

Finding What You Seek: Analyzing Therapies for Nonvalvular Atrial Fibrillation

Nonvalvular atrial fibrillation is common and can be associated with few hemodynamic symptoms. However, one of its consequences, systemic embolization, produces substantial morbidity and mortality. Over the past decade, the management of patients with nonvalvular atrial fibrillation has been the subject of many clinical trials, numerous conferences, and more papers than any clinician has time to digest. New drugs and therapeutic options abound. Clinicians managing these patients are awash with data and, perhaps, conflicting interpretations of those data. In this issue, Catherwood and colleagues (1) extend a simpler model published 5 years ago (2) to offer a new cost-effectiveness analysis of therapies for nonvalvular atrial fibrillation. They conclude that patients with nonvalvular atrial fibrillation are best and most cost-effectively served by cardioversion followed by antithrombotic therapy with aspirin. When atrial fibrillation recurs, as it will eventually in most of these patients (3, 4), the authors suggest a second attempt at cardioversion, continuation of aspirin therapy (or initiation of warfarin therapy in patients who remain in atrial fibrillation), and initiation of amiodarone therapy in patients with a moderate or high risk for systemic emboli.

Because cost-effectiveness analyses are explicit, they allow us to explore diverse assumptions and their implications. But decision models always simplify the real world: by limiting the number of strategies considered, by ignoring crossovers among therapies, by constraining the potential outcomes examined, or by considering a limited time horizon. Various recently published analyses of nonvalvular atrial fibrillation, although more similar than different, have simplified the decision in different ways. Two considered only antithrombotic therapies (5, 6); one considered only a 5-year time horizon (2); two considered only a single level of risk for systemic embolization (2, 7); and one considered health effectiveness but not cost (2). Their differing assumptions lead to somewhat different recommendations. In the latest analysis, Catherwood and colleagues (1) consider the patient's full lifetime, anti-

arrhythmic and antithrombotic therapies (alone and in combination), three levels of risk for systemic emboli, and cost. Catherwood and colleagues (1) and previous analyses estimated similar survival rates and costs when projected across the patient's lifetime, but the conclusions of these studies differ somewhat.

Although clinicians reading Catherwood and colleagues' more recent analysis (1) might assume that its conclusions supersede those of the studies that served as its foundation, critical readers should compare the analyses, their assumptions, and their conclusions. In particular, we must ascertain whether any of the simplifying assumptions of an analysis have shaped or possibly biased its conclusions. As we read the new analysis, several questions arise.

First, the primary recommendation is for cardioversion followed by antithrombotic therapy with aspirin as the initial management of patients with nonvalvular atrial fibrillation. Given the high rate of recurrence (3, 4), clinicians should understand that Catherwood and colleagues (1) assumed that aspirin would be prescribed even while the patient remained in sinus rhythm.

Second, we did not understand why amiodarone was recommended after relapse but not initially. Although patients who revert to atrial fibrillation in the first months after cardioversion may be at higher risk for reversion after subsequent cardioversion, it is hard to support this assumption from the literature (4). Catherwood and colleagues (1) do not seem to have increased recurrence rate after initial recurrence. Why, then, does their model suggest amiodarone therapy only after initial recurrence? The answer could lie in the authors' assumptions or, perhaps, in a bug in their model. The authors considered repeated cardioversion only once after recurrent atrial fibrillation. Would a strategy of serial cardioversion (4) have been validated if it had been examined?

Third, although Catherwood and colleagues (1) stratified the risk for embolic stroke in patients in atrial fibrillation into three levels, they assumed that the risk for ischemic stroke in patients in sinus rhythm was fixed at 0.5% per year. Atrial fibrillation can be a marker for other disorders associated with

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an increased risk for stroke in patients in sinus rhythm (for example, previous myocardial infarction, stroke, congestive heart failure, diabetes, or hypertension) (8). Hence, after cardioversion, these patients' risk for stroke should also be stratified. The result of not linking stroke risk while in atrial fibrillation to stroke risk while in normal sinus rhythm is to overstate the benefit of cardioversion and the maintenance of normal sinus rhythm in patients at higher risk for stroke. Analogously, it may understate the benefit of cardioversion in patients at lower risk for stroke. This potential bias would make antiarrhythmic therapy seem to be more strongly indicated in patients at high risk for stroke, precisely the finding of Catherwood and colleagues.

Fourth, almost a decade ago, a meta-analysis by Coplen and associates (3) identified consistent data about the substantial proarrhythmic effects of quinidine. Disch and associates' analysis (2), on which the current study by Catherwood and colleagues is based, suggested that treatment with warfarin (while allowing atrial fibrillation to persist) was superior to treatment with quinidine (in an attempt to maintain sinus rhythm). Nonetheless, Catherwood and colleagues (1) now suggest that clinicians consider quinidine therapy if the risk for stroke is high and amiodarone therapy is contraindicated or is unappealing to the patient. We believe that in such settings, rate control and antithrombotic therapy with warfarin to maintain an international normalized ratio between 2.0 and 3.0 are preferable, unless some bleeding diathesis precludes the use of warfarin.

What should the clinician take away from this new study? First, cardioversion should be the first-line therapy for patients with nonvalvular atrial fibrillation. Even after successful cardioversion, anti-thrombotic therapy with aspirin is indicated because of the high rates of reversion to atrial fibrillation in these patients. Second, the choice of antithrombotic therapy might be affected by patients' risk for thromboembolic or bleeding events. Patients at the highest risk for emboli may benefit more from warfarin therapy. Patients with substantial risk factors for coronary artery disease may benefit more from aspirin therapy. (By the way, such benefits were not included in any of the decision models described here.) Third, we believe that after cardioversion, antiarrhythmic therapy could be used to diminish the chance of recurrent atrial fibrillation. Current data seem to support the use of amiodarone for this purpose. For some patients who require an atrial kick for hemodynamic support, extra efforts and additional attempts at maintaining sinus rhythm might be indicated. For patients remaining in atrial fibrillation, adequate rate control is needed, either by pharmacologic means or, perhaps, radiofrequency assault on the atrioventricular node (9).

Finally, decision and cost-effectiveness analyses, just like other forms of clinical science, are incremental. Studies build on one another, and their results sometimes disagree. Even with such differences, the careful reader can often find underlying similarities that support the basic approach and provide enhanced understanding of the clinical conundrum being considered. Even though explicit analyses might seem particularly vulnerable to simplifying assumptions about the strategies, events, or outcomes in a particular model, the same issues arise in intuitive, clinical judgment; in consensus processes; and, indeed, in the design and interpretation of clinical trials. The benefit of decision analyses lies in their explicitness and in their ability to reveal their own weaknesses and the weaknesses in the implicit reasoning they often reflect. One must always simplify complex problems to begin to think about them. Catherwood and colleagues' model provides clinicians with insights about the treatment of nonvalvular atrial fibrillation.

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