Newer Anticoagulants Should Not Be Used for Off-Label Indications

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We are presented here with a sketchy story of a presumed recent stroke onset that is embolic-looking while taking aspirin and clopidogrel for a coronary stent that had been inserted some 6 months earlier. Presumably, imaging consisting of computed tomography or magnetic resonance had shown large artery infarcts in differing arterial territories and of varying ages. Whether earlier infarcts had occurred before the introduction of antiplatelet agents is unknown. Also unknown is the duration of telemetry, which was reported as normal. In this context, should we prescribe a new oral anticoagulant (NOAC)? I will say no, but let’s go back to the beginning.

My first reaction is that I need more information. I might be old-fashioned, but a thorough history and examination would be a good start. Were there any previous stroke symptoms? What were the clinical details of the decision to insert the coronary stent? Are there any potential contraindications to anticoagulant therapy such as peptic ulcer or poorly controlled hypertension? I would like to review the films to confirm the presence of the imaging characteristics described earlier. Depending on our overall assessment at that time, further investigation may be required. In particular, a transesophageal echocardiography may be useful to determine whether aortic arch atheroma is present or ventricular clot. Given that we now have information that increasing the duration of telemetry ≤21 days may increase the yield of finding occult atrial fibrillation ≤23%, this would be a useful step. Clearly, if atrial fibrillation was found, anticoagulation should be considered based on the knowledge that episodic atrial fibrillation carries a similar stroke risk to established AF. However, if this was the case, there is only evidence that clopidogrel plus warfarin is safer than clopidogrel plus aspirin plus warfarin. There is no evidence of what the risk–benefit ratio may be with NOAC plus an antiplatelet agent.

Let us assume that further investigation has not advanced the case and we are left with a diagnosis of recent onset ischemic stroke of presumed cardioembolic origin but with the complication of having a coronary artery stent inserted 6 months before requiring dual antiplatelet therapy for ≥12 months based on current guidelines. With a 25% cardiac ejection fraction, this would fulfill the requirements for a diagnosis of cardioembolic stroke for classification systems such as Trial of Org 10172 in Acute Ischemic Stroke Treatment (TOAST). From several observational and epidemiological studies, it seems that the natural history of this stroke subtype is a mortality rate of ≈14% at 1 year. Interestingly, for truly cryptogenic stroke in which no source of embolism or other mechanism can be identified, the stroke risk is at least as great as other stroke subtypes, or in some studies even worse for fatal events. ¹

How should our patient be treated and what is the evidence? The investigators from the Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial studied 2305 patients with cardiac failure based on the presence of an ejection fraction ≤35%. ² A significant proportion of patients had a history of previous cerebrovascular events. Patients were randomized to receive either warfarin or aspirin. Antiplatelet therapy was as effective as anticoagulation in preventing stroke or death, although warfarin prevented more ischemic strokes.

The additional and equally important point is that there is a need to balance the stroke subtype management with the need to provide ongoing evidence-based therapy for the coronary stent put in place some 6 months before. As mentioned earlier, American Heart Association guidelines stipulate that the P-glycoprotein inhibitor should be continued for ≥12 months.² Can we contemplate adding an NOAC to clopidogrel? Certainly, there is no evidence to support this view, and one would be concerned about the unknown bleeding risk.

Based on all of this information, should an NOAC be used in this clinical situation? I would say no on several counts. First, given that the commonly used anticoagulant warfarin was not found to be superior in this situation (WARCEF), the likelihood that an NOAC would provide benefit over and above the existing combination antiplatelet therapy seems unlikely. Furthermore, there have been no clinical trials using NOACs, as yet, to provide any such evidence. Granted, a potential advantage of NOACs is their favorable risk profile when compared with aspirin. Specifically, in Apixaban Versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) in which a head-to-head comparison between apixaban and aspirin was undertaken in patients with atrial fibrillation who were deemed unsuitable for vitamin K antagonists, similar major bleeding risks were experienced.⁴ However, I would argue that this creates a situation of clinical equipoise rather than evidence, the perfect scenario in which to conduct a large

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randomized controlled trial to provide clinicians with definitive evidence for patient management.

In the mean time, continued dual antiplatelet therapy would seem to be the most sensible option in this particular clinical situation while awaiting the answer.

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References

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