The Case
A 77-year-old man with ischemic cardiomyopathy and an ejection fraction of 25% presents with a recurrent embolic-looking stroke while taking aspirin and clopidogrel for a coronary stent placed 6 months ago. Computed tomographic angiography of the head and neck is unrevealing. Telemetry reveals a normal sinus rhythm. Renal functions are normal.

The Question
(1) Should one of the newer oral anticoagulant agents be prescribed for this patient?

The Controversy
OFF-LABEL USE OF NEW ORAL ANTICOAGULANTS

Controversies in Stroke
Section Editors: Carlos A. Molina, MD, PhD, and Magdy H. Selim, MD, PhD

Newer Anticoagulants Can Be Used Off-Label

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What is the diagnosis? Stroke neurologists make use of inductive reasoning, a probabilistic exercise, to determine stroke mechanism. Where ≥1 possible mechanism exists, we typically adopt the philosophy of Occam’s razor, assuming that 1 mechanism is dominant. The ensuing approach to preventive treatmentrationally follows the determination of stroke mechanism. The appearance of an embolic-looking stroke on brain imaging usually implies a wedge-shaped cortical infarct or multiple scattered infarcts in one or multiple arterial territories. Embolic stroke may be of arterial, cardiac or less commonly, venous origin (paradoxical embolism).

From the case history, we infer that arteroembolic stroke arising from a ruptured atherosclerotic plaque is less likely given the unrevealing computed tomographic angiogram. We have no immediate evidence of atrial fibrillation (AF), and we assume that the echocardiographic assessment done to determine the low ejection fraction does not show any alternate source of cardioembolism. The low ejection fraction suggests a cardioembolic source, but what kind?

Results from a recent randomized controlled trial support the use of prolonged cardiac monitoring in patients after transient ischemic attack or embolic stroke after negative standard vascular and cardiac investigations. Assuming that there is no evidence of AF, then the working diagnosis of stroke mechanism becomes a small, unseen, intracardiac mural thrombus formed because of poor cardiac function that embolized to the intracranial circulation causing a stroke. An additional careful look at the heart with transesophageal echocardiography may be considered, but the yield is likely to be low. Newer techniques, such as cardiac computed tomography or MR, may yet yield further insights into nonvalvular, non–AF-specific causes of cardioembolic stroke, but their use has yet to be proven.

The prevention of subsequent stroke in this scenario was examined in a large, double-blind randomized controlled trial, Warfarin and Aspirin in Patients With Heart Failure and Sinus Rhythm (WARCEF) which tested whether warfarin or aspirin was superior for stroke or systemic embolism prevention among subjects with low ejection fraction but in sinus rhythm. There was no significant overall difference in the primary composite end point of stroke and all-cause mortality between the 2 treatment groups. Warfarin was effective in preventing ischemic strokes (0.72 versus 1.36 events per 100 patient-years; hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.33–0.82; \( P=0.005 \)), but it was associated with more major bleeding (1.78 versus 0.87 events per 100 patient-years; odds ratio, 2.05; 95% CI, 1.36–3.12; \( P<0.001 \)) when compared with aspirin. Less than half of the participants in WARCEF had ischemic cardiomyopathy, myocardial infarction, or stroke at the time of enrollment, factors that are strong stroke risk factors. Thus, exactly how WARCEF applies to our patient remains uncertain. Furthermore, in Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-W), aspirin and clopidogrel were associated with at least as much bleeding as warfarin but was less effective in preventing stroke. Thus, the fact that our patient was already on dual antiplatelet therapy is not particularly relevant.
The novel anticoagulants are effective in preventing stroke among patients with AF. A pooled analysis of Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE), Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) With Dabigatran Etxilate, and Rivaroxaban vs Warfarin in Patients With Atrial Fibrillation (ROCKET-AF), the 3 trials that compared apixaban, dabigatran, and rivaroxaban, respectively, versus warfarin, demonstrate that these agents are associated with lower hemorrhagic or ischemic stroke (relative risk, 0.77; 95% CI, 0.67–0.88) and all-cause mortality (relative risk, 0.88; 95% CI, 0.82–0.95). Furthermore, they are associated with lower risk of intracerebral hemorrhage when compared with warfarin: HR, 0.42; 95% CI, 0.30 to 0.58; HR, 0.30; 95% CI, 0.19 to 0.45; HR, 0.41; 95% CI, 0.28 to 0.60; and HR, 0.67; 95% CI, 0.49 to 0.94, for apixaban, dabigatran 110 and 150 mg, and rivaroxaban, respectively. The increased risk of intracerebral hemorrhage in warfarin users is not limited to those with supratherapeutic international normalized ratios; in fact, most warfarin-associated intracerebral hemorrhages occur among those within the therapeutic international normalized ratio range. Specifically, dabigatran is associated with lower intracranial bleeding when compared with warfarin, irrespective of the quality of warfarin administration and monitoring. In A Phase III Study of Apixaban in Patients With Atrial Fibrillation (AVERROES), apixaban was as safe as aspirin. However, the recent early termination of the Dabigatran Etxilate in Patients With Mechanical Heart Valves (RE-ALIGN) trial using dabigatran for anticoagulation for patients with prosthetic heart valves, because of both increased embolic events and increased bleeding, is a reminder that we cannot assume that the novel anticoagulants are equivalent to warfarin.

Our patient has a high probability of a cardioembolic stroke mechanism. He could still have paroxysmal AF. In the absence of identifiable AF, he ought to be anticoagulated and counseled about the risk of hemorrhage. Given the safety benefit of the novel anticoagulants, the lack of overall benefit of warfarin in WARCEF, it would be reasonable to choose a novel anticoagulant for long-term stroke prevention. Today, we would choose apixaban or rivaroxaban instead of dabigatran given the uncertainty over the association between dabigatran and coronary artery disease. We would add a proton pump inhibitor, particularly because the patient would likely be counseled by his cardiologist to stay on aspirin long term because of his coronary stent. We would follow his renal function. Multiple testable hypotheses have arisen from this case analysis, and we hope that future randomized trials will aid us in decision making on the use of these new agents.

**Disclosures**

None.

**References**


**Key Words:** atrial fibrillation • heart • heart failure • stroke • transient ischemic attack
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