

## EDITORIAL COMMENT

# Economic Implications of Transesophageal Echocardiography-Guided Cardioversion of Atrial Fibrillation\*

Mark Hlatky, MD, FACC,† Alan S. Go, MD‡  
*Stanford and Oakland, California*

Ischemic stroke is the most feared complication of atrial fibrillation, and many studies have investigated strategies to reduce cerebral embolism. Anticoagulation with warfarin is remarkably effective in reducing the risk of ischemic stroke among patients with chronic atrial fibrillation (1) and has become standard therapy. More recently, four randomized trials (2–5) have shown that a strategy of aggressive rhythm control was no better than a strategy of rate control in preventing ischemic stroke and other adverse clinical outcomes. Many of the ischemic strokes in patients assigned to the rhythm control strategy in these trials occurred after normal sinus rhythm had been re-established and anticoagulation had been discontinued.

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Cardioversion will continue to be needed for patients with symptoms due to atrial fibrillation, and optimal management of these individuals remains an important issue. Cardioversion increases transiently the risk of stroke, presumably because of dislodgement of left atrial thrombi. Three weeks of anticoagulation before and after cardioversion has been the standard approach for patients whose atrial fibrillation has persisted for 48 h or longer (6). The development of transesophageal echocardiography (TEE) has offered the possibility of avoiding anticoagulation before cardioversion (7). If no clots were visible in the left atrium, it was hypothesized that immediate cardioversion could be performed with a low short-term risk of stroke. The advantage of this strategy lies in reducing the duration of warfarin therapy (with its attendant inconvenience and risk of bleeding), and in allowing immediate cardioversion. The Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) trial tested this strategy rigorously by randomizing 1,222 patients to either TEE-guided or conventional cardioversion (8). There was no significant difference in the rate of embolism between the two patient

groups, but the rate of any bleeding complication over the eight-week follow-up period was halved in the TEE group (8) because of their shorter duration of warfarin therapy. The strategy of TEE-guided cardioversion therefore appears to be a reasonable clinical alternative to preprocedure anticoagulation. However, if long-term anticoagulation will be recommended for most patients even after successful cardioversion, the major advantage of the TEE-guided approach in shorter duration of anticoagulation would be greatly diluted.

## ECONOMIC EVALUATION

Assessment of the economic consequences of clinical management strategies has become an important aspect of clinical research. Economic analyses are particularly valuable when performed alongside randomized clinical trials, which are the “gold standard” of evaluation in medicine. Consequently, in this issue of the *Journal*, the report by Klein et al. (9) from the ACUTE investigators about medical resource use and costs in their randomized trial of TEE-guided cardioversion is of great interest and importance. We will first discuss some issues in economic evaluation and then the particular findings of the ACUTE trial.

The costs in a clinical trial can be usefully separated into two components: the cost of initial management strategies and the costs of the clinical outcomes associated with the strategies. Initial costs are the planned and relatively predictable cost of each management strategy and are relatively straightforward to measure. In contrast, the costs of clinical outcomes are neither simple to measure nor readily predictable, and these costs may accumulate over an extended period of time. Total cost is the sum of these two components, one of which can be measured fairly accurately, and the other of which is measured with much more uncertainty.

## COST OF THE PLANNED STRATEGIES

The alternative strategies tested in the ACUTE trial entail predictable initial resource consumption patterns and costs. The clinical strategies differ only before cardioversion, and the resource comparison is basically one transesophageal echo versus three weeks of warfarin therapy. Based on the costs assigned to these resources by the ACUTE investigators, one TEE (\$277) costs about six times more than the combination of three weeks of warfarin (\$14.70) and three additional prothrombin times tests (\$31.20). Although the cost of these resources may be higher or lower in different practice settings, there is little doubt that the TEE strategy has significantly higher planned costs. Nevertheless, this cost difference is modest in size (\$231) and could easily be recouped if later expensive complications were prevented by TEE-guided cardioversion.

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From the †Department of Health Research and Policy and Department of Medicine, Stanford University School of Medicine, Stanford, California; and the ‡Division of Research, Kaiser Permanente of Northern California, Oakland, California.

## COST OF OUTCOMES

An economic evaluation of the TEE-guided and conventional cardioversion strategies must also account for the costs of unplanned events, such as stroke, bleeding, and TEE-related complications. These are all real and important costs, yet when event rates are low, they cannot be measured precisely. Furthermore, because these complications can be very costly to treat, even a small difference in incidence between the two groups could completely overshadow the modest \$231 difference in the cost of the planned strategies.

The cost of the clinical outcomes is measured as follows:

$$\sum p_i q_i$$

where  $q_i$  indicates the number (quantity) of event "i," and  $p_i$  indicates the mean cost (price) of treating event "i." In the ACUTE trial, the measurement of  $p_i$  and  $q_i$  was based on only a handful of events, and there was no statistically significant difference in the rates of death, stroke, major bleeding, or minor bleeding between TEE-guided and conventional cardioversion (8). There was a modest difference ( $p = 0.03$ ) in major plus minor bleeding in the parent trial, but this difference is not significantly different in the subset of patients enrolled in the economic analysis. Thus, the economic comparison of the clinical outcomes of these strategies is based on a series of small and statistically insignificant differences. The ACUTE trial lacked sufficient power to measure precisely the low rates of expensive complications and, as a result, the cost measurements have very wide confidence intervals.

A second issue in the economic analysis of the ACUTE trial is the measurement of  $p_i$ : the cost weights (prices) associated with the clinical events. The economic portion of the study was restricted to the 833 patients enrolled in the U.S. clinical sites. Hospital billing data were sought from all patients but were available from only 369 patients (44%). Any study missing over one-half of the data loses considerable credibility because the patients for whom data are available may be quite different from the remaining patients. Faced with very sparse data, the investigators tried to fill the holes by statistical imputation. Imputation is a reasonable strategy when data are missing for only a few percent of subjects but not when over half the data are missing. The costs they estimated for infrequent, expensive events like stroke (\$28,200), major bleeding (\$30,200), and death (\$7,400) are inconsistent and measured with great uncertainty. It would have been more prudent to use Medicare DRG reimbursements as price weights. Medicare DRG weights are a credible national standard, and their use would eliminate the problems of missing billing data and insufficient numbers of events to estimate per episode costs accurately. Assuming a reimbursement of \$5,000 for a DRG weight of 1.00, the costs of hospitalization for a stroke would be \$6,259, a gastrointestinal bleed would be \$4,971, and a fatal myocardial infarction would be \$7,743. If Medicare costs had been used, we suspect the TEE-guided

strategy would have higher costs than the conventional cardioversion strategy.

## CONCLUSIONS

The data from the ACUTE trial show that: 1) the planned costs of TEE-guided cardioversion are modestly higher than the costs of conventional cardioversion, and 2) the added cost of TEE-guided therapy might be partially or completely offset by savings due to fewer complications, but the data are quite inconclusive on this question because of the low incidence and imprecise cost estimates. Although the authors' statement that total costs "did not significantly differ" between the groups is technically correct, they lacked sufficient statistical power to document important cost differences in the range of \$200 to \$300.

Economic evaluations are very hard indeed when low frequency-high cost outcomes must be considered. These are real events that cannot be ignored, and the best approach may be to examine datasets of sufficient size to provide accurate measurement of their cost and frequency ( $p_i$  and  $q_i$ ). These analyses may need to be performed in larger nonrandomized cohorts of patients with atrial fibrillation. One suggestion is that clinical trials should report separately the initial (or planned costs) and the subsequent (unplanned) costs so the reader can see their relative contribution to the total. Decision models and other tools can then be applied to judge the potential cost-effectiveness of alternative strategies (10).

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**Reprint requests and correspondence:** Dr. Mark A. Hlatky, Stanford University School of Medicine, HRP Redwood Building, Room 150, Stanford, California 94305-5405. E-mail: hlatky@stanford.edu.

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