Dabigatran and Warfarin in Vitamin K Antagonist–Naive and –Experienced Cohorts With Atrial Fibrillation

Michael D. Ezekowitz, MBChB, DPhil, FRCP; Lars Wallentin, MD, PhD; Stuart J. Connolly, MD; Amit Parekh, MD; Michael R. Chernick, PhD; Janice Pogue, MSc; Timothy H. Aikens, BA; Sean Yang, MSc; Paul A. Reilly, PhD; Gregory Y.H. Lip, MD; Salim Yusuf, FRCP, DPhil; and the RE-LY Steering Committee and Investigators

Background—The comparison of anticoagulants dabigatran and warfarin might be most equitable in vitamin K antagonist (VKA)–naive patients.

Methods and Results—Warfarin and 2 doses of dabigatran—110 mg BID (D110) and 150 mg BID (D150)—were compared in a balanced population of VKA-naive (≥62 days of lifetime VKA exposure, with 33% never prescribed a VKA) and VKA-experienced patients with atrial fibrillation (n=18 113). For VKA-naive and -experienced patients assigned warfarin, the time in therapeutic range (international normalized ratio 2.0 to 3.0) was 62% and 67%, respectively, and 61% and 66% for those never and ever prescribed a VKA. In VKA-naive patients, stroke and systemic embolism rates were 1.57%, 1.07%, and 1.69% per year for D110, D150, and warfarin, respectively. D110 was similar to warfarin (P=0.65); D150 was superior (P=0.005). Major bleeding rates were 3.11%, 3.34%, and 3.57% per year, respectively. D110 and D150 were similar to warfarin (P=0.19 and P=0.55). Intracranial bleeding rates were 0.19%, 0.33%, and 0.73% per year, respectively. D110 and D150 were lower than warfarin (P<0.001 and P=0.005). In VKA-experienced patients, stroke and systemic embolism rates were 1.51%, 1.15%, and 1.74% per year for D110, D150, and warfarin, respectively. D110 was similar to warfarin (P=0.32); D150 was superior (P=0.007). Major bleeding rates were 2.66%, 3.30%, and 3.57% per year, respectively. D110 was lower than warfarin (P=0.003); D150 was similar (P=0.41). Intracranial bleeding rates were 0.26%, 0.32%, and 0.79% per year, respectively. D110 and D150 were lower than warfarin (P<0.001 for both). Results were similar for patients never on a VKA.

Conclusions—Previous VKA exposure does not influence the benefits of dabigatran at either dose compared with warfarin.


Key Words: anticoagulants ■ arrhythmia ■ atrial fibrillation ■ stroke ■ prevention

The Randomized Evaluation of Long-term anticoagulation therapy (RE-LY) trial was a global trial that evaluated 2 doses of the novel anticoagulant dabigatran (110 mg BID [D110] and 150 mg BID [D150]) against usual therapy with warfarin (international normalized ratio [INR] 2.0 to 3.0) for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The design and main results have been published. This analysis is a prespecified substudy of the RE-LY trial comparing 2 subpopulations: patients naive to and experienced with vitamin K antagonists (VKAs). All patients in the RE-LY trial fell into 1 of these 2 distinct subgroups. The primary study outcome of RE-LY was stroke or systemic embolism. The primary safety outcome was major hemorrhage. Other outcomes included myocardial infarction, pulmonary embolism, transient ischemic attack, hospitalization, and death. An international team of adjudicators reviewed documents in local languages after blinding. Each primary and secondary outcome was adjudicated by 2 independent investigators who were blinded to assigned treatment. All transient ischemic attacks were reviewed to ensure that strokes had not been missed. To detect possible unreported events, symptom questionnaires were regularly administered to patients, and adverse event and hospitalization reports were scrutinized to detect unreported primary or secondary outcomes.

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Post hoc analyses of clinical trials and reviews of registry cohorts suggest that patients with atrial fibrillation who are naive to VKAs have a different response when first treated...
with warfarin compared with those who are VKA experienced. It is believed that patients who are VKA experienced have demonstrated the ability to comply with an anticoagulation regimen, have a determined, personalized dose of the VKA that achieves a therapeutic INR value between 2.0 and 3.0, and have “passed the VKA stress test,” thereby reducing the chance that sources of major bleeding are yet to be uncovered.

Dabigatran is a direct thrombin inhibitor. After oral administration, patients are therapeutically anticoagulated within 2 hours. It is 80% renally excreted. In the primary analysis, D110 was not inferior and D150 was superior to warfarin for prevention of stroke and systemic embolism, whereas major bleeding rates were lower for D110 and similar for D150 compared with warfarin, and intracranial bleeding rates were lower for both dabigatran doses. Given the uncertainty relative to the evaluation of a novel anticoagulant in VKA-naive and -experienced patients, RE-LY was designed to have a balanced enrollment of VKA-naive and -experienced patients. It is the first trial to prospectively evaluate a novel anticoagulant in VKA-naive and -experienced populations.

Hypothesis
It is expected that there will be an interaction between treatment groups and prior VKA experience on the outcomes of the study.

Methods

Study Participants
Patients (18 113) were recruited from 951 clinical centers in 44 countries. Patients were eligible if they had atrial fibrillation documented on ECG at screening or within 6 months before and at least 1 of the following characteristics: previous stroke or transient ischemic attack, a left ventricular ejection fraction of <40%, New York Heart Association class II or higher heart failure symptoms within 6 months before screening, an age of at least 75 years, or an age of 65 to 74 years with diabetes mellitus, hypertension, or coronary artery disease. Reasons for exclusion were presence of a severe heart valve disorder, stroke within 14 days or severe stroke within 6 months before screening, a condition that increased the risk of hemorrhage, a creatinine clearance of ≤30 mL/min, active liver disease, and pregnancy or chance of becoming pregnant.

In the RE-LY trial, VKA-naive was defined as having a total of ≤62 days of lifetime VKA exposure. This time frame was chosen to allow for identification of new-onset atrial fibrillation in the hospital and recruitment as an outpatient. Initially, the trial did not mandate but encouraged sites to voluntarily recruit equal proportions of VKA-naive and -experienced patients. After 8 months of enrollment, it became clear that this goal would not be met. To achieve a balanced cohort, the RE-LY operations committee implemented a quota system that required every site to enroll ≥50% VKA-naive patients from then on.

Because there is no standard definition of VKA naive, secondary analyses of the relative impacts of the 2 therapies were performed with 2 alternative definitions of VKA naive: patients not on a VKA at randomization and patients who had never been on a VKA. These secondary analyses were performed to evaluate the sensitivity of the results to the choice of definition.

Administration
The study was funded by Boehringer Ingelheim and coordinated by the Population Health Research Institute (Hamilton, Ontario, Canada). An operations committee composed of the 2 co–principal investigators (M.D.E., S.J.C.), 2 cochairmen (L.W., S.Y.), and 2 pharmaceutical company representatives (P.A.R., M. Haehl), with assistance from an international steering committee, was responsible for the design, conduct, data analysis, and reporting of the study. The study was approved by all appropriate national regulatory authorities and ethics committees. All patients provided written, informed consent. All authors vouch for the accuracy and completeness of the data and this analysis.

Statistical Analysis
The baseline characteristics of the VKA-naive and -experienced cohorts were compared by Fisher exact test, as were the reasons for permanent study drug discontinuation between treatment groups. To examine study outcomes, hazard ratios (equivalent to relative risk [RR]) were calculated comparing D110 and D150 with warfarin in VKA-naive and -experienced patients. Two-sided 95% confidence intervals (CIs) were presented in each case, and P values for interactions were used to determine whether the relative effects of treatment on the major outcomes varied by the subgroups of interest.

With each subgroup, P values comparing dabigatran with warfarin are reported with the use of a test for superiority. This analysis was repeated for the 2 additional definitions of VKA-naive patients: patients not on a VKA at randomization and patients who have never been on a VKA.

We planned to enroll 15 000 patients, which we estimated would provide 84% power to evaluate the noninferiority of each dose of dabigatran. A protocol change was made by the operations committee during the enrollment period without knowledge of emerging treatment effects to increase the sample size to 18 000 patients to maintain the statistical power in case of a low event rate. No formal power calculations were made for the VKA-naive and -experienced cohorts.

Results

Characteristics of the Study Participants
With the use of the RE-LY definition, approximately half of the patients were VKA naive (50.4%) (Table 1). Compared with the VKA-experienced cohort, the VKA-naive cohort had fewer men (58.9% versus 68.4%; P<0.001), fewer patients with diabetes mellitus (22.5% versus 24.2%; P=0.007), more patients with hypertension (80.4% versus 77.3%; P<0.001), and a higher use of aspirin (54.5% versus 24.8%; P<0.001). There were fewer patients with prior myocardial infarction (14.9% versus 18.3%; P<0.001), coronary artery disease (24.7% versus 30.9%; P<0.001), stroke (11.0% versus 14.1%; P<0.001), and transient ischemic attack (7.9% versus 10.4%; P<0.001).

There was no significant difference in congestive heart failure rates between cohorts. The mean CHADS2 score was 2.11 in the VKA-naive cohort and 2.18 in the VKA-experienced cohort (P<0.001; CHADS2 is an acronym for cardiac failure, hypertension, age, diabetes mellitus, and prior stroke or TIA).

With the use of the not-on-a-VKA-at-randomization and never-been-on-a-VKA definitions of VKA naive, VKA-naive patients were more likely to have congestive heart failure than VKA-experienced patients but were otherwise similar to the patient population according to the RE-LY definition (Table 1).

Mean time in therapeutic INR range (TTR) for patients on warfarin was 64% for the study overall and 62% and 67% for VKA-naive (RE-LY definition) and -experienced cohorts, respectively, with the use of the Rosendaal method. The differences occurred primarily in the early months of the study; the TTR in VKA-naive patients was 43%, 62%, and 67% in months 1, 6, and 12 after randomization, whereas that
for VKA-experienced patients was 55%, 68%, and 69% in months 1, 6, and 12.

**Permanent Study Drug Discontinuation Rates**

In each of the 3 treatment groups, VKA-naive patients had higher rates of permanent study drug discontinuation compared with VKA-experienced patients. In the warfarin and D110 groups, this was statistically significant (P<0.001 and P=0.02, respectively).

Rates of discontinuation because of gastrointestinal symptoms in both the VKA-naive and -experienced populations were higher for dabigatran compared with warfarin (D110 versus warfarin, VKA naive, 2.3% versus 0.9%, P<0.001; VKA experienced, 2.1% versus 0.4%, P<0.001; D150 versus warfarin, VKA naive, 2.1% versus 0.9%, P<0.001; VKA experienced, 2.1% versus 0.4%, P<0.001) (Table 2).

Discontinuation due to patient decision was lower in the VKA-experienced cohort than in the VKA-naive cohort for both D150 and warfarin (P=0.03 and P<0.001, respectively) and was similar in each for D110 (Table 3). With the use of the never-been-on-a-VKA and not-on-a-VKA-at-randomization definitions of VKA naive, comparisons of discontinuation rates were similar to those with the use of the RE-LY definition.

**Primary Outcome**

Combined stroke and systemic embolism rates were similar in the D110 group for both the VKA-naive and -experienced cohorts compared with warfarin (RR=0.93; 95% CI, 0.70 to 1.25; P=0.65 and RR=0.87; 95% CI, 0.66 to 1.15; P=0.32, respectively; P for interaction=0.72) (Table 4 and Figure 1).

In the D150 group, both VKA-naive (RR=0.63; 95% CI, 0.46 to 0.87; P=0.005) and -experienced patients (RR=0.66; 95% CI, 0.49 to 0.89; P=0.007) had a statistically significantly lower risk of stroke or systemic embolism compared with warfarin (P for interaction=0.84). With the use of the 2 alternative definitions of VKA naive, comparisons of primary outcome rates were similar, and interactions were nonsignificant.

**Major Bleeding**

Major bleeding rates were lower in VKA-experienced patients when D110 was compared with warfarin (RR=0.74; 95% CI, 0.60 to 0.90; P=0.003) (Table 4 and Figure 2). VKA-naive patients in the D110 group (RR=0.87; 95% CI, 0.72 to 1.07; P=0.19) and VKA-naive (RR=0.94; 95% CI, 0.77 to 1.15; P=0.55) and -experienced patients (RR=0.92; 95% CI, 0.76 to 1.12; P=0.41) in the D150 group were similar compared with warfarin. The P values for the interaction of treatment group and VKA status are 0.25 for D110 versus warfarin and 0.90 for D150 versus warfarin. With the use of the 2 alternative definitions of VKA naive, comparisons of primary outcome rates were similar, and interactions were nonsignificant.

**Intracranial Bleeding**

Intracranial bleeding rates were lower in the D110 VKA-naive and -experienced cohorts (RR=0.27; 95% CI, 0.14 to 0.52; P<0.001; RR=0.32; 95% CI, 0.18 to 0.56; P<0.001, respectively; P for interaction=0.66) and the D150 VKA-naive and -experienced cohorts (RR=0.46; 95% CI, 0.27 to 0.78; P=0.005; RR=0.40; 95% CI, 0.24 to 0.67; P<0.001, respectively; P for interaction=0.71) compared with warfarin (Table 4 and Figure 3).

Table 1. Treatment Groups and Baseline Characteristics of the Study Participants by VKA Cohort and VKA Status Definition*

<table>
<thead>
<tr>
<th></th>
<th>VKA Naive</th>
<th>VKA Experienced</th>
<th>P</th>
<th>Never Been on a VKA</th>
<th>Ever Been on a VKA</th>
<th>P</th>
<th>No VKA at Randomization</th>
<th>VKA at Randomization</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total randomized</td>
<td>9123 (50.4)</td>
<td>8989 (49.6)</td>
<td></td>
<td>5748 (32.7)</td>
<td>11830 (67.3)</td>
<td></td>
<td>6924 (38.2)</td>
<td>11189 (61.8)</td>
<td></td>
</tr>
<tr>
<td>Dabigatran, 110 mg BID</td>
<td>3004 (49.9)</td>
<td>3011 (50.1)</td>
<td></td>
<td>1868 (31.1)</td>
<td>3952 (65.7)</td>
<td></td>
<td>2264 (37.6)</td>
<td>3751 (62.4)</td>
<td></td>
</tr>
<tr>
<td>Dabigatran, 150 mg BID</td>
<td>3026 (49.8)</td>
<td>3049 (50.2)</td>
<td></td>
<td>1909 (31.4)</td>
<td>3979 (65.5)</td>
<td></td>
<td>2317 (38.1)</td>
<td>3759 (61.9)</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>3093 (51.4)</td>
<td>2929 (48.6)</td>
<td></td>
<td>1972 (32.7)</td>
<td>3899 (64.7)</td>
<td></td>
<td>2344 (38.9)</td>
<td>3678 (61.1)</td>
<td></td>
</tr>
<tr>
<td>Mean age, y</td>
<td>71.6</td>
<td>71.4</td>
<td>0.27</td>
<td>71.6</td>
<td>71.4</td>
<td>0.12</td>
<td>71.5</td>
<td>71.5</td>
<td>0.71</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>4755 (52.1)</td>
<td>4675 (52.0)</td>
<td>0.89</td>
<td>3081 (53.6)</td>
<td>6275 (53.0)</td>
<td>0.49</td>
<td>3705 (53.5)</td>
<td>5955 (53.2)</td>
<td>0.71</td>
</tr>
<tr>
<td>Male</td>
<td>5369 (58.9)</td>
<td>6145 (68.4)</td>
<td>&lt;0.001</td>
<td>3318 (57.7)</td>
<td>7867 (66.5)</td>
<td>&lt;0.001</td>
<td>4095 (59.1)</td>
<td>7419 (66.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
With the use of both the never-been-on-a-VKA and the not-on-a-VKA-at-randomization definitions of VKA naive, intracranial bleeding rates for D150 VKA-naive patients were similar to those for warfarin. Rates for D150 VKA-experienced and D110 VKA-naive and -experienced patients were lower compared with warfarin. Interactions were non-significant (Table 4).

**Other Outcomes**

**Life-Threatening Bleeding, Disabling Stroke, and Death**

Rates of life-threatening bleeding, disabling stroke, and death (when combined) were statistically significantly lower in the VKA-experienced cohort in both the D110 (RR=0.82; 95% CI, 0.70 to 0.96; P=0.01) and D150 groups (RR=0.80; 95% CI, 0.68 to 0.93; P=0.004) compared with warfarin but similar for VKA-naive patients (Table 4).

**Gastrointestinal Bleeding**

Gastrointestinal bleeding rates were similar for D110 compared with warfarin but significantly higher in both the D150 VKA-naive (RR=1.56; 95% CI, 1.15 to 2.10; P=0.004) and -experienced cohorts (RR=1.42; 95% CI, 1.06 to 1.89; P=0.02) compared with warfarin.

With the use of the 2 alternative definitions of VKA naive, rates of these outcomes were similar except for a significant interaction between treatment group and VKA status for D150 versus warfarin on the life-threatening bleeding, disabling stroke, and death outcome with the not-on-a-VKA-at-randomization definition (P for interaction=0.04) (Table 4).

**Comparison of VKA-Naive and -Experienced Patients Within Treatment Groups**

With the use of the RE-LY definition of VKA naive, in the D110 group the life-threatening bleeding, disabling stroke, and death (combined) rate was lower in VKA-experienced patients than in VKA-naive patients (RR=0.83; 95% CI, 0.71 to 0.98; P=0.03), as was the cardiovascular death rate
(RR = 0.73; 95% CI, 0.58 to 0.92; P = 0.007) (Table 3). In the D150 group, the life-threatening bleeding, disabling stroke, and death and cardiovascular death rates trended lower in VKA-experienced patients compared with VKA-naive patients. There were no other significant differences in RR for any outcomes between VKA-naive and -experienced patients within treatment groups.

Discussion

RE-LY was the first prospective study evaluating a novel oral anticoagulant to include a VKA-naive cohort for comparison with a VKA-experienced cohort as a prespecified analysis.1,2 The hypothesis tested was supported by the lower TTR in VKA-naive patients compared with VKA-experienced patients. Despite higher permanent assigned therapy discontinuation rates in VKA-naive patients, the higher withdrawal rates in the VKA-naive cohort irrespective of treatment assignment. VKA-naive patients had a lower TTR than VKA-experienced in the early months of therapy. Despite higher permanent assigned therapy discontinuation rates in VKA-naive patients (the analysis was on an intention-to-treat basis) and a higher TTR in VKA-experienced patients, there was no significant interaction between treatment and prior VKA use on major outcomes. The only exception was for the combined secondary outcome measure of life-threatening bleeding, disabling stroke, and death in the D150 group compared with warfarin and only for the not-on-a-VKA-at-randomization definition (P = 0.04) (Table 4 and Figure 1). The alternative definitions were not part of the prespecified analysis, and the importance of this interaction remains unclear.

There were differences in baseline characteristics (particularly prior stroke, myocardial infarction, and transient ischemic attack, gender, coronary artery disease, and baseline aspirin use) between the VKA-naive and -experienced cohorts. Some, but not all, of these differences might be explained by multiple testing and/or the large sample size that enables small, clinically nonsignificant effects to be detected.15 Despite demographic differences between VKA-naive and -experienced patients, the outcome of the study was not affected.

There has been inconsistency in the definition of VKA-naive in previous studies. Several early studies of warfarin versus placebo or aspirin recruited patients who were VKA naive, but the definition of VKA naive varied. For example, the Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation (AFASAK) trial excluded patients with >6 months of previous anticoagulation therapy.7 The Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) trial had patients stop anticoagulation for 6 months before randomization to warfarin or placebo.8 More recent trials, such as the Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) III and V trials, which compared ximelagatran with warfarin for stroke risk reduction in atrial fibrillation, included VKA-naive patients defined as those not on a VKA at study entry. These patients constituted 27% and 15% of the total number in the warfarin arms of SPORTIF III and V, respectively.3,4 With the use of the SPORTIF definition, a post hoc analysis found higher INR variability for VKA-naive patients versus -experienced patients (SD, 0.85 versus 0.61; P < 0.001),9 a finding similar to that reported here. Greater INR variability and lower TTR values are strong predictors of high event rates on VKAs.16 The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W) trial compared a combination of clopidogrel and aspirin with warfarin for prevention of vascular events in patients with atrial fibrillation. Like the SPORTIF trials, ACTIVE W did not prospectively recruit a cohort of VKA-naive patients. In a post hoc analysis of the trial, 22% of patients in the warfarin arm were VKA naive (not on a VKA at study entry). With the use of this definition,
unlike the findings from RE-LY, VKA-naive patients randomized to warfarin had higher rates of stroke and systemic embolism (4.71% versus 3.72% per year) and major hemorrhage (2.92% versus 2.02% per year) compared with VKA-experienced patients, but, like RE-LY, they had a higher rate of warfarin discontinuation (P = 0.008) and worse INR control (P < 0.001). The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial compared warfarin with...
aspirin for stroke risk reduction in elderly patients with atrial fibrillation. Sixty percent of patients randomized to warfarin were VKA naive (not on a VKA at study entry). By this definition, as in RE-LY (although in an older population), stroke and systemic embolism and major hemorrhage rates in the warfarin arm were similar in the VKA-naive and -experienced cohorts (stroke and systemic embolism, 2.0% versus 1.4% per year; major hemorrhage, 2.1% versus 1.6% per year).6

Because there is no standard definition of VKA naive, the analyses for the current report were done with the use of the prespecified definition from the RE-LY trial (≤62 days of lifetime VKA use) and 2 alternative definitions (not on a VKA at randomization and were never on a VKA). The
results were similar for all 3 definitions, demonstrating that dabigatran is a safe and effective alternative to warfarin in this context regardless of length or timing of prior VKA use. The definitions evaluated represent extremes, and thus one can conclude that the choice of definition did not matter. If differences in outcomes between VKA-experienced and -naive patients are only important for a short time after onset of treatment, the relatively long mean duration of exposure of 2 years in the RE-LY trial may have masked the short-term differences. The differences in INR control for the first 6 months in the warfarin treatment group suggest that this may be the case for VKAs.

The clinical implications of this analysis of the RE-LY trial are important. The results of this analysis demonstrate that both patients starting dabigatran without prior VKA experience and those switching to dabigatran from a VKA benefit from dabigatran at either dose compared with warfarin.

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Disclosures

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References


CLINICAL PERSPECTIVE

This report compares the novel anticoagulant dabigatran with the current standard, warfarin, in vitamin K antagonist-naive and –experienced populations of patients with atrial fibrillation who are at risk of stroke. It was believed that patients who were vitamin K antagonist experienced were likely to do better than patients who are new to anticoagulation because they have demonstrated the ability to comply with an anticoagulation regimen, they have a personalized dose of warfarin that achieves a therapeutic international normalized ratio value, and they have passed the “vitamin K antagonist stress test,” thereby reducing the chance of uncovering major sources of bleeding. This report found that dabigatran, the novel direct thrombin inhibitor, was better than the comparator warfarin for both vitamin K antagonist-naive and –experienced patients and therefore could be used clinically in both cases.
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