, SEE, or major bleeding. The comparisons of the 2 dabigatran doses together versus warfarin were not prespecified and are presented for information and hypothesis generation only.

Events prespecified in the net clinical benefit analysis were 0.92 (95% CI 0.84–1.01, \( P = 0.09 \)) for dabigatran 110 mg and 0.90 (95% CI 0.82–0.99, \( P = 0.02 \)) for dabigatran 150 mg (Table 1; Figure 1). As a sensitivity analysis, an on-treatment analysis of cardiac events during RE-LY was
performed with results consistent with the intention-to-treat analysis (Table 2).

### Baseline Characteristics of Patients With New MIs and Myocardial Ischemic Events

Table 3 shows characteristics of patients with or without coronary events during the RE-LY trial. Patients who had at least 1 myocardial ischemic event were older and had more coronary risk factors, particularly more prior MIs, than the remainder of the study population. Across all treatment groups, these patients received more antiplatelet medications, \( H9252 \)-blockers, and statins at baseline. They also more often had a \( CHADS2 \) score.

### Timing of Clinical MI in Relation to Study Drug Intake

Fifty-six of 87 clinical MIs in the dabigatran 110-mg group, 59 of 89 in the dabigatran 150-mg group, and 46 of 66 in the warfarin group occurred on study drug treatment (Table 4). MIs that occurred \( >6 \) days after study drug discontinuation were observed in 17, 20, and 12 patients in the 3 groups. Accordingly, 33\%, 34\%, and 30\% of all clinical MIs were diagnosed when patients were not taking the study drug in the respective treatment arms.

### Effects of Dabigatran Versus Warfarin in Patients With and Without Prior CAD

Patients with a baseline history of CAD or previous MI are at risk for recurrent ischemic events. There were 1886 (31\%) CAD/MI patients in the dabigatran 110-mg group, 1915 (31\%) in the dabigatran 150-mg group, and 1849 (31\%) in the warfarin group. Figure 2 shows the effects of dabigatran and warfarin on important outcomes and composite outcomes for the subgroups of patients with previous CAD/MI compared with those without. The effects of dabigatran compared with warfarin were highly consistent between patients with prior CAD/MI compared with those without (all probability values for interaction were nonsignificant).

### Discussion

#### Main Findings

The present detailed analysis of the RE-LY trial demonstrates a trend to an increase in MIs but a lack of significant excess in other myocardial ischemic events in AF patients receiving dabigatran compared with warfarin. Dabigatran exerts consistent effects in patients with and without previous manifestations of CAD. In this large cohort of AF patients treated for stroke prevention, coronary events were less common than cerebrovascular events, even in patients with previous CAD. The predefined net clinical benefit, which included major ischemic and thrombotic events as well as major bleeding, was statistically less common with dabigatran 150 mg BID than with warfarin. Thus, there was an overall net benefit with dabigatran compared with warfarin, even in patients with previous MI or CAD.

#### Myocardial Ischemic Events in Patients Taking Dabigatran

The publication of the RE-LY trial raised the issue that dabigatran may be associated with an elevated rate of new MI in patients with AF.\(^3\) The original finding was corrected after...
a repeated data analysis, requested by the Food and Drug Administration, which showed 4 previously unreported clinical MIs and 28 silent MI events.4 There were no longer any statistically significant differences in the rate of new MIs among the 3 groups, and all HRs were associated with wide CIs. Of note, one third of all MIs occurred in patients not taking the study drug, as shown in the present analysis.

RE-LY was not designed to detect a difference in MI between treatments, and because of the low MI rates observed, the study does not have the power to conclude either that there is a difference in MI between treatments or that there is not. The present analysis provides more information on MI events and on other myocardial ischemic events, including unstable angina, need for coronary revascularization, cardiac arrest, or cardiac death. There was no evidence that dabigatran treatment was associated with an excess in any of these other events. Furthermore, there was no sign of a dose-dependent effect of the dabigatran on coronary events. The prespecified net clinical benefit analysis, which included a combination of thromboembolic and major bleeding events, demonstrated a significant benefit for the dabigatran 150-mg dose.

Effects of Dabigatran in High-Risk Coronary Patients

Patients with a known history of CAD are at high risk for recurrent coronary events and for bleeding. Accordingly, we examined the effects of dabigatran versus warfarin for this important subgroup of patients in the RE-LY trial. There was no significant interaction between the treatment effects and the presence or absence of a history of previous CAD/MI, which indicates that the beneficial effects of dabigatran over...
warfarin were similarly present in this high-risk group of patients. Analysis of the net clinical benefit confirmed the superiority of dabigatran 150 mg concerning stroke and the net clinical benefit and the benefit of the dabigatran 110-mg dose concerning major bleeding compared with warfarin even in these subgroups.

**Previous Studies**
Several large randomized trials of new anticoagulant drugs versus warfarin have been completed in recent years. In all of these trials, rates of new MIs were low across all treatment groups. For instance, in the ACTIVE W trial (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events), only 23 of 3371 patients in the warfarin group and 36 of 3335 patients treated with aspirin plus clopidogrel had a new MI during a median follow-up of 1.28 years. Similarly low MI rates were observed in the SPORTIF (Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation) III and V studies. These low MI rates are in agreement with those observed in RE-LY and imply that any differences in new MI events between treatment groups may be subject to a play of chance. All of these studies were underpowered to detect an effect of treatment on risk of MI.

A few studies have specifically examined the effects of direct thrombin inhibitors on recurrent MI in patients who

**Table 4. Timing of Myocardial Ischemic Events**

<table>
<thead>
<tr>
<th>Patients With MI</th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total randomized, n</td>
<td>6015</td>
<td>6076</td>
<td>6022</td>
</tr>
<tr>
<td>First event on study drug only, n (%)</td>
<td>56 (0.9)</td>
<td>59 (1.0)</td>
<td>46 (0.8)</td>
</tr>
<tr>
<td>First event 1 to 6 d off study drug, n (%)</td>
<td>13 (0.2)</td>
<td>10 (0.2)</td>
<td>8 (0.1)</td>
</tr>
<tr>
<td>First event &gt;6 d off study drug, n (%)</td>
<td>17 (0.3)</td>
<td>20 (0.3)</td>
<td>12 (0.2)</td>
</tr>
<tr>
<td>First event &gt;90 d off study drug, n (%)</td>
<td>13 (0.2)</td>
<td>14 (0.2)</td>
<td>6 (0.1)</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; UA, unstable angina; CABG, coronary artery bypass graft; and PCI, percutaneous coronary intervention.

**Figure 2.** Cardiovascular events and bleeding in patients with prior coronary artery disease (CAD) or myocardial infarction (MI). D110 indicates dabigatran 110 mg BID; D150, dabigatran 150 mg BID; WAR, warfarin; SEE, systemic embolic event; UA, unstable angina; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; and P(INTER), P for interaction.
had survived a recent acute coronary syndrome. Wallentin et al reported that ximelagatran plus acetylsalicylic acid was more effective than acetylsalicylic acid alone in preventing major cardiovascular events, including new MIs, during a 6-month treatment period. In a similar trial evaluating dabigatran, Oldgren et al reported a small and nonsignificantly higher number of MIs in dabigatran-treated patients than in a placebo group, but cardiovascular deaths occurred less frequently with dabigatran 110 or 150 mg than in the placebo group (all differences not statistically significant). A recent meta-analysis of randomized dabigatran studies similarly reported a higher incidence of MI or acute coronary syndromes in patients taking the thrombin inhibitor. However, the control arms of these studies included placebo, warfarin, or enoxaparin treatments, and thus, a more detailed analysis of the effects of dabigatran on coronary events against the different comparators appears to be necessary.

The above data suggest that the available information is too sparse to assess the effects of direct thrombin inhibitors on MI. Furthermore, given that in the AF trials, the comparison of direct thrombin inhibitors is versus warfarin, even if there is a higher rate of MI with direct thrombin inhibitors, this may be because warfarin is very effective and direct thrombin inhibitors may be less so (but more effective than no treatment). Previous controlled trials have shown that warfarin is very effective at reducing recurrent MI in coronary patients. In AF trials with new antithrombotic agents, concomitant use of clopidogrel or platelet inhibitors other than low-dose aspirin and recent coronary events have usually been exclusion criteria, which lowers the MI risk in the exposed population. The current dilemma can therefore only be resolved by large trials of direct thrombin inhibitors versus placebo or aspirin in individuals at high risk of coronary events. Given the higher rates of stroke and systemic embolic events in AF patients and the relatively low rates of MI, the current evidence from RE-LY indicates that in AF patients, the benefits on stroke reduction and bleeding with dabigatran compared with warfarin are likely to outweigh any potential impact on MI.

**Study Limitations**

The analyses presented in the present report were not prespecified and are post hoc. Thus, some of the outcome events were not prespecified and adjudicated. Although all deaths and MIs were adjudicated, other events, such as unstable angina or need for revascularization, were derived from hospitalization forms or adverse events/serious adverse events reports. It would be preferable if all the events presented in the present report had been prespecified, collected on purpose-designed case report forms, and adjudicated. Nonetheless, the collection of adverse events was performed assiduously and provides reliable information.

**Conclusions**

A nonsignificantly higher number of MIs were observed with dabigatran than with warfarin in RE-LY, but there was no excess of other myocardial ischemic events. The composite of MI, stroke, other thrombotic events, and major bleeding occurred less frequently with each dose of dabigatran than with warfarin and for the higher dose of dabigatran was nominally statistically significant.

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**Disclosures**

Dr. Hohnloser reports having received consulting and lecture fees from Boehringer Ingelheim, BMS, Bayer, Pfizer, and Sanofi-aventis. Dr. Oldgren has received institutional grant support from Boehringer Ingelheim and consulting fees and lecture fees from Bayer, Boehringer Ingelheim, and BMS. Dr. Wallentin has received consulting fees, lecture fees, and grant support from Boehringer Ingelheim; consulting fees from Regado and Atera; lecture fees from Boehringer Ingelheim, Astrazeneca, and Eli Lilly; and grant support from Astrazeneca, Bristol-Myers Squibb, GlaxoSmithKline, and Schering-Plough. Dr. Ezekowitz has received consulting fees, lecture fees, and grant support from Boehringer Ingelheim and Arix Therapeutics; consulting fees from sanofi-aventis; and lecture fees and grant support from Portola Pharmaceuticals. Drs. Reilly and Brueckmann are employees of Boehringer Ingelheim. Dr. Eikelboom has received consulting fees, lecture fees, and grant support from Boehringer Ingelheim, Astrazeneca, Sanofi-aventis, and GlaxoSmithKline; consulting fees and lecture fees from Eisai Pharmaceuticals, Eli Lilly, and McNeil; and consulting fees from Bristol-Myers Squibb, Corinex Medical Corporation, and Daiichi-Sankyo. Dr. Yusuf has received consulting fees, lecture fees, and grant support from Boehringer Ingelheim and consulting fees from Astrazeneca, Bristol-Myers Squibb, and sanofi-aventis. Dr. Connolly reports receiving consulting fees, lecture fees, and grant support from Boehringer Ingelheim. Dr. Yang reports no conflicts.

**References**

10. Wallentin L, Wilcox RG, Weaver WD, Emanuelsson H, Goodvin A, Nyström P, Bylock A; for the ESTEEM Investigators. Oral ximelagatran...
Dabigatran etexilate is a novel, potent, competitive, and reversible direct thrombin inhibitor that recently has been compared with warfarin for prevention of thromboembolic events in 18,113 patients with nonvalvular atrial fibrillation (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY trial]). At a dose of 110 mg twice daily, dabigatran had similar efficacy as warfarin in preventing stroke and systemic embolism but lower rates of major hemorrhage. At a dose of 150 mg twice daily, dabigatran was associated with lower rates of stroke and systemic embolism than warfarin but similar rates of major hemorrhage. This post hoc study evaluated the incidence of myocardial ischemic events, including myocardial infarction (MI), in the 3 treatment arms. MI occurred at annual rates of 0.82% and 0.81% with dabigatran 110 mg or 150 mg BID compared with 0.64% in patients taking warfarin (hazard ratio 1.29, 95% confidence interval 0.96–1.75, \( P = 0.09 \) for dabigatran 110 mg; hazard ratio 1.27, 95% confidence interval 0.94–1.71, \( P = 0.12 \) for dabigatran 150 mg). Events prespecified as “net clinical benefit” (all strokes, systemic embolism, MI, pulmonary embolism, major bleeding, and all-cause death) occurred at a rate of 7.34% per year with dabigatran 110 mg, 7.11% per year with dabigatran 150 mg, and 7.91% per year with warfarin (hazard ratio 0.92, 95% confidence interval 0.84–1.01, \( P = 0.09 \) for dabigatran 110 mg; 0.90, 95% confidence interval 0.82–0.99, \( P = 0.02 \) for dabigatran 150 mg). In conclusion, in patients with atrial fibrillation, there was a nonsignificant increase in MIs with dabigatran compared with warfarin, but other myocardial ischemic events were not increased. The net clinical benefit favors dabigatran over warfarin in patients with or without a baseline history of MI or coronary artery disease.
Myocardial Ischemic Events in Patients With Atrial Fibrillation Treated With Dabigatran or Warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) Trial

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Dabigatran이 심근고혈압을 증가시키지는 않는다

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Summary

배경
심방세동 환자에서는 심근경색과 심근고혈압의 위험이 존재한다.

방법 및 결과
심근경색, 불안정형 협심증, 심정지 및 심장사의 발생률과 warfarin에 대한 dabigatran의 임상적 이점 및 치료 효과를 보고하기 위해 RE-LY(Randomized Evaluation of Long-Term Anticoagulation Therapy) 연구의 데이터를 이용하였다. 심근경색의 연간 발생률은 dabigatran 110mg 및 150mg 군에서 각각 0.82%, 0.81%였으며, warfarin군에서는 0.64%였다(dabigatran 110mg 군: HR 1.29; 95% CI, 0.96–1.75; P=0.09; dabigatran 150mg 군: HR 1.27; 95% CI, 0.94–1.71; P=0.12). 심근경색, 불안정형 협심증, 심정지, 심장사의 연간 복합 발생률은 dabigatran 110mg 및 150mg 군에서 각각 3.16%, 3.33%였으며, warfarin군에서는 3.41%였다(dabigatran 110mg 군: HR 0.93; 95% CI, 0.80–1.06; P=0.28; dabigatran 150mg 군: HR 0.98; 95% CI, 0.85–1.12; P=0.77). 총 임상적 이점에서 규정한 사건들(모든 뇌졸중, 전신 색전증, 심근경색, 폐색전증, 주요 출혈, 모든 사망)의 연간 발생률은 dabigatran 110mg 및 150mg 군에서 각각 7.34%, 7.11%였으며, warfarin군에서는 7.91%였다(dabigatran 110mg 군: HR 0.92; 95% CI, 0.84–1.01; P=0.09; dabigatran 150mg 군: HR 0.90; 95% CI, 0.82–0.99; P=0.02). Warfarin에 대해 dabigatran의 심근고혈압 사건에 대한 상대적인 효과는 환자의 심근경색 또는 혈심증의 과거력 유무와 상관없이 일관되게 나타났다.

결론
Dabigatran 사용 환자들에게는 warfarin 사용군에 비해 유의하지 않은 정도의 심근경색 증가가 관찰되었으나, 다른 심근고혈압 사건은 증가하지 않았다. Dabigatran의 치료 효과는 심근요혈 사건의 위험도가 높은 군이나 낮은 군에서 모두 일관되었다.
Commentary

RE-LY 연구 결과가 발표되면서 약제의 긍정적인 면이 많이 부각되었지만, 동시에 잠재적인 약제의 문제점들도 제기되었는데 위장관 출혈과 심근경색의 증가가 그 것이다. 다른 thrombin 억제제인 ximelagatran도 급성 심부정맥 혈전증 환자에서 심근경색의 발생을 증가시킨다고 보고된 바 있다. 하지만 또 다른 연구에서는 ximelagatran이 급성 심근경색증 환자에서의 재경색 발생을 줄여준다고 보고하였다. 따라서 심근경색 발생에 thrombin의 직접적인 억제가 영향을 주는지는 불명확하다.

RE-LY 연구의 첫 보고에서는 임상적인 심근경색(다음 3가지 중 2가지 이상을 만족하는 경우: (1) 전형적인 흉통 또는 심전도에서의 ST/T파의 변화; (2) troponin 또는 creatine kinase-MB의 증가; (3) 적어도 2개의 인접한 심전도 유도에서 유의한 Q파의 존재)만 분석되었고, dabigatran 150mg 군에서는 통계적으로 유의한 심근경색의 발생 증가가 관찰되었다. 본 연구에서는 임상적인 심근경색과 함께 무증상(silent) 심근경색(적어도 2개의 인접한 유도에서 폭이 40ms 이상인 유의한 Q파가 무증상으로 새로이 발생한 경우) 환자 28명을 분석에 추가로 포함시켰는데, 무증상 심근경색만 보면 warfarin군과 dabigatran군 사이에 차이가 없다. 따라서 전체 심근경색 발생률은 무증상 심근경색 환자들이 추가됨으로써 다소 희석되었고, 증가하는 경향은 보이지만 통계적으로 유의하지 않는다는 결론에 도달할 수 있게 된다. 물론 RE-LY 연구가 심근경색 발생을 보기 위해 디자인된 연구가 아닌 사후(post hoc) 분석이므로 명확한 결론을 얻기 위해서는 새로운 연구에서 증명되어야 할 것이다. 하지만 적어도 dabigatran은 전체 심근경색 사건에는 영향이 없으며, 증 임상적인 이점 면에서는 warfarin에 비해 이득이 있을 것으로 판단된다.

References
Myocardial Ischemic Events in Patients With Atrial Fibrillation Treated With Dabigatran or Warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) Trial

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Background—There is a modest risk of myocardial infarction (MI) and myocardial ischemic events in patients with atrial fibrillation.

Methods and Results—Data from the RE-LY study (Randomized Evaluation of Long-Term Anticoagulation Therapy) were used to report rates of MI, unstable angina, cardiac arrest, and cardiac death and the prespecified net clinical benefit and treatment effects of dabigatran versus warfarin. MI occurred at annual rates of 0.82% and 0.81% with dabigatran 110 or 150 mg BID compared with 0.64% with warfarin (hazard ratio [HR] 1.29, 95% confidence interval [CI] 0.96–1.75, \( P = 0.09 \) for dabigatran 110 mg; HR 1.27, 95% CI 0.94–1.71, \( P = 0.12 \) for dabigatran 150 mg). Annual rates of a composite of MI, unstable angina, cardiac arrest, and cardiac death were 3.16% per year with dabigatran 110 mg, 3.33% per year with dabigatran 150 mg, and 3.41% per year with warfarin (HR versus warfarin 0.93, 95% CI 0.80–1.06, \( P = 0.28 \) for dabigatran 110 mg and HR 0.98, 95% CI 0.85–1.12, \( P = 0.77 \) for dabigatran 150 mg). Events prespecified as “net clinical benefit” (all strokes, systemic embolism, MI, pulmonary embolism, major bleeding, and all-cause death) occurred at a rate of 7.34% per year with dabigatran 110 mg, 7.11% per year with dabigatran 150 mg, and 7.91% per year with warfarin (HR 0.92, 95% CI 0.84–1.01, \( P = 0.09 \) for dabigatran 110 mg and HR 0.90, 95% CI 0.82–0.99, \( P = 0.02 \) for dabigatran 150 mg). The relative effects of dabigatran versus warfarin on myocardial ischemic events were consistent in patients with or without a baseline history of MI or coronary artery disease.

Conclusions—There was a nonsignificant increase in MI with dabigatran compared with warfarin, but other myocardial ischemic events were not increased. Treatment effects of dabigatran were consistent in patients at higher and lower risk of myocardial ischemic events.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT 00262600.

(Circulation. 2012;125:669-676.)

Key Words: atrial fibrillation ■ stroke ■ myocardial infarction ■ coronary artery disease ■ dabigatran

Vitamin K antagonists have long been the mainstay of stroke prevention therapy in atrial fibrillation (AF); however, vitamin K antagonist therapy is difficult to use because of its narrow therapeutic window, the need for coagulation monitoring, and its interactions with diets and medications.1 Dabigatran etexilate is a novel, potent, competitive, and reversible direct thrombin inhibitor that recently has been compared with warfarin for prevention of thromboembolic events in 18 113 patients with nonvalvular AF (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY trial]).2–4 At a dose of 110 mg twice daily, dabigatran had similar efficacy as warfarin in preventing stroke and systemic embolism but lower rates of major hemorrhage.3 At a dose of 150 mg twice daily, dabigatran was associated with lower rates of stroke and systemic embolism than warfarin but similar rates of major hemorrhage.3 However, there were numerically more nonfatal clinical myocardial infarctions (MIs) in dabigatran patients than in warfarin patients.3–4 The number of MIs (both clinical and silent) was relatively few (compared with stroke), and thus, the trial had low power to detect differences in this outcome, and the results may be exaggerated or diluted by chance. However, a recent meta-

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analysis of randomized noninferiority trials concluded that dabigatran was associated with an increased risk of MI or acute coronary syndrome.\textsuperscript{5}

\textbf{Clinical Perspective on p 49}

To better understand the effects of dabigatran on myocardial ischemic events relative to warfarin, the present report presents detailed analyses of MIs and other clinical events typically related to myocardial ischemia and the relative effects of dabigatran and warfarin, both overall and in patients at higher risk of myocardial ischemia, such as those with prior coronary disease.

\section*{Methods}

\subsection*{Patients and Study Conduct}

Details of the RE-LY study protocol and its main results have been reported previously.\textsuperscript{2--4} In brief, RE-LY was a randomized trial designed to compare 2 fixed doses of dabigatran (110 or 150 mg BID), each administered in a blinded manner, with open-label use of warfarin in patients with AF who were at increased risk for stroke. Patients with documented AF were eligible if they had at least 1 of the following characteristics: Previous stroke or transient ischemic attack, left ventricular ejection fraction <0.40, New York Heart Association class 2 or higher heart failure symptoms within 6 months of screening, and an age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease (CAD). A total of 18,113 patients were randomly assigned to 1 of the treatment arms and followed up for a median of 2 years. The primary study outcome of the RE-LY trial was stroke or systemic embolism, and the primary safety end point was major hemorrhage.

\subsection*{Definition of MI}

Clinical MI was defined as the presence of at least 2 of the following 3 criteria: (1) Typical prolonged severe chest pain or related symptoms or signs (eg, ST changes or T-wave inversion in the ECG) suggestive of MI; (2) elevation of troponin or creatine kinase-MB to more than the upper level of normal, or if creatine kinase-MB was elevated at baseline, reevaluation to more than 50\% increase above the previous level; and (3) development of significant Q waves in at least 2 adjacent ECG leads. In patients after percutaneous coronary intervention (within 24 hours) or after coronary bypass surgery (within 72 hours), elevation of troponin or creatine kinase-MB to more than 3 or 5 times the upper limit of normal, respectively, or if creatine kinase-MB was elevated at baseline, reevaluation to more than 3 or 5 times the upper limit of normal, respectively, and a more than 50\% increase above the previous level, and/or development of significant Q waves in at least 2 adjacent ECG leads was required.

Silent MI was defined as new asymptomatic ECG changes with significant new Q waves (>40 ms in 2 related leads).\textsuperscript{5} The first report of RE-LY included only clinical MI, because data on silent MI had not been centrally reported or adjudicated. After database lock and during the review process of the Food and Drug Administration, an analysis of silent MI was performed by assessment of all reports of routine ECGs in which a new significant Q wave was observed. All original ECGs from such patients were reviewed by 2 blinded adjudicators, and 28 cases of silent MI were diagnosed.\textsuperscript{6}

\subsection*{Definition of Other Myocardial Ischemic Events}

The outcomes of unstable angina and cardiac arrest were collected as adverse or serious adverse events. All deaths were classified as either cardiac, noncardiac vascular, or nonvascular. Cardiac deaths included sudden/arrhythmic, pump failure, and post-MI deaths.

\section*{Other Events}

Coronary artery bypass graft surgery was collected as a cause of hospitalization. Percutaneous coronary intervention was collected either as a cause of hospitalization or associated with a report of MI.

Net clinical benefit was a protocol-prespecified outcome that included stroke, systemic embolism, pulmonary embolism, MI, death, or major hemorrhage.

\section*{Statistical Analysis}

We examined the effects of dabigatran 110 mg BID, dabigatran 150 mg BID, and warfarin on the occurrence of clinical and silent MI; the composite of MI and other clinical events typically related to myocardial ischemia, including unstable angina, cardiac arrest, and cardiac death; a composite of MI, unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, cardiac arrest, or cardiac death; the latter composite with the addition of stroke or systemic embolism; and the prespecified net clinical benefit. Cox regression was used to calculate hazard ratios (HRs), confidence intervals (CIs), and probability values. Kaplan-Meier curves were constructed for each of the 3 treatment groups for the outcome of MI. We also determined the risk of other study outcomes and composite outcomes for the subgroup of patients with CAD or previous MI at baseline, who were considered to be at particularly high risk for developing new MI. The net clinical benefit (prespecified in the RE-LY trial as the composite of stroke, systemic embolism, pulmonary embolism, all-cause death, MI, and major hemorrhage) was calculated in this subgroup and compared with that of patients without a history of MI or CAD.

All analyses were based on the intention-to-treat principle and were performed with SAS software version 9.1 (SAS Institute Inc, Cary, NC). In addition, an on-treatment analysis was performed as a sensitivity analysis. A 2-sided probability value of less than 0.05 was considered statistically significant.

\section*{Results}

\subsection*{Impact of Treatments on Myocardial Ischemic Events}

In the dabigatran 110- and 150-mg arms, there were 98 and 97 MIs at annual rates of 0.82\% per year and 0.81\% per year, respectively, compared with the warfarin arm, in which there were 75 MIs (0.64\% per year; Table 1). The HR was 1.29 (95\% CI 0.96--1.75, \textit{P}=0.09) for dabigatran 110 mg versus warfarin and 1.27 (95\% CI 0.94--1.71, \textit{P}=0.12) for dabigatran 150 mg versus warfarin. Figure 1 shows the cumulative Kaplan-Meier incidence curves for new MIs in the 3 treatment arms. When both dabigatran doses together were compared with warfarin, results were similar to those obtained by the 2 separate comparisons (Table 1).

To capture a broader spectrum of myocardial ischemic events (many of which may be caused by plaque rupture with superimposed coronary thrombosis), a composite outcome was analyzed that included MI, unstable angina, cardiac arrest, and cardiac death. The annual rates of this composite were 3.16\% per year with dabigatran 110 mg, 3.33\% per year with dabigatran 150 mg, and 3.41\% per year in the warfarin group. The HRs versus warfarin were 0.93 (95\% CI 0.80--1.06, \textit{P}=0.28) for dabigatran 110 mg and 0.98 (95\% CI 0.85--1.12, \textit{P}=0.77) for dabigatran 150 mg. When revascularization events were also included, again no significant differences emerged among the 3 treatment groups (Table 1).

A broader composite that included these events and both stroke and systemic embolic events occurred at annual rates of 4.76\% per year with dabigatran 110 mg, 4.47\% per year with dabigatran 150 mg, and 5.10\% per year with warfarin. The HRs versus warfarin were 0.93 (95\% CI 0.83--1.05, \textit{P}=0.24) for dabigatran 110 mg and 0.88 (95\% CI 0.78--0.98, \textit{P}=0.03) for dabigatran 150 mg (Table 1; Figure 1).
Events prespecified in the net clinical benefit analysis occurred at annual rates of 7.34% per year with dabigatran 110 mg, 7.11% per year with dabigatran 150 mg, and 7.91% per year with warfarin. The HRs versus warfarin were 0.92 (95% CI 0.84–1.01, \( P = 0.09 \)) for dabigatran 110 mg and 0.90 (95% CI 0.82–0.99, \( P = 0.02 \)) for dabigatran 150 mg (Table 1; Figure 1). As a sensitivity analysis, an on-treatment analysis of cardiac events during RE-LY was

### Table 1. Cardiac Events During RE-LY

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg BID (n=6015)</th>
<th>Dabigatran 150 mg BID (n=6076)</th>
<th>Warfarin (n=6022)</th>
<th>Dabigatran 110 mg BID vs Warfarin</th>
<th>Dabigatran 150 mg BID vs Warfarin</th>
<th>Dabigatran vs Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Rate per 100 Person-Years</td>
<td>Rate per 100 Person-Years</td>
<td>Rate per 100 Person-Years</td>
<td>HR 95% CI ( P )</td>
<td>HR 95% CI ( P )</td>
<td>HR 95% CI ( P )</td>
</tr>
<tr>
<td>Total MI</td>
<td>98</td>
<td>97</td>
<td>75</td>
<td>0.64</td>
<td>1.29</td>
<td>0.96–1.75</td>
</tr>
<tr>
<td>Clinical MI</td>
<td>87</td>
<td>89</td>
<td>66</td>
<td>0.56</td>
<td>1.30</td>
<td>0.95–1.80</td>
</tr>
<tr>
<td>Silent MI</td>
<td>11</td>
<td>8</td>
<td>9</td>
<td>0.08</td>
<td>1.22</td>
<td>0.50–2.93</td>
</tr>
<tr>
<td>Fatal MI (death within 30 d)</td>
<td>16</td>
<td>13</td>
<td>12</td>
<td>0.10</td>
<td>1.32</td>
<td>0.63–2.80</td>
</tr>
</tbody>
</table>

Other myocardial events

<table>
<thead>
<tr>
<th></th>
<th>Rate per 100 Person-Years</th>
<th>Rate per 100 Person-Years</th>
<th>Rate per 100 Person-Years</th>
<th>HR 95% CI ( P )</th>
<th>HR 95% CI ( P )</th>
<th>HR 95% CI ( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, UA, cardiac arrest, or cardiac death</td>
<td>376</td>
<td>401</td>
<td>402</td>
<td>3.41</td>
<td>0.93</td>
<td>0.80–1.06</td>
</tr>
<tr>
<td>PCI or CABG surgery</td>
<td>48</td>
<td>44</td>
<td>46</td>
<td>0.39</td>
<td>1.04</td>
<td>0.69–1.55</td>
</tr>
<tr>
<td>MI, UA, CABG, PCI, cardiac arrest, or cardiac death</td>
<td>402</td>
<td>425</td>
<td>424</td>
<td>3.60</td>
<td>0.94</td>
<td>0.82–1.07</td>
</tr>
<tr>
<td>Stroke, SEE, MI, UA, CABG, PCI, cardiac arrest, cardiac death</td>
<td>567</td>
<td>538</td>
<td>601</td>
<td>5.10</td>
<td>0.93</td>
<td>0.83–1.05</td>
</tr>
<tr>
<td>Net clinical benefit</td>
<td>873</td>
<td>7.34</td>
<td>855</td>
<td>7.11</td>
<td>933</td>
<td>7.91</td>
</tr>
</tbody>
</table>

RE-LY indicates Randomized Evaluation of Long-Term Anticoagulation Therapy; BID, twice daily; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; UA, unstable angina; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; and SEE, systemic embolic event.

Net clinical benefit was defined as a composite of stroke, MI, cardiovascular death, pulmonary embolism, SEE, or major bleeding. The comparisons of the 2 dabigatran doses together versus warfarin were not prespecified and are presented for information and hypothesis generation only.

Events prespecified in the net clinical benefit analysis occurred at annual rates of 7.34% per year with dabigatran 110 mg, 7.11% per year with dabigatran 150 mg, and 7.91% per year with warfarin. The HRs versus warfarin were 0.92 (95% CI 0.84–1.01, \( P = 0.09 \)) for dabigatran 110 mg and 0.90 (95% CI 0.82–0.99, \( P = 0.02 \)) for dabigatran 150 mg (Table 1; Figure 1). As a sensitivity analysis, an on-treatment analysis of cardiac events during RE-LY was
performed with results consistent with the intention-to-treat analysis (Table 2).

Baseline Characteristics of Patients With New MIs and Myocardial Ischemic Events

Table 3 shows characteristics of patients with or without coronary events during the RE-LY trial. Patients who had at least 1 myocardial ischemic event were older and had more coronary risk factors, particularly more prior MIs, than the remainder of the study population. Across all treatment groups, these patients received more antiplatelet medications, β-blockers, and statins at baseline. They also more often had a CHADS2 score ≥2.

Timing of Clinical MI in Relation to Study Drug Intake

Fifty-six of 87 clinical MIs in the dabigatran 110-mg group, 59 of 89 in the dabigatran 150-mg group, and 46 of 66 in the warfarin group occurred on study drug treatment (Table 4). MIs that occurred >6 days after study drug discontinuation were observed in 17, 20, and 12 patients in the 3 groups. Accordingly, 33%, 34%, and 30% of all clinical MIs were diagnosed when patients were not taking the study drug in the respective treatment arms.

Effects of Dabigatran Versus Warfarin in Patients With and Without Prior CAD

Patients with a baseline history of CAD or previous MI are at risk for recurrent ischemic events. There were 1886 (31%) CAD/MI patients in the dabigatran 110-mg group, 1915 (31%) in the dabigatran 150-mg group, and 1849 (31%) in the warfarin group. Figure 2 shows the effects of dabigatran and warfarin on important outcomes and composite outcomes for the subgroups of patients with previous CAD/MI compared with those without. The effects of dabigatran compared with warfarin were highly consistent between patients with prior CAD/MI compared with those without (all probability values for interaction were nonsignificant).

Discussion

Main Findings

The present detailed analysis of the RE-LY trial demonstrates a trend to an increase in MIs but a lack of significant excess in other myocardial ischemic events in AF patients receiving dabigatran compared with warfarin. Dabigatran exerts consistent effects in patients with and without previous manifestations of CAD. In this large cohort of AF patients treated for stroke prevention, coronary events were less common than cerebrovascular events, even in patients with previous CAD. The predefined net clinical benefit, which included major ischemic and thrombotic events as well as major bleeding, was statistically less common with dabigatran 150 mg BID than with warfarin. Thus, there was an overall net benefit with dabigatran compared with warfarin, even in patients with previous MI or CAD.

Myocardial Ischemic Events in Patients Taking Dabigatran

The publication of the RE-LY trial raised the issue that dabigatran may be associated with an elevated rate of new MI in patients with AF. The original finding was corrected after
a repeated data analysis, requested by the Food and Drug Administration, which showed 4 previously unreported clinical MIs and 28 silent MI events.4 There were no longer any statistically significant differences in the rate of new MIs among the 3 groups, and all HRs were associated with wide CIs. Of note, one third of all MIs occurred in patients not taking the study drug, as shown in the present analysis.

RE-LY was not designed to detect a difference in MI between treatments, and because of the low MI rates observed, the study does not have the power to conclude either that there is a difference in MI between treatments or that there is not. The present analysis provides more information on MI events and on other myocardial ischemic events, including unstable angina, need for coronary revascularization, cardiac arrest, or cardiac death. There was no evidence that dabigatran treatment was associated with an excess in any of these other events. Furthermore, there was no sign of a dose-dependent effect of the dabigatran on coronary events. The prespecified net clinical benefit analysis, which included a combination of thromboembolic and major bleeding events, demonstrated a significant benefit for the dabigatran 150-mg dose.

Effects of Dabigatran in High-Risk Coronary Patients

Patients with a known history of CAD are at high risk for recurrent coronary events and for bleeding. Accordingly, we examined the effects of dabigatran versus warfarin for this important subgroup of patients in the RE-LY trial. There was no significant interaction between the treatment effects and the presence or absence of a history of previous CAD/MI, which indicates that the beneficial effects of dabigatran over

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients With MI in RE-LY</th>
<th>Patients Without MI in RE-LY</th>
<th>P</th>
<th>Patients With MI/UA/CABG/PCI/Cardiac Death/Cardiac Arrest</th>
<th>Patients Without MI/UA/CABG/PCI/Cardiac Death/Cardiac Arrest</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized patients, n</td>
<td>270</td>
<td>17 843</td>
<td></td>
<td></td>
<td>1251</td>
<td>16 862</td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td>73.0 (7.8)</td>
<td>71.5 (8.7)</td>
<td>0.002</td>
<td>71.6 (9.1)</td>
<td>71.5 (8.6)</td>
<td>0.600</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>93 (34)</td>
<td>6505 (37)</td>
<td>0.495</td>
<td>383 (31)</td>
<td>6215 (37)</td>
<td>0.000</td>
</tr>
<tr>
<td>History of CAD/MI, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>100 (37)</td>
<td>2905 (16)</td>
<td>0.000</td>
<td>432 (35)</td>
<td>2573 (15)</td>
<td>0.000</td>
</tr>
<tr>
<td>Other CAD</td>
<td>140 (52)</td>
<td>4894 (27)</td>
<td>0.000</td>
<td>598 (48)</td>
<td>4436 (26)</td>
<td>0.000</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>95 (35)</td>
<td>4126 (23)</td>
<td>0.000</td>
<td>412 (33)</td>
<td>3809 (23)</td>
<td>0.000</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>229 (85)</td>
<td>14 054 (79)</td>
<td>0.016</td>
<td>998 (80)</td>
<td>13 285 (79)</td>
<td>0.408</td>
</tr>
<tr>
<td>Prior heart failure, n (%)</td>
<td>105 (39)</td>
<td>5688 (32)</td>
<td>0.014</td>
<td>594 (48)</td>
<td>5199 (31)</td>
<td>0.000</td>
</tr>
<tr>
<td>Prior stroke/TIA, n (%)</td>
<td>58 (22)</td>
<td>3565 (20)</td>
<td>0.540</td>
<td>230 (18)</td>
<td>3393 (20)</td>
<td>0.138</td>
</tr>
<tr>
<td>Type of AF, n (%)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Paroxysmal</td>
<td>96 (36)</td>
<td>5847 (33)</td>
<td>0.333</td>
<td>430 (34)</td>
<td>5513 (33)</td>
<td>0.222</td>
</tr>
<tr>
<td>Persistent</td>
<td>87 (32)</td>
<td>5702 (32)</td>
<td>0.926</td>
<td>377 (30)</td>
<td>5412 (32)</td>
<td>0.151</td>
</tr>
<tr>
<td>Permanent</td>
<td>87 (32)</td>
<td>6288 (35)</td>
<td>0.303</td>
<td>444 (36)</td>
<td>5931 (35)</td>
<td>0.820</td>
</tr>
<tr>
<td>CHADS2 score, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>58 (22)</td>
<td>5725 (32)</td>
<td>0.000</td>
<td>278 (22)</td>
<td>5505 (33)</td>
<td>0.000</td>
</tr>
<tr>
<td>2</td>
<td>95 (35)</td>
<td>6358 (36)</td>
<td>0.879</td>
<td>458 (37)</td>
<td>5995 (36)</td>
<td>0.451</td>
</tr>
<tr>
<td>3-6</td>
<td>117 (43)</td>
<td>5759 (32.3)</td>
<td>0.000</td>
<td>515 (41)</td>
<td>5361 (32)</td>
<td>0.000</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD), mL/min</td>
<td>67.7 (26)</td>
<td>73.7 (65.7)</td>
<td>0.000</td>
<td>69.6 (28)</td>
<td>73.9 (67)</td>
<td>0.000</td>
</tr>
<tr>
<td>30–49 mL/min, n (%)</td>
<td>77 (29)</td>
<td>3484 (20)</td>
<td>0.000</td>
<td>330 (26)</td>
<td>3231 (19)</td>
<td>0.000</td>
</tr>
<tr>
<td>50–79 mL/min, n (%)</td>
<td>115 (43)</td>
<td>8432 (47)</td>
<td>0.128</td>
<td>543 (43)</td>
<td>8004 (48)</td>
<td>0.005</td>
</tr>
<tr>
<td>≥80 mL/min, n (%)</td>
<td>76 (28)</td>
<td>5778 (32)</td>
<td>0.140</td>
<td>363 (29)</td>
<td>5491 (33)</td>
<td>0.010</td>
</tr>
<tr>
<td>Baseline medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>130 (48)</td>
<td>7023 (39)</td>
<td>0.003</td>
<td>604 (48)</td>
<td>6549 (39)</td>
<td>0.000</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>29 (11)</td>
<td>991 (6)</td>
<td>0.000</td>
<td>134 (11)</td>
<td>886 (5)</td>
<td>0.000</td>
</tr>
<tr>
<td>ASA and clopidogrel</td>
<td>20 (8)</td>
<td>641 (4)</td>
<td>0.000</td>
<td>96 (8)</td>
<td>565 (3)</td>
<td>0.000</td>
</tr>
<tr>
<td>β-blocker</td>
<td>188 (70)</td>
<td>11 210 (63)</td>
<td>0.021</td>
<td>837 (67)</td>
<td>10 561 (63)</td>
<td>0.003</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>188 (70)</td>
<td>11 795 (66)</td>
<td>0.224</td>
<td>900 (72)</td>
<td>11 083 (66)</td>
<td>0.000</td>
</tr>
<tr>
<td>Statins</td>
<td>160 (59)</td>
<td>7897 (44)</td>
<td>0.000</td>
<td>653 (52)</td>
<td>7404 (44)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; UA, unstable angina; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; CAD, coronary artery disease; TIA, transient ischemic attack; AF, atrial fibrillation; CHADS2, score based on congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or TIA; ASA, acetylsalicylic acid; ACE, angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.
warfarin were similarly present in this high-risk group of patients. Analysis of the net clinical benefit confirmed the superiority of dabigatran 150 mg concerning stroke and the net clinical benefit and the benefit of the dabigatran 110-mg dose concerning major bleeding compared with warfarin even in these subgroups.

Previous Studies
Several large randomized trials of new anticoagulant drugs versus warfarin have been completed in recent years.6–9 In all of these trials, rates of new MIs were low across all treatment groups. For instance, in the ACTIVE W trial (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events), only 23 of 3371 patients in the warfarin group and 36 of 3335 patients treated with aspirin plus clopidogrel had a new MI during a median follow-up of 1.28 years.6 Similarly low MI rates were observed in the SPORTIF (Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation) III and V studies.7,8 These low MI rates are in agreement with those observed in RE-LY and imply that any differences in new MI events between treatment groups may be subject to a play of chance. All of these studies were underpowered to detect an effect of treatment on risk of MI.

A few studies have specifically examined the effects of direct thrombin inhibitors on recurrent MI in patients who

<table>
<thead>
<tr>
<th>Table 4. Timing of Myocardial Ischemic Events</th>
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<tbody>
<tr>
<td>Patients With MI</td>
</tr>
<tr>
<td>Dabigatran 110 mg</td>
</tr>
<tr>
<td>Dabigatran 150 mg</td>
</tr>
<tr>
<td>Warfarin</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Total randomized, n</td>
</tr>
<tr>
<td>First event on study drug only, n (%)</td>
</tr>
<tr>
<td>First event 1 to 6 d off study drug, n (%)</td>
</tr>
<tr>
<td>First event &gt;6 d off study drug, n (%)</td>
</tr>
<tr>
<td>First event &gt;90 d off study drug, n (%)</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; UA, unstable angina; CABG, coronary artery bypass graft; and PCI, percutaneous coronary intervention.

Figure 2. Cardiovascular events and bleeding in patients with prior coronary artery disease (CAD) or myocardial infarction (MI). D110 indicates dabigatran 110 mg BID; D150, dabigatran 150 mg BID; WAR, warfarin; SEE, systemic embolic event; UA, unstable angina; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; and P(INTER), P for interaction.
had survived a recent acute coronary syndrome.\textsuperscript{10,11} Wallentin et al\textsuperscript{10} reported that ximelagatran plus acetylsalicylic acid was more effective than acetylsalicylic acid alone in preventing major cardiovascular events, including new MIs, during a 6-month treatment period. In a similar trial evaluating dabigatran, Oldgren et al\textsuperscript{11} reported a small and nonsignificantly higher number of MIs in dabigatran-treated patients than in a placebo group, but cardiovascular deaths occurred less frequently with dabigatran 110 or 150 mg than in the placebo group (all differences not statistically significant). A recent meta-analysis of randomized dabigatran studies similarly reported a higher incidence of MI or acute coronary syndromes in patients taking the thrombin inhibitor.\textsuperscript{5} However, the control arms of these studies included placebo, warfarin, or enoxaparin treatments, and thus, a more detailed analysis of the effects of dabigatran on coronary events against the different comparators appears to be necessary.

The above data suggest that the available information is too sparse to assess the effects of direct thrombin inhibitors on MI. Furthermore, given that in the AF trials, the comparison of direct thrombin inhibitors is versus warfarin, even if there is a higher rate of MI with direct thrombin inhibitors, this may be because warfarin is very effective and direct thrombin inhibitors may be less so (but more effective than no treatment). Previous controlled trials have shown that warfarin is very effective at reducing recurrent MI in coronary patients.\textsuperscript{12,13} In AF trials with new antithrombotic agents, concomitant use of clopidogrel or platelet inhibitors other than low-dose aspirin and recent coronary events have usually been exclusion criteria, which lowers the MI risk in the exposed population. The current dilemma can therefore only be resolved by large trials of direct thrombin inhibitors versus placebo or aspirin in individuals at high risk of coronary events. Given the higher rates of stroke and systemic embolic events in AF patients and the relatively low rates of MI, the current evidence from RE-LY indicates that in AF patients, the benefits on stroke reduction and bleeding with dabigatran compared with warfarin are likely to outweigh any potential impact on MI.

\textbf{Study Limitations}

The analyses presented in the present report were not prespecified and are post hoc. Thus, some of the outcome events were not prespecified and adjudicated. Although all deaths and MIs were adjudicated, other events, such as unstable angina or need for revascularization, were derived from hospitalization forms or adverse events/serious adverse events reports. It would be preferable if all the events presented in the present report had been prespecified, collected on purpose-designed case report forms, and adjudicated. Nonetheless, the collection of adverse events was performed assiduously and provides reliable information.

\textbf{Conclusions}

A nonsignificantly higher number of MIs were observed with dabigatran than with warfarin in RE-LY, but there was no excess of other myocardial ischemic events. The composite of MI, stroke, other thrombotic events, and major bleeding occurred less frequently with each dose of dabigatran than with warfarin and for the higher dose of dabigatran was nominally statistically significant.

\textbf{Sources of Funding}

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\textbf{Disclosures}

Dr Hohnloser reports having received consulting and lecture fees from Boehringer Ingelheim, BMS, Bayer, Pfizer, and Sanofi-aventis. Dr Oldgren has received institutional grant support from Boehringer Ingelheim and consulting fees and lecture fees from Bayer, Boehringer Ingelheim, and BMS. Dr Wallentin has received consulting fees, lecture fees, and grant support from Boehringer Ingelheim; consulting fees from Regado and Athera; lecture fees from Boehringer Ingelheim, AstraZeneca, and Eli Lilly; and grant support from AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, and Schering Plough. Dr Ezekowitz has received consulting fees, lecture fees, and grant support from Boehringer Ingelheim and Aryx Therapeutics; consulting fees from sanofi-aventis; and lecture fees and grant support from Portola Pharmaceuticals. Drs Reilly and Bruceckmann are employees of Boehringer Ingelheim. Dr Eikelboom has received consulting fees, lecture fees, and grant support from Boehringer Ingelheim, AstraZeneca, Sanofi-aventis, and GlaxoSmithKline; consulting fees and lecture fees from Eisai Pharmaceuticals, Eli Lilly, and McNeil; and consulting fees from Bristol-Myers Squibb, Coragen, Medical Corporation, and Daiichi-Sankyo. Dr Yusuf has received consulting fees, lecture fees, and grant support from Boehringer Ingelheim and consulting fees from AstraZeneca, Bristol-Myers Squibb, and sanofi-aventis. Dr Connolly reports receiving consulting fees, lecture fees, and grant support from Boehringer Ingelheim. Dr Yang reports no conflicts.

\textbf{References}


Dabigatran etexilate is a novel, potent, competitive, and reversible direct thrombin inhibitor that recently has been compared with warfarin for prevention of thromboembolic events in 18,113 patients with nonvalvular atrial fibrillation (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY trial]). At a dose of 110 mg twice daily, dabigatran had similar efficacy as warfarin in preventing stroke and systemic embolism but lower rates of major hemorrhage. At a dose of 150 mg twice daily, dabigatran was associated with lower rates of stroke and systemic embolism than warfarin but similar rates of major hemorrhage. This post hoc study evaluated the incidence of myocardial ischemic events, including myocardial infarction (MI), in the 3 treatment arms. MI occurred at annual rates of 0.82% and 0.81% with dabigatran 110 mg or 150 mg BID compared with 0.64% in patients taking warfarin (hazard ratio 1.29, 95% confidence interval 0.96–1.75, \( P = 0.09 \) for dabigatran 110 mg; hazard ratio 1.27, 95% confidence interval 0.94–1.71, \( P = 0.12 \) for dabigatran 150 mg). Events prespecified as “net clinical benefit” (all strokes, systemic embolism, MI, pulmonary embolism, major bleeding, and all-cause death) occurred at a rate of 7.34% per year with dabigatran 110 mg, 7.11% per year with dabigatran 150 mg, and 7.91% per year with warfarin (hazard ratio 0.92, 95% confidence interval 0.84–1.01, \( P = 0.09 \) for dabigatran 110 mg; 0.90, 95% confidence interval 0.82–0.99, \( P = 0.02 \) for dabigatran 150 mg). In conclusion, in patients with atrial fibrillation, there was a nonsignificant increase in MIs with dabigatran compared with warfarin, but other myocardial ischemic events were not increased. The net clinical benefit favors dabigatran over warfarin in patients with or without a baseline history of MI or coronary artery disease.