Cardioembolic stroke in atrial fibrillation (AF) causes 15% to 20% of all ischemic strokes. For 2 decades, there has been solid evidence that strokes in AF can be prevented much more effectively by oral anticoagulants than by antiplatelets. Shockingly, it has remained a daily experience of stroke physicians that stroke in patients with known AF has not been adequately prevented. This corresponds to registries consistently reporting that only ≈60% of eligible patients with AF are actually anticoagulated. Vitamin K antagonists (VKAs) are inconvenient because they require coagulation monitoring and frequent dose adjustments. Moreover, patients and physicians are concerned about major bleeding complications particularly in the elderly.

Insufficient acceptance of VKAs has led to the development of direct oral anticoagulants (DOACs). DOACs target a single-activated key coagulation factor and result in largely predictable anticoagulation without the need for coagulation monitoring. Three previous large randomized trials have shown consistently that DOACs are at least as effective as warfarin for prevention of stroke in AF. Remarkably, the direct thrombin inhibitor dabigatran and the factor Xa inhibitors, rivaroxaban and apixaban, also halved the incidence of intracerebral hemorrhage, the most feared complication of long-term anticoagulation. Weighing safety and efficacy of DOACs versus warfarin, European and American guidelines are in favor of starting patients with first diagnosed AF on DOACs, but there is a debate whether stable stroke-free patients on VKA should be switched to DOACs.

The Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation (ENGAGE-AF) trial has added valuable information to the matter. ENGAGE-AF, the latest and largest trial of a DOAC, was a randomized, double-blind, double-dummy trial comparing 1 of 2 doses of edoxaban to dose-adjusted warfarin (target international normalized ratio, 2–3). The edoxaban doses were 30 and 60 mg once daily. The edoxaban dose was adjusted to 15 and 30 mg, respectively, at the time of randomization or during the trial if creatinine clearance was 30 to 50 mL/min, weight was <60 kg, and there was concomitant use of potent P-glycoprotein inhibitors. ENGAGE-AF enrolled >21,000 patients with nonvalvular AF with a moderate to high risk of an embolic event (congestive heart failure, hypertension, age, diabetes, prior stroke/TIA [CHADS2] score, ≥2). The primary hypothesis was that edoxaban would be noninferior to warfarin about the composite primary efficacy end point of ischemic and hemorrhagic stroke and systemic embolism. The mean CHADS2 score of patients enrolled in ENGAGE was 2.8. A total of 28% of patients had a previous stroke or transient ischemic attack when compared with ≈20% in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial (ARISTOTLE), and 55% in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared to Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF).

Thus, the ENGAGE-AF population was expected to be at lower risk for stroke than ROCKET-AF. The mean follow-up of 2.8 years exceeded that of all previous trials considerably. Both doses of edoxaban were noninferior to warfarin about primary efficacy. Annual event rates for the composite primary end points were 1.50% with warfarin, 1.18% with high-dose, and 1.61% with low-dose edoxaban. In prespecified analysis, high-dose edoxaban tended to be of superior efficacy (P=0.08) to warfarin. Rates of ischemic stroke were similar between warfarin and high-dose edoxaban (1.25% versus 1.25%; P=0.97), whereas low-dose edoxaban was inferior to warfarin (1.77% versus 1.25%; P<0.001) for ischemic stroke prevention. Thus, the benefits of edoxaban were driven by the significantly lower risk of hemorrhagic stroke among both low- and high-dose groups when compared with that of warfarin. In the group of patients taking VKA at baseline, high-dose edoxaban and warfarin were not different in the primary outcome (1.62% versus 1.60%), whereas high-dose edoxaban was superior in VKA-naive patients (1.49% versus 2.12%; P=0.03 for interaction). In the primary safety end point, major bleeding occurred significantly less frequently in both edoxaban groups (high-dose, 2.75%; low-dose, 1.61%; warfarin, 3.43%). Similar to all other DOAC AF trials, intracranial hemorrhage and intracerebral hemorrhage were substantially less frequent in both edoxaban groups. In contrast, gastrointestinal bleeding was more frequent in the high-dose edoxaban group when compared with that in the warfarin-treated group.
patients (1.51% versus 1.23%; \( P=0.03 \)). This corresponds to a higher rate of gastrointestinal bleeding complications with rivaroxaban and high-dose dabigatran but not with apixaban in previous AF trials.

Direct comparisons between edoxaban and other direct anticoagulants should only be made with caution. Nevertheless, it is important to note some differences between trials and drugs. Similar to the other factor Xa inhibitors, edoxaban has good bioavailability and some interaction with P-glycoprotein inhibitors and cytochrome P450 inducers. It is dosed once daily which presumably improves adherence but may have the disadvantage of longer periods without anticoagulation in case of a missed dose. Comparing trials, ENGAGE had the longest follow-up of all DOAC trials and also had the highest average time in therapeutic range for patients on warfarin (68.4%), well above the required 58% time in therapeutic range that confers benefit of warfarin instead of aspirin.7 When compared with clinical practice where time in therapeutic range is achieved in 55% of patients in the United States and 72% in Sweden and to other DOAC trials (RE-LY, 64%; ROCKET-AF, 58%; ARISTOTLE, 66%), the ENGAGE experience is commensurate. Another achievement of the ENGAGE-AF-TIMI48 investigators was a master plan for transitioning from study medication to open-label anticoagulation, which led to small and identical numbers of incident strokes among groups.

As with the recent meta-analysis of the all DOAC AF trials,9 high-dose edoxaban conferred a modest mortality benefit (hazard ratio, 0.92; 95% confidence interval, 0.83–1.01) when compared with warfarin. For secondary prevention of stroke, a key subgroup for practicing stroke neurologists, data from ENGAGE prespecified subgroup of patients with previous stroke or transient ischemic attack suggest a similar benefit of high-dose edoxaban when compared with that of warfarin (2.44% versus 2.85%) although this did not reach statistical significance. Overall, these data place high-dose edoxaban in good company and provide clinicians with yet another alternative to warfarin for prevention of stroke in AF. The potential role of low-dose edoxaban remains to be defined. In certain situations, such as a patient with a previous major bleeding event, it may be preferable to use a drug with a very low risk of bleeding although it may only have reasonable instead of optimal efficacy.

The use of DOACs in AF now builds on experience in 5 megatrends with some 70,000 patients in primary and secondary stroke prevention.3–6,10 Reassuringly, these trials consistently underscore the validity of the therapeutic principle rather than just the effectiveness of a single drug. Intriguingly, some observations in these trials, such as the dissociation of the risk of intracranial and systemic bleeding in patients treated with DOACs in contrast to VKA, deserve a better understanding of the underlying biology to support the development of safer antithrombotic drugs in the future. For stroke physicians, adequate emergency management strategies for acute ischemic and hemorrhagic stroke have to be established. Also, there is some concern that DOACs may not hold the promises of randomized trials in real life. Remarkably, the Food and Drug Administration sentinel audit registry data on dabigatran back the validity of key trial safety data in clinical practice.11 Nevertheless, it may be too optimistic to conclude that the success of DOACs in clinical trials will automatically result in closure of the prevention gap in AF. Instead, recent data from the global anticoagulant registry in the field (GARFIELD) indicate that DOACs have replaced VKAs in some 20% of patients with AF, but that the proportion of untreated patients in the entire AF population has remained largely unchanged.

Another open question is whether the success story of DOACs, including edoxaban in AF, provides a roadmap for other pathogenic scenarios in stroke prevention. The disappointing efficacy and safety results of the Phase 2 Randomized Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etxilate in Patients After Heart Valve Replacement (REALIGN) study12 comparing dabigatran against warfarin in patients with artificial heart valves should send a message of caution to advocates of translation to other fields without evidence from specific prospective trials. However, it is conceivable that DOACs may have a role in other thromboembolic conditions, such as carotid atherosclerotic disease, whether these occur in isolation or in concomitance with AF. A particularly interesting topic is secondary stroke prevention in the 30% of patients with stroke in whom stroke pathogenesis remains cryptogenic, despite a thorough diagnostic work-up. The recently presented CRYSTAL AF trial using implanted event recorders suggest a prevalence of 10% to 30% of paroxysmal atrial fibrillation in patients with cryptogenic stroke. These patients would likely have benefited from anticoagulation. Finally, the pathogenic nonentity of cryptogenic stroke has been conceptually refined, yielding the pathophysiologically more homogenous subcategory of embolic stroke of undetermined source, and trials of DOACs in this indication are being planned.

Disclosures
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Roland Veltkamp and Shyam Prabhakaran

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