The justification for implanting a left atrial appendage (LAA) exclusion device is based on the assumption that the pathogenesis of stroke in every patient with atrial fibrillation (AF) is the embolism of clot from the LAA to the brain. This hypothesis, although true in some patients, is a simplistic view of a more complex disease. What is well established is that AF is often accompanied by hypertension, diabetes mellitus, systolic left ventricular dysfunction, vascular disease, and previous stroke, conditions that are independent risk factors for stroke.1 In an individual patient it is often impossible to determine which among these factors is responsible for a stroke. Of interest, AF may be the underlying cause of an ischemic stroke but may also go undetected, and lead to the erroneous diagnosis of cryptogenic stroke.2,3 The common pathogenesis of ischemic stroke is thrombosis, and anticoagulation is a highly effective preventative measure particularly when AF is present.1,4 Noteworthy, warfarin, against which the novel anticoagulants and Watchman device have been compared, is very effective for stroke prevention in patients with AF, with a reduction of up to 81% against placebo in open-label trials and 79% in the only completed double-blind trial.5,7 The novel anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) were developed primarily to obviate the difficulties of using warfarin. The expectation was to show noninferiority for both efficacy and safety compared with warfarin.9–12 In definitive clinical trials these agents have either exceeded or met expectations against warfarin. Dabigatran 150 mg twice daily (BID) and apixaban (5 mg BID down-titrated to 2.5 mg BID for age ≥80 years, body weight ≤60 kg, and serum creatinine ≥1.5 mg/dL) were superior in efficacy to well-controlled warfarin.13,14 Rivaroxaban (20 mg down-titrated to 15 mg daily if creatinine clearance, CrCl, 30–49 mL/min) and Edoxaban (60 mg down-titrated to 30 mg daily if CrCl 30–50 mL/min, body weight ≤60 kg or if a P-glycoprotein inhibiting drug was used) were noninferior to warfarin.15,16 In addition, all novel anticoagulants achieve the objective of obviating the difficulties of warfarin in having a rapid onset of action, a short half-life, and not requiring monitoring.13–18 The characteristics of the novel anticoagulants are summarized in Table 1.13–18 None were tested with an antidote, and none of the studies of the novel agents had excess bleeding compared with warfarin.13–16 Three studies in fact demonstrated that 1 of the doses tested had a reduction in major bleeding compared with warfarin without compromising efficacy.13,14,16 The novel anticoagulants mark a significant advance over warfarin therapy and thus provide a formidable hurdle for the LAA exclusion devices.

The LAA exclusion devices (Watchman, Lariat, Amplatzer, and Plaato; Table 2) are limited in their scope of study with less patient exposure than the novel anticoagulants and only 2 warfarin-controlled studies.19–28 The trials...
testing LAA exclusion devices have a sample size ranging from 60 to 707 patients, whereas the size of the trials for novel anticoagulants ranges from approximately 14,000 to 21,000 patients. All of the trials testing novel anticoagulant were randomized, controlled, prospective studies with a direct comparison with warfarin. The mean follow-up period ranges from 11.8 months to 3.75 years for the device studies (Table 2) and 1.8 to 4.3 years for the novel anticoagulants.

In addition to evaluation in far fewer patients and only 1 device compared against warfarin (Watchman), all LAA exclusion devices have procedural risks that are an immediate event that may be life threatening. Complications include implant failure, cardiac tamponade, hemopericardium, and

Table 1. NOAC Pharmacological Profiles

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Function</th>
<th>Higher dose</th>
<th>Lower dose</th>
<th>Food interactions</th>
<th>Bioavailability</th>
<th>Metabolism</th>
<th>Plasma protein bound</th>
<th>Onset of action</th>
<th>T1/2</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibitor</td>
<td>150 mg BID (CrCl &gt;30 mL/min)</td>
<td>75 mg BID (CrCl 15–30 mL/min)</td>
<td>None</td>
<td>6%</td>
<td>Conversion by serum esterase to active metabolite, dabigatran</td>
<td>0.5–2 h</td>
<td>12–14 h</td>
<td>Renal, 80%; P-gp efflux</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Factor Xa inhibitor</td>
<td>20 mg/d (CrCl &gt;50 mL/min)</td>
<td>15 mg/d (CrCl 15-50 mL/min)</td>
<td>Taken with evening meal to increase bioavailability</td>
<td>66% (fasting), 100% (with meal)</td>
<td>CYP3A4; no active circulating metabolites</td>
<td>95%</td>
<td>5–9 h (young), 11–13 h (elderly)</td>
<td>Renal, 66% (36% active, unchanged); Fecal, 28%; P-gp, ABCG2 efflux</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>Factor Xa inhibitor</td>
<td>5 mg BID</td>
<td>2.5 mg BID (if two of the following present: age &gt;80, weight &lt; 60 kg, serum creatinine &gt;1.5)</td>
<td>None</td>
<td>50%</td>
<td>CYP3A4/5; active metabolites modest</td>
<td>87%</td>
<td>3 - 4 h</td>
<td>Renal, 27%; P-gp efflux</td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Factor Xa inhibitor</td>
<td>60 mg/d</td>
<td>30 mg/d</td>
<td>None</td>
<td>62%</td>
<td>CYP3A4/5; active metabolites modest</td>
<td>40% to 59%</td>
<td>8–15 h</td>
<td>Fecal, 60%; Renal, 35%; 70% unchanged; P-gp efflux</td>
<td></td>
</tr>
</tbody>
</table>

BID indicates twice daily; CrCl, creatinine clearance; h, hours; NOAC, novel oral anticoagulant; P-gp, permeability glycoprotein; and T1/2, half-life.

*Dabigatran 110 mg BID was not approved by the Food and Drug Administration in the United States; it is approved in other countries for patients with an elevated bleeding risk.

Table 2. Left Atrial Appendage Exclusion Device Background

<table>
<thead>
<tr>
<th>Device</th>
<th>Year</th>
<th>Design</th>
<th>Concept</th>
<th>Subjects, n</th>
<th>Follow-up, mean</th>
<th>CHADS2 score, mean</th>
<th>Warfarin TTR</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREVAIL</td>
<td>2014</td>
<td>Randomized, controlled, multi-center</td>
<td>Watchman vs. Warfarin</td>
<td>407</td>
<td>11.8 mo</td>
<td>2.6</td>
<td>68%</td>
<td>Watchman vs. Warfarin</td>
</tr>
<tr>
<td>ASAP</td>
<td>2012</td>
<td>Prospective, uncontrolled, multi-center</td>
<td>Watchman vs. Warfarin</td>
<td>150</td>
<td>14 mo</td>
<td>2.8</td>
<td>—</td>
<td>Watchman vs. Warfarin</td>
</tr>
<tr>
<td>PROTECT</td>
<td>2009</td>
<td>Randomized, controlled, multi-center</td>
<td>Watchman initial experience</td>
<td>707</td>
<td>2.3 yr</td>
<td>2.2</td>
<td>—</td>
<td>Watchman initial experience</td>
</tr>
<tr>
<td>AF</td>
<td>2007</td>
<td>Prospective, uncontrolled, single-center</td>
<td>Lariat initial experience</td>
<td>75</td>
<td>2 yr</td>
<td>1.8</td>
<td>—</td>
<td>Lariat initial experience</td>
</tr>
<tr>
<td>Sick et al.</td>
<td>2012</td>
<td>Prospective, uncontrolled, single-center</td>
<td>Anticoagulation contraindicated†</td>
<td>89</td>
<td>1 yr</td>
<td>1.9</td>
<td>—</td>
<td>Anticoagulation contraindicated†</td>
</tr>
<tr>
<td>Bartus et al.</td>
<td>2014</td>
<td>Retrospective, uncontrolled, single-center</td>
<td>Warfarin</td>
<td>60</td>
<td>1.8 yr</td>
<td>2.6</td>
<td>—</td>
<td>ACP 10-year experience‡</td>
</tr>
<tr>
<td>Wiebe et al.</td>
<td>2013</td>
<td>Retrospective, uncontrolled, single-center</td>
<td>Warfarin</td>
<td>152</td>
<td>2.6 yr</td>
<td>CHA2DS2-Vasc (3.4)</td>
<td>—</td>
<td>Anticoagulation contraindicated†</td>
</tr>
<tr>
<td>Nietlispach et al.</td>
<td>2009</td>
<td>Prospective, uncontrolled, multi-center</td>
<td>ACP 10-year experience‡</td>
<td>64</td>
<td>3.75 yr</td>
<td>2.6</td>
<td>—</td>
<td>Anticoagulation contraindicated†</td>
</tr>
<tr>
<td>Block et al.</td>
<td>2009</td>
<td>Prospective, uncontrolled, multi-center</td>
<td>ACP 10-year experience‡</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

ACP indicates Amplatz cardiac plug; CHADS2 score for stroke risk, ranges from 0 to 6, 2 points are assigned for previous stroke, and 1 point for each of the following: congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus; INR, international normalized ratio; LAA, left atrial appendage; and TTR, time in therapeutic range (INR 2.0–3.0).

*Data based on 2.3-year study.
†Risk of bleeding, risk of falling, and labile INR were the most common reasons for contraindication.
‡Dedicated and nondedicated devices used.
pericardial effusion, device embolization, and stroke. Operator experience is critical to minimize procedural complications. Experience with the trans-septal puncture procedure is a prerequisite. After implantation, the status of the device must be monitored by transesophageal echo (TEE), requiring an additional procedure necessitating conscious sedation. For the novel anticoagulants the complication rate at the initiation of therapy is no higher than at later periods of treatment. The safety profiles in anticoagulation-naive patients are similar to anticoagulation-experienced patients. Furthermore, in patients at high risk for bleeding, current devices pose a limitation. Devices require anticoagulation after implantation to prevent thrombus formation as the device surface endothelializes and therefore place the patient at excess risk for bleeding. Chronic anticoagulation may be needed in patients with a peri-device leak in which the LAA is not completely occluded to prevent thromboembolic complication. Patients receive anticoagulation therapy (aspirin and clopidogrel) in the months after device implantation. Thus, patients with contraindications to anticoagulation or antiplatelet therapy are not ideal candidates for LAA exclusion devices. The major rationale for device implantation is to circumvent anticoagulation therapy in patients in whom anticoagulation is contraindicated. An elevated risk of bleeding, risk of falling, and labile international normalized ratio (INR) were common reasons for warfarin contraindications in LAA device studies. However, LAA device use is inseparable from short-term anticoagulation or antiplatelet therapy post-procedure. Therefore, it is impossible for LAA exclusion devices to completely obviate the need for conventional anticoagulant or antiplatelet therapy. We now describe the evidence in support of the main proposition.

**Clinical Trial Comparison**

There are no trials that directly compare novel anticoagulants and LAA devices. Therefore, we use indirect comparisons between novel anticoagulants and LAA exclusion devices on the basis of the warfarin-controlled trials and the stroke risk (CHADS score) of each trial. The efficacy, safety, and mortality outcomes for the novel anticoagulant trials are summarized in Tables 3, 4, and 5, respectively. The results from the device trials are summarized in Table 6. The mean CHADS score in the patient population varies by study. The CHADS score estimates stroke risk, and it ranges from 0 to 6, with 2 points assigned for previous stroke, and 1 point for each of the following: congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus. The mean CHADS score for the device studies ranges from 1.8 to 2.8 (Table 2) and for the novel anticoagulant trials are 2.1 (RE-LY, ARISTOTLE), 2.8 (ENGAGE AF-TIMI 48), and 3.5 (ROCKET AF). The RE-LY, ARISTOTLE, and PROTECT AF studies had a similar mean CHADS score (2.1, 2.1, and 2.2, respectively) as well as a similar distribution of patients by stroke risk. In RE-LY, 32% of patients had a CHADS score of 0 to 1, 36% a score of 2, and 32% a score ≥3. The CHADS score distribution in ARISTOTLE was 1 (34%), 2 (35%), and ≥3 (30%). PROTECT AF studied patients with a CHADS score distribution in ARISTOTLE was 1 (34%), 2 (35%), and ≥3 (30%).

### Table 3. Efficacy of NOACs Compared With Warfarin

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>RE-LY</th>
<th>ROCKET AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE AF-TIMI 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td>D. 110%/yr</td>
<td>D. 150%/yr</td>
<td>W.%/yr (PValue*)</td>
<td>D. 110%/yr</td>
</tr>
<tr>
<td>Stroke or</td>
<td>1.53 1.11</td>
<td>1.69 1.69</td>
<td>0.91 (0.34)</td>
<td>0.66 (0.001)</td>
</tr>
<tr>
<td>systemic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>embolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.44 1.01</td>
<td>1.57 1.57</td>
<td>0.92 (0.41)</td>
<td>0.64 (0.001)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0.12 0.10</td>
<td>0.38 0.38</td>
<td>0.31 (0.01)</td>
<td>0.26 (0.001)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>1.34 0.92</td>
<td>1.20 1.20</td>
<td>1.11 (0.35)</td>
<td>0.76 (0.03)</td>
</tr>
<tr>
<td>Nondisabling</td>
<td>0.50 0.37</td>
<td>0.58 0.58</td>
<td>0.86 (0.40)</td>
<td>0.62 (0.01)</td>
</tr>
<tr>
<td>Disabling</td>
<td>0.94 0.66</td>
<td>1.00 1.00</td>
<td>0.94 (0.65)</td>
<td>0.66 (0.01)</td>
</tr>
</tbody>
</table>

A. indicates apixaban; D. 110, dabigatran 110 mg; D. 150, dabigatran 150 mg; E. hd, edoxaban high-dose group (60 mg, halved to 30 mg if CrCl 30 - 50 mL/min, body weight ≤60 kg, or P-gp inhibitor use); HR, hazard ratio; NOAC, novel oral anticoagulant; R., rivaroxaban; RR, relative risk; and W., warfarin.

*P value for superiority, unless otherwise indicated; †P value for noninferiority.

§Safety, on treatment analysis.

§Modified intention-to-treat population.
score $\geq 1$. In PROTECT AF, patients receiving a device (n = 463) had a CHADS$_2$ score of 1 (34%), 2 (34%), or $\geq 3$ (32%); in the warfarin group (n = 244) patients had a CHADS$_2$ score of 1 (27%), 2 (36%), or $\geq 3$ (37%).$^{22}$ Thus, the RE-LY and ARISTOTLE trials are compared to PROTECT AF on the basis of similar stroke risk in the study populations.

RE-LY was the first completed phase III trial of a novel anticoagulant in which patients (n=18 113) with AF were randomized to either open label warfarin (mean time in therapeutic range [TTR], 64%) or to 1 of 2 blinded doses of dabigatran, 110 mg or 150 mg BID.$^{13}$ The largest LAA exclusion device trial, PROTECT AF (n=707), studied the Watchman LAA occlusion device in comparison with warfarin therapy (TTR 66%) in patients with AF.$^{22}$ ARISTOTLE was a randomized, double-blind trial comparing apixaban (at a dose of 5 mg BID, down-titrated to 2.5 mg BID if 2 of the following were present: age >80 years, weight <60 kg, serum creatinine > 1.5) to warfarin (TTR 62%) in 18 201 patients with AF.$^{14}$

In PROTECT AF, the Watchman device was shown to be noninferior to warfarin for the primary efficacy end point of stroke (ischemic or hemorrhagic, systemic embolism, or cardiovascular/unexplained death (Watchman, 3.0%/yr versus warfarin, 4.9%/yr).$^{22}$ The event rate for ischemic stroke was greater in patients receiving the device (2.2%/yr) compared with warfarin (1.6%/yr; $P>0.05$).$^{22}$ At 2.3 years of follow-up in PROTECT AF the rate of ischemic stroke was higher in patients receiving the device (1.9%/yr) compared with warfarin (1.4%/yr; hazard ratio [HR], 1.30; 95% confidence interval [CI], 0.66–3.60), which did not achieve noninferiority ($P=0.76$).$^{23}$ In RE-LY, the 150-mg BID dose was superior to warfarin for efficacy (stroke or systemic embolism) by 34% and noninferior for safety, and the 110-mg BID dose was noninferior for efficacy and superior for safety by 20% compared with warfarin.$^{13}$ The dabigatran 150-mg BID dose reduced ischemic stroke by 24% versus warfarin.$^{13}$ In ARISTOTLE, apixaban was superior to warfarin for the primary efficacy end point (stroke or systemic embolism) by 21%.$^{14}$ The rate of ischemic stroke was similar with apixaban (0.97%/yr compared with warfarin (1.05%/yr) (HR 0.92, $P=0.42$). Taken together, dabigatran and apixaban were superior and Watchman noninferior to warfarin for primary efficacy.$^{13,14,22}$ Furthermore, dabigatran significantly reduced ischemic stroke, and apixaban was similar to warfarin, whereas the Watchman device demonstrated higher rates of ischemic stroke in comparison with warfarin, all in patients with AF at a similar risk of stroke (Tables 3 and 6).$^{13,14,21,22}$

On safety, in PROTECT AF the event rate for the primary safety end point (excessive bleeding or procedural complication) was greater in patients in the device group (7.4%/yr) compared with patients receiving warfarin (4.4%/yr).$^{22}$ Procedural complications, including pericardial effusion (5.2% of patients) and stroke attributable to air embolism (0.9%), demonstrate the challenges that LAA devices present.$^{22}$ In addition, patient hospitalization time is extended as a result of LAA device procedure-related complications.$^{22}$ The primary safety event rates at 2.3 years of follow-up in PROTECT AF were higher with Watchman (5.5%/yr) than warfarin (3.6%/yr).$^{21}$ In RE-LY, the rates of major bleeding were similar for dabigatran 150 mg BID and warfarin, and significantly reduced with dabigatran 110 mg BID.$^{13}$ Gastrointestinal bleeding was significantly elevated with dabigatran 150 mg BID compared with warfarin.$^{13}$ Dabigatran 150 mg BID reduced intracranial bleeds by 60% and dabigatran 110 mg BID by 69% versus warfarin.$^{13}$ In ARISTOTLE, apixaban reduced major bleeding compared with warfarin by 31%.$^{14}$ Intracranial bleeds were reduced by 58% with apixaban.$^{14}$ Overall, Watchman does not show any improved safety benefit compared with warfarin, whereas dabigatran and apixaban provide significant advantages over warfarin on safety (Tables 4 and 6).$^{13,14,21,22}$

Mortality rates were similar in PROTECT AF for patients receiving Watchman (3.2%/yr) compared with warfarin (4.5%/yr; HR, 0.71; 95% CI, 0.46–1.28).$^{21}$ In RE-LY mortality was similar for dabigatran 110 mg (3.75%/yr) and warfarin (4.13%/yr), and trended lower with dabigatran 150 mg (3.64%/yr) compared with warfarin (HR, 0.88; 95% CI, 0.77–1.00; $P=0.051$).$^{13}$ In ARISTOTLE, apixaban (3.52%/yr) demonstrated significantly reduced mortality compared with warfarin (3.94%/yr; HR, 0.89; 95% CI, 0.80–0.998; 0.97%).

### Table 4. Safety Outcomes With NOACs Compared With Warfarin$^{13,16}$

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>RE-LY$^{23}$</th>
<th>ROCKET AF$^{15}$</th>
<th>ARISTOTLE$^{14}$</th>
<th>ENGAGE AF-TIMI 48$^{18}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td>D. 110%/$\text{yr}$</td>
<td>D. 150%/$\text{yr}$</td>
<td>D. 110% vs. D. 150%/$\text{yr}$</td>
<td>D. 150%/$\text{yr}$</td>
</tr>
<tr>
<td>Major bleeding*</td>
<td>2.71</td>
<td>3.11</td>
<td>3.36</td>
<td>0.80</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.23</td>
<td>0.30</td>
<td>0.74</td>
<td>0.31</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1.12</td>
<td>1.51</td>
<td>1.02</td>
<td>1.10</td>
</tr>
</tbody>
</table>

A. indicates apixaban; D. 110, dabigatran 110 mg; D. 150, dabigatran 150 mg; E. hd, edoxaban high-dose group (60 mg, halved to 30 mg if CrCl 30 - 50 mL/min, body weight < 60 kg, or P-gp inhibitor use); HR, hazard ratio; NOAC, novel oral anticoagulant; R., rivaroxaban; RR, relative risk; and W., warfarin.

*Major bleeding defined by $\geq 1$ of the following criteria: bleeding associated with reduction in hemoglobin level of at least 2.0 g/dL; leading to transfusion of at least 2 U of blood or packed cells; bleeding in a critical site or organ; permanent disability; or fatal outcome.
In summary, the annualized mortality rates were lower for Watchman, dabigatran, and apixaban compared with their respective warfarin control rates, however the Watchman device did not make a statistically significant difference on mortality (Tables 5 and 6).

In ARISTOTLE, there was consistent benefit with apixaban in patients regardless of age, body weight, CHADS2 score, heart failure, quality of INR control, renal impairment, stroke history, or length of exposure to warfarin. Across age levels in ARISTOTLE apixaban consistently demonstrated lower rates of major bleeding compared with warfarin, which extended to patients aged ≥80 years. In PROTECT AF at 2.3 years of follow-up, the HR for primary safety in comparison with warfarin was 1.53 (95% CI, 0.95–2.70). Thus, a similar safety benefit by age is not available with LAA exclusion devices.

In RE-LY, an analysis of sites stratified by TTR quartiles with warfarin showed comparable benefits in reduction of stroke, systemic emboli, and intracranial bleeding for both doses of dabigatran. Major bleeding, mostly gastrointestinal, trended higher in comparison with warfarin for the 150-mg BID dose when the TTR was >65%. Analysis by warfarin control in ARISTOTLE showed reduced stroke or systemic embolism, major bleeding, and mortality for apixaban compared with warfarin across all TTR quartiles. Similar analysis by TTR stratification is needed for LAA exclusion devices.

Across all CHADS2 strata (1–6) in RE-LY dabigatran 150 mg BID was superior to warfarin for stroke or systemic embolism. Dabigatran 110 mg BID demonstrated reduced major bleeding, and similar efficacy, compared with warfarin across all CHADS2 levels. For apixaban in ARISTOTLE results were similar. The Watchmen device was noninferior to warfarin across CHADS2 levels (1–6) in PROTECT AF for preventing stroke, systemic embolism, or death. It is important clinically to consider the performance of novel anticoagulants and LAA exclusion devices in patients at an elevated risk of stroke. In PROTECT AF, for patients with a CHADS2 score ≥2 (n = 484), the HR for stroke, systemic embolism, or death in favor of devices was 0.68 (95% CI, 0.34–1.36) compared with warfarin. In RE-LY, for patients with a CHADS2 score ≥3 (n = 5882) the HR for stroke or systemic embolism was 0.69 (95% CI, 0.51–0.93), which was significant in favor of patients receiving dabigatran 150 mg BID compared with warfarin. In ARISTOTLE, the HR comparing apixaban to warfarin for stroke or systemic embolism in patients with a CHADS2 score ≥3 (n = 5502) was 0.70 (95% CI, 0.54–0.91; P<0.05). Although the mean HRs against warfarin are similar for Watchman, dabigatran, and apixaban in patients at elevated risk for stroke, the HR for Watchman crossed unity (95% CI, 0.34–1.36) and is therefore not significant, whereas the HRs for dabigatran and apixaban are statistically significant reductions in stroke. In an indirect comparison, patients with elevated risk of stroke might benefit more from receiving novel anticoagulation than LAA exclusion.

Following RE-LY, patients were uniquely allowed to continue dabigatran in RELY-ABLE (n=12,091) providing up to 6.7 years of total continuous follow-up. Long-term experience and outcomes data with LAA exclusion devices are limited. The long-term data for dabigatran show a reduced rate of stroke or systemic embolism with dabigatran 150 mg BID (1.25%/yr) compared with dabigatran 110 mg BID (1.54%/yr) (HR, 0.81; 95% CI, 0.68–0.96; P=0.015). The rates of hemorrhagic stroke were very low over the long-term follow-up and similar on both the 150-mg (0.11%/yr) and 110-mg (0.13%/yr) doses of dabigatran (HR, 0.91; 95% CI, 0.51–1.62; P=0.75). Major bleeding was elevated with 150 mg (3.34%/yr) compared with 110 mg (2.76%/yr) over the long term (HR, 1.22; 95% CI, 1.08–1.37; P=0.0008). Most bleeding was extracranial, and specifically gastrointestinal in nature, whereas intracranial bleeding was rare. Total mortality rate was similar on both doses of dabigatran, 150 mg (3.43%/yr) and 110 mg (3.55%/yr; HR, 0.97; 95% CI, 0.87–1.08; P=0.54). Patients with AF, and its associated comorbidities, require life-long therapy for thromboembolic protection.

### Table 5. Mortality with NOACs Compared With Warfarin

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>RE-LY13</th>
<th>ROCKET AF15</th>
<th>ARISTOTLE14</th>
<th>ENGAGE AF-TIMI 4814</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D. 110%/ yr</td>
<td>D. 150%/ yr</td>
<td>D. 110 vs. D. 150 RR (P Value)*</td>
<td>R. %/ yr</td>
</tr>
<tr>
<td>Death from vascular causes</td>
<td>2.43 (0.21)</td>
<td>2.28 (0.04)</td>
<td>2.69 (0.44)</td>
<td>0.90 (0.85)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>3.75 (0.13)</td>
<td>3.64 (0.051)</td>
<td>4.13 (0.66)</td>
<td>0.91 (0.88)</td>
</tr>
</tbody>
</table>

A. indicates apixaban; D. 110, dabigatran 110 mg; D. 150, dabigatran 150 mg; E. hd, edoxaban high-dose group (60 mg, halved to 30 mg if CrCl 30 – 50 mL/min, body weight ≤60 kg, or P-gp inhibitor use); HR, hazard ratio; NOAC, novel oral anticoagulant; R., rivaroxaban; RR, relative risk; and W., warfarin.

*P value for superiority.
†Safety, on treatment analysis.
Long-term novel anticoagulation sustains efficacy and safety as originally observed in the shorter term,\textsuperscript{13,29} and comparable long-term patient experience with LAA exclusion needs investigation.

**ENGAGE AF-TIMI 48 Versus PREVAIL**

Edoxaban is the most recent Factor Xa inhibitor to be tested in a phase III trial. Edoxaban is not yet approved by the U.S. Food and Drug Administration (FDA). ENGAGE AF-TIMI 48 was a 1:1:1 randomized, double-blind trial comparing edoxaban 60 mg daily or edoxaban 30 mg daily to warfarin (TTR 68%).\textsuperscript{16} Both doses of edoxaban could be reduced by 50\% in subjects with ≥ 1 of the following conditions: CrCl 30 to 50 mL/min, weight ≤ 60 kg, or concomitant use of the strong P-gp inhibitors verapamil or quinidine. The PREVAIL trial evaluated the Watchman device versus warfarin (TTR 68%).\textsuperscript{19} Patients were randomized in PREVAIL 2:1 to either Watchman (n = 269) or warfarin (n = 138).

In contrast to RE-LY, ARISTOTLE, and PROTECT AF the level of stroke risk and its distribution in the patient populations in ENGAGE AF-TIMI 48\textsuperscript{16} and PREVAIL\textsuperscript{19} were slightly higher. Both trials recruited patients with a CHADS\textsubscript{2} score ≥ 2. The mean CHADS\textsubscript{2} scores were 2.8 (ENGAGE) and 2.6 (PREVAIL).\textsuperscript{16,19} The distribution of patients in ENGAGE AF-TIMI 48\textsuperscript{16} and PREVAIL\textsuperscript{19} were at a similar risk of stroke.

In ENGAGE, the annualized rates for the primary end point of stroke or systemic embolism on-treatment were 1.18%/yr for high-dose edoxaban and 1.61%/yr for low-dose edoxaban, compared with 1.50%/yr with warfarin.\textsuperscript{16} The HR comparing high-dose edoxaban to warfarin for stroke or systemic embolism was 0.79 (97.5\% CI, 0.63–0.99; \( P < 0.001 \); Table 3). Edoxaban was noninferior to warfarin for preventing stroke or systemic embolism. In comparison, PREVAIL demonstrated that LAA occlusion with Watchman was noninferior to warfarin for preventing ischemic stroke or systemic embolism > 7 days postprocedure.\textsuperscript{19} However, the coprimary end point of stroke, systemic embolism, and cardiovascular/unexplained death did not achieve noninferiority for Watchman compared to warfarin.

<table>
<thead>
<tr>
<th>Device</th>
<th>PREVAIL\textsuperscript{19}</th>
<th>ASAP\textsuperscript{20}</th>
<th>PROTECT AF\textsuperscript{21,22,23}</th>
<th>Sick et al.\textsuperscript{24}</th>
<th>Lariat et al.\textsuperscript{25}</th>
<th>Wiebe et al.\textsuperscript{26}</th>
<th>Nielispach et al.\textsuperscript{27}</th>
<th>Block et al.\textsuperscript{28}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Dev.</td>
<td>W.</td>
<td>Dev.</td>
<td>Dev.</td>
<td>W.</td>
<td>HR (95% CI; ( P ) noninferiority)†</td>
<td>Dev.</td>
<td>Dev.</td>
</tr>
<tr>
<td>All stroke</td>
<td>2.3%</td>
<td>0.7%</td>
<td>2.3%/yr</td>
<td>2.0%/yr</td>
<td>2.7%/yr</td>
<td>0.77 (0.42–1.62; &gt; 0.99)</td>
<td>0%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Ischemic</td>
<td>1.9%</td>
<td>0.7%</td>
<td>1.7%/yr</td>
<td>1.9%/yr</td>
<td>1.4%/yr</td>
<td>1.30 (0.66–3.60; 0.76)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0.4%</td>
<td>0%</td>
<td>0.6%/yr</td>
<td>0.3%/yr</td>
<td>1.2%/yr</td>
<td>0.23 (0.04–0.79; &gt; 0.99)</td>
<td>0%</td>
<td>2.2%</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2.6%</td>
<td>2.2%</td>
<td>5%/yr</td>
<td>3.2%/yr</td>
<td>4.5%/yr</td>
<td>0.71 (0.46–1.28; &gt; 0.99)</td>
<td>2.7%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Primary safety</td>
<td>2.2% d.</td>
<td>—</td>
<td>8.7%‡</td>
<td>5.5%/yr</td>
<td>3.6%/yr</td>
<td>1.53 (0.95–2.70)§</td>
<td>22.7%¶</td>
<td>6.7%#</td>
</tr>
<tr>
<td>Device success</td>
<td>95.1%</td>
<td>—</td>
<td>94.7%</td>
<td>88%</td>
<td>—</td>
<td>—</td>
<td>93%</td>
<td>96%</td>
</tr>
<tr>
<td>Anticoagulation discontinuation, % (at follow-up)</td>
<td>99.3% (1 yr)‖</td>
<td>—</td>
<td>93.2% (1 yr)‖</td>
<td>—</td>
<td>—</td>
<td>&gt; 90% (2 yr)</td>
<td>45% (1 yr)</td>
<td>—‖</td>
</tr>
</tbody>
</table>

ACP indicates Amplatzer cardiac plug; CI, confidence interval; CT, cardiac tamponade; Dev., device; HR, hazard ratio; and W., warfarin.

*Data based on 2.3-year study.\textsuperscript{29}

†Watchman vs. Warfarin

‡Device embolization, pericardial effusion, tamponade, device thrombus with ischemic stroke, femoral pseudoaneurysm, femoral hematoma, bleeding, or intraprocedural hypotension.

§Major bleeding, pericardial effusion, or device embolization.

¶Air embolism, device embolization, internal bleeding attributable to device retrieval, pericardial effusion, tamponade, device thrombus, transient ischemic attack, femoral pseudoaneurysm.

‖Patients received clopidogrel and life-long aspirin postprocedure.

‡‡Device embolization, device thrombus, air embolism, pericardial effusion.

§§The safety end point was only evaluated in the device group (device embolization, arteriovenous fistula, cardiac perforation, pericardial effusion with tamponade, major bleed).
with warfarin in PREVAIL. Furthermore, the rate of ischemic stroke was greater with the Watchman device (1.9%) than with warfarin therapy (0.7%) in PREVAIL, for which the mean patient follow-up time was nearly 1 year (11.8 months), making these rates approximately annualized (Table 6). In ENGAGE, ischemic stroke rate was the same with high-dose edoxaban or warfarin (1.25%/yr), and the hemorrhagic stroke rate was reduced with edoxaban (0.26%/yr) compared with warfarin (0.47%/yr; HR, 0.54; P=0.001). Hemorrhagic stroke occurred with the Watchman device (0.4%) but not with warfarin (0.0%) in PREVAIL. Therefore, on efficacy, both high-dose edoxaban and Watchman were shown to be noninferior to warfarin for preventing stroke or systemic embolism, ischemic stroke was elevated with Watchman but not edoxaban, and hemorrhagic stroke was significantly reduced with edoxaban.

On safety, in ENGAGE, major bleeding was significantly reduced with high-dose edoxaban (2.75%/yr) compared with warfarin (3.43%/yr; HR, 0.80; P<0.001) as well as with low-dose edoxaban (1.61%/yr). Gastrointestinal bleeding was higher on the 60-mg dose of edoxaban than on warfarin (1.51%/yr versus 1.23%/yr), but lower with 30 mg edoxaban (0.82%/yr). In PREVAIL, the primary safety event rate was 2.2% for the Watchman device, representing device embolization, arteriovenous fistula, cardiac perforation, pericardial effusion with tamponade, and major bleeding, however a safety end point was not evaluated in the warfarin group. In addition to major bleeding, cardiovascular death was significantly reduced with edoxaban (2.74%/yr) versus warfarin (3.17%/yr; HR, 0.86; P=0.013; Table 5). All-cause mortality was reduced with edoxaban (3.99%/yr) compared with warfarin (4.35%/yr). In PREVAIL, mortality was elevated with the Watchman group (2.6%) in comparison with the warfarin arm (2.2%) (Table 6).

Thus, in an indirect comparison edoxaban may provide patients with a greater safety benefit than Watchman while maintaining similar protection from stroke or systemic embolism. In addition, the PREVAIL investigators acknowledge that short-term warfarin therapy is an important consideration for patients receiving the Watchman device, which poses a challenge to patients absolutely contraindicated to warfarin. Edoxaban may prove to be a better alternative than Watchman for patients contraindicated to warfarin.

**ROCKET AF**

The ROCKET AFtrial studied patients at the highest risk profile for stroke among trials for novel anticoagulants and LAA exclusion devices. The mean CHADS2 score in ROCKET AF was 3.5. There is no comparable LAA exclusion study, making indirect comparisons difficult. Patients with an elevated CHADS2 score have multiple comorbidities that place them at a higher risk of a stroke. High stroke-risk patients, especially those with history of a previous stroke, may not be candidates for anticoagulation therapy because of high bleed risk. More study is needed in these patients with regard to using LAA exclusion devices.

The ROCKET AF study was a double-blind trial of 14,264 patients with nonvalvular atrial fibrillation randomized to receive either rivaroxaban (at a daily dose of 20 mg, down-titrated to 15 mg daily in patients with CrCl of 30–49 mL/min) or dose-adjusted warfarin (TTR 55%). Rivaroxaban was noninferior to warfarin for efficacy and safety (Tables 3, 34, and 5). Intracranial bleed rates (0.5 versus 0.7%/yr; P=0.02) and fatal bleed rates (0.2 versus 0.5%/yr; P=0.003) were significantly lower with rivaroxaban compared with warfarin. Gastrointestinal bleeds were more frequent on rivaroxaban than on warfarin (3.15%/yr versus 2.16%/yr). The efficacy and safety of rivaroxaban compared to warfarin were similar across CHADS2 levels. Treatment with rivaroxaban compared with warfarin was consistent across TTR levels for preventing stroke or systemic embolism. Major bleeding attributable to rivaroxaban increased relative to warfarin with groups at a higher TTR. However, intracranial hemorrhage was reduced with rivaroxaban compared to warfarin and this effect was maintained across TTR levels.

**LAA Exclusion by Ligation: Lariat**

The Lariat suture device used to ligate the LAA is the newest device to be studied. In an uncontrolled study of 89 patients (mean CHADS2 score 1.9) undergoing the ligation procedure complete LAA closure was achieved in 98% of patients. Although delivered percutaneously like the Watchman device, the Lariat procedure requires pericardial access in addition to trans-septal passage. Therefore, manipulation of the LAA with the Lariat device is both endocardial and intrapericardial. The dual access approach with Lariat adds greater opportunity for complication. Procedural risks include left ventricular puncture, epigastric vessel laceration, hemopericardium, pericarditis, and incomplete ligation. At 1-year post LAA ligation no thromboembolic events occurred, and 55% of patients remained on warfarin therapy, which increased to 61% in follow-up beyond 1 year. Thus, LAA exclusion with the Lariat does not necessarily exclude anticoagulation therapy.

**FDA Approval**

Dabigatran, rivaroxaban, and apixaban have been approved worldwide. The Lariat suture ligation device is the only percutaneous LAA exclusion device approved by the FDA. The Watchman device has not yet received approval. The Amplatzer cardiac plug is not approved in the United States. The Plato device is no longer being evaluated. Dabigatran was approved at 150 mg BID for CrCl >30 mL/min. The FDA approved dabigatran 75 mg BID for patients with a CrCl of 15 to 30 mL/min for use in the United States. In all other countries, dabigatran 110 mg BID is approved for patients at a higher bleeding risk. The FDA reported that real-world bleeding data on dabigatran 150 mg BID reflect the data reported from RE-LY. Real-world reports are expected for the other agents soon. Rivaroxaban is approved at a daily dose of 20 mg for patients with a CrCl >50 mL/min, down-titrated to 15 mg daily in patients with CrCl of 15 to 50 mL/min. Apixaban
is approved at a dose of 5 mg BID, down-titrated to 2.5 mg BID if 2 of the following are present: age >80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL. Edoxaban is currently being reviewed by the U.S. FDA for approval.

Translation Into Clinical Practice
The clinical trials for the novel anticoagulants are translatable into clinical practice, whereas the data for LAA exclusion devices is less robust. Dabigatran and apixaban may be taken with or without food. Rivaroxaban must be taken with the evening meal to maximize bioavailability to almost 100%. Rivaroxaban can be crushed and mixed with applesauce immediately before ingestion, or suspended in 50 mL of water through a nasogastric or gastric feeding tube, followed immediately by enteral feeding, whereas dabigatran cannot. There is a clear process for converting patients from warfarin to a novel anticoagulant. For dabigatran and apixaban, the INR must be below 2.0. For rivaroxaban, the INR must be <3.0. The rapid onset of action of the novel agents eliminates the need for bridging and for a hospital admission unless oral administration of the drug is not possible or the drugs are contraindicated. When converting from dabigatran back to warfarin, start warfarin 3 days before stopping dabigatran for a CrCl >50 mL/min; for a CrCl between 31 to 50 mL/min, start warfarin 2 days before stopping dabigatran; and for a CrCl of 15 to 30 mL/min, start warfarin 1 day before stopping dabigatran. For both rivaroxaban and apixaban, discontinue the drug and begin both parenteral anticoagulation and warfarin at the time of the scheduled next dose; discontinue parenteral administration once the therapeutic INR is reached. Dabigatran elevates APTT levels. Thus the APTT can be used to determine whether patients have recently ingested dabigatran. For the Factor Xa inhibitors, there is no measure available clinically to assess drug effect. Before starting parenteral anticoagulation, dabigatran should be withheld for 12 hours in patients with normal renal function. For decreased kidney function (CrCl ≤30 mL/min), hold 3 to 4 doses (up to 2 days) is advised, but a longer hold may be needed, depending on the patient’s creatinine clearance. The need for complete hemostasis (for spinal puncture, spinal/epidural catheter, or major surgery, for example) will necessitate a longer period of discontinuation. APTT is advised immediately before surgery. A level close to control (≤1.5) will necessitate a longer period of discontinuation. APTT will rise if renal function is poor. Dialysis is not useful for rivaroxaban or apixaban, as the drugs are highly protein bound (Table 1). Activated oral charcoal may be considered for use in both rivaroxaban and apixaban to reduce drug absorption, although this does not serve as an antidote.

The need for anticoagulation pre- and postcardioversion is an accepted practice. There is no experience regarding cardioversion in patients with LAA exclusion devices. Inadequate anticoagulation places cardioverted patients at a higher risk of thromboembolic events. An analysis of patients cardioverted in the RE-LY study found that stroke, systemic emboli, and bleeding rates within 30 days postcardioversion were low for subjects assigned 110 mg and particularly with 150 mg and were comparable with the rates on warfarin. Thus for patients treated with dabigatran for longer than 3 weeks, cardioversion is possible, particularly for those on the 150-mg BID dose at which stroke rates were very low at 30 days (0.3%). A review of patients in the ROCKET AF and ARISTOTLE who underwent cardioversion and AF ablation found no differences in long-term rates of stroke, systemic emboli, or cardiovascular death compared with warfarin groups. Prospective studies are underway. Cardioversion in the context of LAA exclusion devices needs study.

Drug–Drug Interactions
Drug–drug interactions that occur with anticoagulants are obviated by LAA exclusion devices. Several medications interact with all novel oral anticoagulants. P-gp inducers reduce drug concentration to subtherapeutic levels. In general, P-gp inducers such as carbamazepine and St. John’s wort should not be used with these novel oral anticoagulants. P-gp inhibitors such as systemic ketoconazole, verapamil, amiodarone, dronedarone, quinidine, and clarithromycin do not require dose adjustments for dabigatran, rivaroxaban, or apixaban; in ENGAGE AF TIMI 48, the edoxaban dose was reduced by 50% if subjects were taking verapamil or quinidine. Other P-gp inhibitors should be used with caution or avoided because they may increase plasma concentration of the drugs. Proton pump inhibitors reduce dabigatran absorption but do not necessitate dose adjustment. Episodes of dyspepsia attributable to dabigatran may be reduced if the drug is taken with food or water. Dabigatran was discontinued more frequently than warfarin in RE-LY. The only symptom leading to more frequent discontinuation of dabigatran was dyspepsia with 2.1% of patients reporting dyspepsia as the cause of their stopping medication permanently. Dyspepsia occurs in both the 110 mg and 150 mg groups (6.2% and 5.7% of subjects respectively) compared with 1.4% per year in the warfarin group. Dyspepsia is not an adverse event with apixaban and rivaroxaban.

Conclusion
The novel anticoagulants make atrial fibrillation-related stroke a preventable disease, benefitting millions of patients
Sources of Funding

Dr Ezekowitz reports research grant support from Boehringer Ingelheim, Pfizer, Bayer, and Daiichi Sankyo. A. P. Kent reports no conflicts.

Disclosures

Dr Ezekowitz is a consultant or on the advisory board for Boehringer Ingelheim, Pfizer, Bayer, Daiichi Sankyo, Sanofi, Bristol Myers-Squibb, Portola, Medtronic, Aegerion, Merck, Johnson & Johnson, Gilead, Janssen Scientific Affairs, Pozen Inc, AmGen, Coherex, and Armetheon; on the Speakers’ Bureau for Boehringer Ingelheim and Pfizer; and has received research grant support from Boehringer Ingelheim, Pfizer, Bayer, and Daiichi Sankyo. A. P. Kent reports no conflicts.

References


Response to Ezekowitz and Kent

Brian Whisenant, MD; Saibal Kar, MD; T. Jared Bunch, MD

We appreciate Drs Ezekowitz and Kent’s insightful review of the novel anticoagulants and concur that they represent tremendous new options to address the persistent need of better stroke prevention in the setting of atrial fibrillation (AF). Left atrial appendage closure similarly represents a tremendous and novel option which today can fill the gap left by AF patients with an increased risk of stroke and reasons to avoid oral anticoagulation. Although there are many causes of stroke in patients with AF, removing the left atrial appendage, the most common source of macroemboli, is a proven means of reducing both stroke and death in the setting of AF without precluding additional medical or procedural therapies directed at atherosclerosis, arrhythmia, and thrombosis. Although novel anticoagulants have favorable safety and efficacy compared with warfarin, all currently available options have some degree of renal clearance, are subject to drug–drug interactions, and are associated with adverse side effects and bleeding risks, rendering them unacceptable for many patients, especially older patients and patients with a requirement for dual antiplatelet therapy. There are no definite antidotes for patients who sustain novel anticoagulant-associated bleeding. For all these reasons, the eagerly anticipated Food and Drug Administration approval of the Watchman device will be a pivotal step to better understand the role of LAA exclusion in conjunction with other therapies that together will provide each unique patient with the lowest risk of stroke and the best quality of life.
Novel Anticoagulants Eliminate the Need for Left Atrial Appendage Exclusion Devices
Michael D. Ezekowitz and Anthony P. Kent

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