Cost-Effectiveness of Preference-Based Antithrombotic Therapy for Patients With Nonvalvular Atrial Fibrillation

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Background and Purpose—Recent atrial fibrillation guidelines recommend the incorporation of patient preferences into the selection of antithrombotic therapy. However, no trial has examined how incorporating such preferences would affect quality-adjusted survival or medical expenditure. We compared 10-year projections of quality-adjusted survival and medical expenditure associated with two atrial fibrillation treatment strategies: warfarin-for-all therapy versus preference-based therapy. The preference-based strategy prescribed whichever antithrombotic therapy, warfarin or aspirin, had the greater projected quality-adjusted survival.

Methods—We used decision analysis stratified by the number of stroke risk factors (history of stroke, transient ischemic attack, hypertension, diabetes, or heart disease). The base case focused on compliant 65-year-old patients who had nonvalvular atrial fibrillation and no contraindications to antithrombotic therapy.

Results—In patients whose only risk factor for stroke was atrial fibrillation, preference-based therapy improved projected quality-adjusted survival by 0.05 quality-adjusted life year (QALY) and saved $670. For patients who had atrial fibrillation and one additional risk factor for stroke, preference-based therapy improved quality-adjusted survival by 0.02 QALY and saved $90. In patients who had atrial fibrillation and multiple additional risk factors for stroke, preference-based therapy increased medical expenditures and did not improve quality-adjusted survival substantially. The benefits of preference-flexible therapy arose from the minority of patients who would have had a longer quality-adjusted survival if they had been prescribed aspirin rather than warfarin.

Conclusions—As do risks of stroke and of hemorrhage, patients' preferences help to determine which antithrombotic therapy is optimal. Preference-based treatment should improve quality-adjusted survival and reduce medical expenditure in patients who have nonvalvular atrial fibrillation and not more than one additional risk factor for stroke. **(*Stroke*. 1998;29:1083-1091.)**

Key Words: aspirin ■ atrial fibrillation ■ costs and cost analysis ■ stroke prevention ■ warfarin

Randomized clinical trials have demonstrated that warfarin sodium can prevent approximately two thirds of ischemic strokes in people who have atrial fibrillation.[1–8] Although aspirin is less effective in preventing strokes,[9–11] because of its ease of administration and safety, aspirin is associated with a greater quality-adjusted survival in some patients who have atrial fibrillation.[12] Many guidelines for stroke prophylaxis recognize the importance of patients' views about the quality of life with alternative antithrombotic therapies; they recommend incorporation of patients' preferences into decisions about stroke prophylaxis.[13,14] Thus, clinicians must either prescribe a treatment that is optimal on average (warfarin) or tailor therapy based on individual patient factors, including patients' preferences.

Although the importance of patients' preferences is clear, several practical clinical questions are unanswered. In which patients is it important to assess preferences? How should patients' preferences be assessed? Available approaches range from casual inquiry to formal utility assessment. Comprehensive assessment of patients' preferences typically requires separate interviews and may be costly. Would the health benefit derived from a comprehensive assessment of patients' preferences justify its cost?

To address these questions, we compared the cost-effectiveness of preference-based therapy to warfarin-for-all therapy in atrial fibrillation populations at low, medium, and high risk of stroke. Preference-based therapy prescribed the stroke prophylaxis (warfarin or aspirin) associated with the greater projected quality-adjusted survival, based on the patients' preferences. To estimate quality-adjusted survival, we assessed each patient's utilities for stroke and for therapy with warfarin or aspirin and incorporated these measures of preferences into a modification of our previously described decision model.[15] Thus, we answered the following question: Could the improvement in quality-adjusted survival from preference-based therapy be large enough to justify the additional time required to assess patients' preferences?

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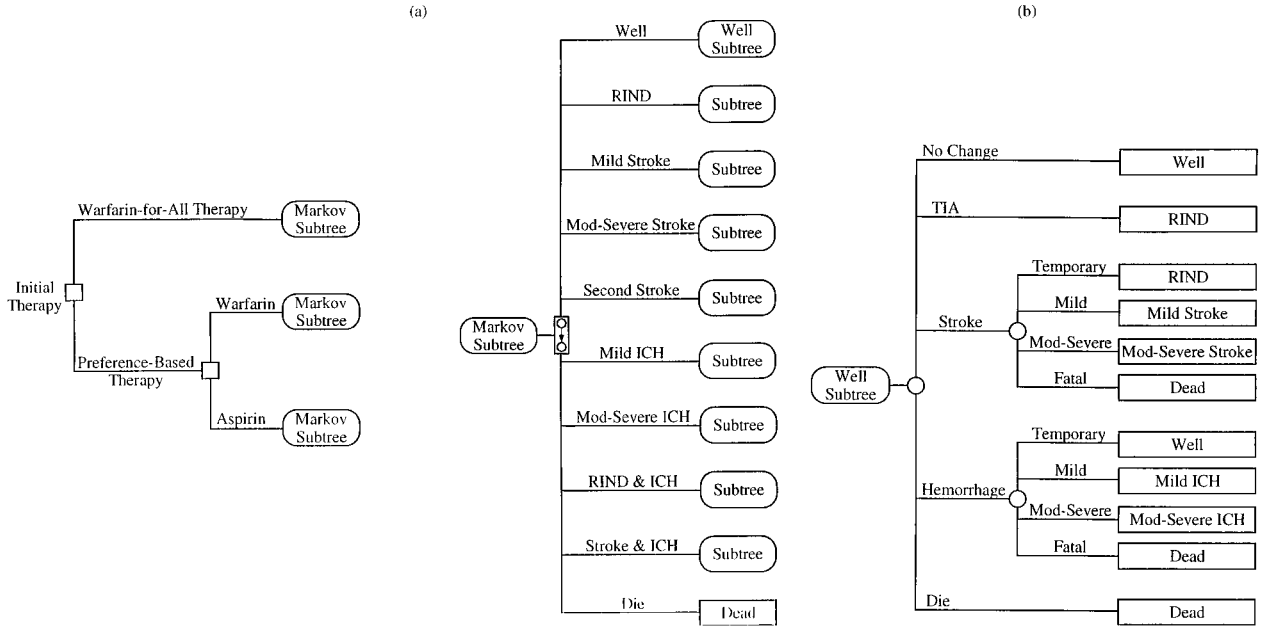

Figure 1. Schematic representation of the decision model. (a), Basic structure of the decision model. The square at the far left symbolizes the choice between two treatment options: warfarin-for-all therapy or preference-based therapy (in which either warfarin or aspirin is prescribed depending on patient preference). The Markov subtree shows the 10 health states for either treatment option. Patients remain in the well state (ie, in good health but taking either warfarin or aspirin) until one of four adverse events occurs: transient ischemic attack (TIA), stroke, hemorrhage, or death. The probabilities of these events depend on the prescribed therapy. (b), Well subtree illustrates adverse events. The boxes on the far right indicate which health state the patient enters after an adverse event. RIND (reversible ischemic neurological deficit) is the health state a patient enters after a TIA or a stroke without residual deficit. Mod-Severe represents a moderate to severe neurological event that results in loss of independence for one or more activities of daily living. ICH indicates intracranial hemorrhage. Although not shown, subtrees from the other health states (excluding death) have a similar structure.

Subjects and Methods

We used the method of Nease and Owens[16] to compare the potential benefits of preference-based therapy with those of warfarin-for-all therapy. We projected the quality-adjusted survival and net medical expenditure over a 10-year time horizon in 65-year-old patients who had nonvalvular atrial fibrillation. We stratified our analysis based on risk of stroke, performing separate analyses for low-, medium-, and high-risk patients. The base case consisted of a hypothetical cohort whose members had no contraindication to antithrombotic therapy, would participate in their treatment decision making, and would be compliant with their therapy. Through sensitivity analyses, we estimated what effectiveness we would obtain from preference-based therapy under other circumstances and whether we could increase that effectiveness by including an option of no antithrombotic therapy.

Quality-of-Life Elicitation

The projections of quality-adjusted survival were based on preferences elicited from volunteers who had atrial fibrillation.[12] After obtaining approval from the Human Subjects' Committees at the Veterans Affairs Palo Alto Health Care System and at Stanford University, we interviewed patients at these two medical centers who had atrial fibrillation, were at least 50 years of age, and could read English. Of the 83 volunteers consenting for the study, we used the results from 69; we excluded the results from 14 volunteers for the following reasons: 5 did not complete the interview, 7 did not understand one or more questions, and 2 had results that could not be interpreted. The 69 included volunteers were primarily white (87%), elderly (mean age, 70 years), and male (86%). Thirty-four of the volunteers were taking warfarin, and 20 had previously suffered a stroke. The utilities from these subgroups did not differ from the utilities in the remaining patients.[12] Utilities are quantitative measures of patients' preferences that we scored on a scale of 0 (equivalent to death) to 1 (usual health). As previously described in full,[12] these utilities were measured with the time-tradeoff method[17,18] implemented with the utility-assessment tool U-titer.[19]

Estimation of the Potential Quality-Adjusted Survival

To compare the potential effects of the two guidelines on quality-adjusted survival, we used the utilities assessed from the 69 volunteers as inputs into a decision-analytic Markov model. We built the decision model by adding our previously described decision model[15] onto the two treatment strategies, warfarin-for-all therapy and preference-based therapy (Figure 1). Preference-based therapy consisted of the two options, warfarin therapy and aspirin therapy.

We analyzed the decision model 207 times, using three different risks of stroke (low, medium, and high) for each of the 69 patients. For each patient we used his own set of utilities for five health states: well with warfarin therapy, well with aspirin therapy, mild stroke, moderate to severe stroke, and recurrent stroke. The utility for mild stroke was also used for the health state mild intracranial hemorrhage, and the utility for moderate-severe stroke was used for moderate-severe intracranial hemorrhage (Figure 1). Thus, rather than computing projected quality-adjusted survival for a population,[15,20–22] the model projected quality-adjusted survival for individuals. By using the individual patient as the unit of analyses, preference-based therapy chose the antithrombotic therapy that would have the greater quality-adjusted survival for each individual. In the base case we assumed that preference-based therapy chose the antithrombotic therapy with the greater quality-adjusted survival with 100% accuracy. In a sensitivity analysis we examined the effect of a preference-based strategy that was less accurate.

Estimation of the Rate and Cost of Adverse Events

In patients with atrial fibrillation, the rate of stroke depends on the patients' age and number of risk factors for stroke.[8,23–27] We used rates of stroke (Table 1) adopted from the Atrial Fibrillation

TABLE 1. Key Model Variables

Input Variable	Base Case	Reference(s)
Stroke parameters		
Rate of stroke without therapy, % per patient-year*		
High risk	5.3	8, 25
Medium risk	3.6	8
Low risk	1.6	8
Proportion of ischemic strokes, %		
Fatal	24	1–7, 79–82
Moderate to severe†	19	1–7, 79
Minor†	32	1–7, 79
Without permanent residua†	25	1–7, 79
Stroke risk reduction with prophylaxis, %		
Warfarin	68	1, 8
Aspirin	22	9
Hemorrhage parameters		
Rate of major hemorrhage, % per patient-year		
Warfarin	1.4	1–7, 79, 83
Aspirin	0.9	1, 4, 6
No therapy	0.8	1–7, 79, 83
Proportion of major hemorrhages, %		
Fatal	20	1–7, 79
Moderate to severe intracranial hemorrhage†	3	8, 42
Mild intracranial hemorrhage†	8	8, 42
Without permanent residua†	69	8, 42
Mortality parameters		
Demographics used to estimate age/sex-specific mortality rate		84
Age at start of 10-year interval, y	65	Assumption
Sex, % male	50	Assumption
Relative risk of nonstroke, nonhemorrhage death		
Atrial fibrillation	1.3	8, 85
Atrial fibrillation and a prior stroke	2.3	81
Cost parameters, 1994 US $		
Cost of eliciting each patient's preferences	50	Estimate
Annual cost of prophylaxis		
Warfarin (including monitoring)	800	Telephone survey, 15, 86
Aspirin	10	Telephone survey, 15
Acute (one-time) cost of neurological event		
Moderate to severe	34 200	87–91
Minor	7800	87–91
Transient ischemic attack	5300	91
Chronic (annual) cost of a neurological event		
Moderate to severe residua	18 000	Estimate, 92
Minor residua	2000	Estimate, 92

Adapted from Gage et al.[15]

*Rate of stroke increased by a factor of 1.4 per decade of life (compounded monthly).[8] Rates shown are for patients aged 65 years.

†These events are not fatal.

Collaborative Analysis because that analysis included pooled data from five prospective trials of stroke prophylaxis.[8] We defined low-risk patients as patients who had an expected rate of stroke of approximately 1.6 per 100 patient-years. This rate of stroke was typical of 60- to 69-year-old patients in the Atrial Fibrillation Collaborative Analysis who had nonvalvular atrial fibrillation but none of the other stroke risk factors—a history of stroke, transient ischemic attack, hypertension, diabetes, or heart disease (heart failure or coronary artery disease).[8] Medium-risk patients were defined as those individuals who had atrial fibrillation and an

estimated stroke rate of 3.6 per 100 patient-years. This rate of stroke was typical of 60- to 69-year-old patients who had nonvalvular atrial fibrillation and one additional risk factor for stroke. High-risk patients were defined as individuals who had atrial fibrillation and a rate of stroke of approximately 5.3 per 100 patient-years. This stroke rate was typical of 60- to 69-year-old patients who had nonvalvular atrial fibrillation and two risk factors for stroke. Because the rate of stroke increases with age, the rates of stroke for each of the three cohorts were increased monthly by a factor equivalent to an increase of 1.4 per decade of life.[8] Note that patients with atrial fibrillation who are at very high risk of stroke (eg, patients with greater than two risk factors for stroke and patients with a recent ischemic event) were not included in this analysis; they are poor candidates for preference-based therapy because warfarin is likely to be the preferred therapy[1,28] across their whole range of preferences.[29] The rate of major hemorrhage used in this analysis, 1.4 per 100 patient-years, was the average rate of major hemorrhage observed in the atrial fibrillation trials.[15]

Costs, as previously reported,[15] included the direct costs of prophylactic therapy (including monitoring for warfarin therapy), adverse events (stroke, transient ischemic attack, hemorrhage, and death), and preference elicitation (the provider time needed to elicit and incorporate a patient's preferences). All costs were estimated from a societal perspective and expressed in 1994 US dollars (Table 1). In the base case we assumed that the cost of eliciting each patient's preferences was $50. This $50 represents the cost of the time needed to assess patients' preferences by using a formal method (eg, utility assessment or a flip-chart approach[30]); in a sensitivity analysis we considered costs up to $200. All future costs and benefits (ie, quality-adjusted life-years [QALYs] gained) were discounted at a rate of 5% per annum.

Results

Use of warfarin for 10 years in low-risk patients projected an average quality-adjusted survival of 6.70 QALYs at an average cost of $9000. Use of preference-based therapy yielded a projection of 6.75 QALYs at an average cost of $8330 (including the cost of assessing each patient's preferences). Thus, on average, the preference-based guideline improved quality-adjusted survival by 0.05 QALY and saved $670 per low-risk patient. The gain in quality-adjusted survival and cost savings accrued from the 14 patients (20%) who would have a longer projected quality-adjusted survival with aspirin than with warfarin therapy if they were at low risk for stroke (Figure 2). Use of aspirin instead of warfarin would have saved an average of $3560 for each of these 14 patients and would have improved their quality-adjusted survival by 0.23 QALY (Table 2). Because the remaining 55 patients would receive warfarin with either approach, their quality-adjusted survival would be identical with warfarin-for-all and preference-based therapy.

Compared with the low-risk cohort, the potential advantages of preference-based therapy were smaller in the medium- and high-risk cohorts (Figure 3, top panel). Preference-based therapy improved projected quality-adjusted survival by 0.02 QALY and saved $90 per medium-risk person (Table 3). The savings in this population arose from the 9 patients (13%) who would have a longer quality-adjusted survival with aspirin therapy than with warfarin therapy if they were at medium-risk of stroke; their quality-adjusted survival increased by an average of 0.18 QALY. In the high-risk cohort, preference-based therapy improved projected quality-adjusted survival by only 0.01 QALY and cost $110 more per patient than did warfarin-for-all treatment (Table 3). Only 6 (9%) of the 69 patients would have a greater quality-adjusted survival with aspirin therapy than with warfarin therapy if they were at high-risk of stroke. Although their quality-adjusted survival would increase by an average of 0.15, these 6 high-risk patients would have greater future medical expenses if they received aspirin therapy.

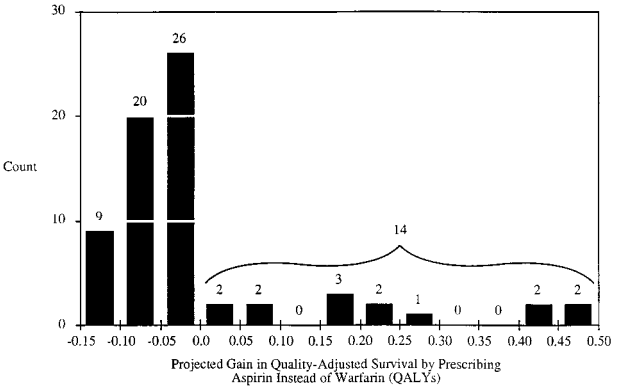

Figure 2. Histogram of the differences in quality-adjusted survival obtained by prescribing aspirin instead of warfarin. The differences shown are for the 69 patients if they were at low risk of stroke. Note that 14 (20%) of these patients would gain between 0.0 and 0.5 quality-adjusted life-years (QALYs) if they were prescribed aspirin rather than warfarin. There is no potential advantage of preference-based therapy for the other patients; their quality-adjusted survival would not increase with aspirin therapy.

Sensitivity Analyses

In the base case we estimated the quality-adjusted survival and net cost of preference-based therapy in hypothetical 65-year-old patients who could have their preferences assessed error-free for an additional $50. Thus, the base case demonstrated the potential benefit of prescribing preference-based atrial fibrillation therapy. In sensitivity analyses we quantified the benefit of using the preference-based approach under other circumstances.

In the base case we considered a strategy of warfarin for low-risk patients because it is prescribed more frequently than aspirin is in patients who have atrial fibrillation[31–39] and because recent guidelines recommend warfarin rather than aspirin for patients 65 years or older.[13,40] In a sensitivity analysis we compared preference-based therapy to aspirin-for-all therapy. In low-risk patients, the 10-year projections of cost and quality-adjusted survival with aspirin therapy were $5440 and 6.69 QALYs. Compared with aspirin therapy, preference-flexible therapy would increase medical costs by $2890 and save 0.06 QALY. By taking the ratio of these two figures, we estimated that prescribing preference-based therapy in low-risk patients would cost $50 000 per additional QALY saved. In medium-risk patients, we found that preference-based therapy would save 0.16 QALY compared with aspirin therapy at a cost of $7000 per QALY saved. In high-risk patients, preference-based therapy would improve quality-adjusted survival by 0.25 QALY and reduce medical expenditure compared with aspirin-for-all therapy. Thus, compared with aspirin-for-all therapy, preference-based therapy would be cost-effective or cost saving in all three cohorts.

TABLE 2. Utilities and Quality-Adjusted Survival in the 14 Patients Who Would Benefit From Preference-Based Therapy if They Were at Low Risk for Stroke

Patient No.	Treatment Utilities*		Stroke Utilities*			Therapy-Specific Life-Expectancy, QALYs		Potential Gain With Preference-Based Treatment, QALY
	Warfarin	Aspirin	Mild	Mod-Sev	2nd	Warfarin	Aspirin	
1	0.978	1	0	0	0	6.56	6.58	0.02
2	0.990	1	1	0.88	0.51	6.76	6.78	0.02
3	0.981	0.997	1	0.97	0	6.70	6.77	0.07
4	0.979	1	1	0.99	0.99	6.69	6.78	0.09
5	0.960	1	0.69	0.04	0	6.50	6.66	0.16
6	0.917	0.958	0.43	0	0	6.18	6.35	0.17
7	0.958	1	1	0	0	6.51	6.70	0.19
8	0.944	0.997	0.51	0	0	6.38	6.61	0.23
9	0.954	1	0.98	0.98	0	6.52	6.77	0.25
10	0.954	1	1	0.76	0.	6.51	6.76	0.25
11	0.917	0.988	0.92	0.89	0.55	6.26	6.67	0.41
12	0.917	1	0.73	0	0	6.21	6.66	0.45
13	0.917	0.997	0.95	0.55	0	6.25	6.71	0.46
14	0.917	0.997	1	0.98	0	6.27	6.75	0.48
Mean	0.949	0.995	0.85	0.51	0.15	6.45	6.68	0.23

QALY indicates quality-adjusted life-year.

*Utilities for all health states were scored on a scale of 0 (equivalent to death) to 1 (usual health). Mod-Sev is a moderate to severe neurological deficit, and 2nd is the neurological deficit after a second stroke. There was no significant relationship between a patient's current antithrombotic therapy and utility for warfarin or aspirin: patients 2 and 5 were not receiving any antithrombotic therapy; patients 3, 8, 12, and 14 were taking aspirin alone; patients 1, 4, 6, 9, and 13 were taking warfarin alone; and patients 7, 10, and 11 were taking aspirin and warfarin therapy.

Because preferences may be difficult to measure consistently or may be labile, we examined how error in the preference elicitation would affect quality-adjusted survival and cost. We examined a 15% error rate, whereby 15% of the population treated with a preference-based approach would be prescribed the therapy with the shorter quality-adjusted survival. With this degree of error in low-risk patients, for example, we found that preference-based therapy would increase quality-adjusted survival by 0.03 QALY at a cost savings of $990. The greater cost savings with an error-prone preference-based therapy would arise from the greater use of aspirin (the cheaper antithrombotic therapy in low-risk patients).

Like error in preference elicitation, the patients' ability to comprehend and complete the preference assessment affected the success of preference-based therapy. In the base case we stipulated that 100% of patients could participate successfully in their decision making. More realistically, some patients would not be able to complete the preference-assessment procedure successfully (and thus, by default, would be prescribed warfarin). For example, only 69 of 83 participants in this study provided a complete set of consistent utilities. If we assume the slightly lower success rate reported from use of a flip-chart atrial fibrillation decision aid (78%),[30] preference-based therapy would improve survival by 0.04 QALY and save $510 per low-risk patient compared with warfarin-for-all therapy.

We also examined whether the potential benefit of preference-based therapy would extend to a hypothetical cohort of patients aged 75 years, the median age of the American atrial fibrillation population.[41] Because their rates of stroke[8] and of hemorrhage[42,43] are approximately 40% greater, 75-year-old patients had lower 10-year projections of quality-adjusted survival regardless of treatment strategy. Compared with 65-year-old patients, the potential benefits of preference-based therapy on quality-adjusted survival and medical expenditure were slightly lower in 75-year-old patients. In low-risk 75-year-old patients, for example, preference-based therapy yielded 0.04 QALY, as contrasted with the 0.05 QALY gain expected in 65-year-old low-risk patients. For patients younger than 65 years, the potential benefits of preference-based therapy were slightly greater than in 65-year-old patients.

Changes in the cost of preference elicitation did not affect the potential gain in quality-adjusted survival of the preference-based approach but did change the net cost of that strategy. However, even if the cost of each preference elicitation was $200, the preference-based approach was cost saving in low-risk patients and cost only $60 per medium-risk patient. Decreasing the discount rate from 5% to 3% had no significant effect on the relative advantage of preference-based therapy.

To calculate a range of cost and quality-adjusted survival estimates for the preference-based approach, we considered worst-case scenarios for all three risk groups (Figure 3, bottom). For the worst-case scenarios, we assumed that preference elicitation cost $200 per patient, could be accomplished successfully in only 78% of patients who attempted it, and prescribed the therapy with the greater quality-adjusted survival only 85% of the time (ie, 15% of the time, it

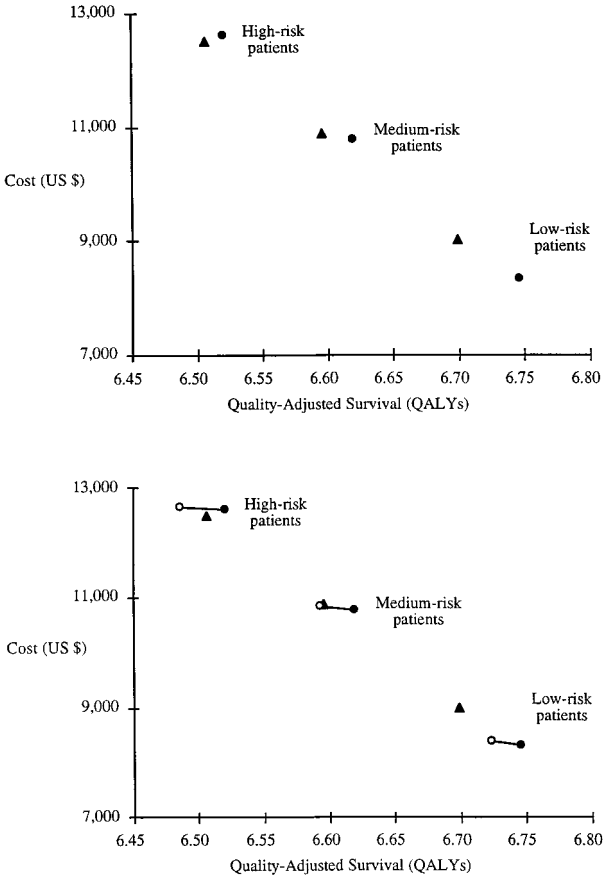

Figure 3. Ten-year projections of cost and quality-adjusted survival stratified by risk of stroke. Top, Base-case projections. ● indicates base-case projections with preference-based therapy; ▲, projections with warfarin therapy. Bottom, Same as top but with the addition of worst-case scenarios for preference-based therapy (○). The line connecting ○ and ● shows a range of possible values for preference-based therapy. Note that in low-risk patients preference-based therapy extends quality-adjusted survival and reduces medical expenditure, even in the worst-case scenario.

prescribed the treatment with the shorter quality-adjusted survival). In the worst-case scenario, preference-based therapy improved quality-adjusted survival by 0.03 QALY and saved an average of $610 per low-risk patient compared with warfarin-for-all therapy. In the worst-case scenario of medium-risk patients, preference-based therapy reduced quality-adjusted survival by 0.003 QALY but saved $14. In the worst-case scenario of high-risk patients, quality-adjusted survival decreased by 0.02 QALY, and expenditure rose by $310.

TABLE 3. Effect of Atrial Fibrillation Guideline on Quality-Adjusted Survival and Cost, Stratified by Risk of Stroke

Stroke Risk	Guideline Type	Projected Cost, $	Projected QALYs*
Low	Warfarin for all	9000	6.70
	Preference based	8330	6.75
Medium	Warfarin for all	10 860	6.60
	Preference based	10 770	6.62
High	Warfarin for all	12 490	6.51
	Preference based	12 600	6.52

*Ten-year projections for costs and quality-adjusted survival (in quality-adjusted life-years [QALYs]).

Finally, we explored the effect of expanding preference-based therapy to include a third option: no antithrombotic therapy. The added option did not improve quality-adjusted survival significantly because only 1 of 69 patients benefited from this option. Furthermore, the no-therapy option improved this patient's quality-adjusted survival only if he was a low-risk patient. There was no net financial advantage of the no-therapy option, because omitting antithrombotic therapy increased medical expenditures associated with strokes.

Discussion

We estimated the quality-adjusted survival and cost of two atrial fibrillation treatment strategies: preference-based therapy and warfarin-for-all therapy. Before this analysis, it was unclear whether the heterogeneity in patients' aversion to stroke and to stroke prophylaxis[12,30,44–49] would justify the use of preference-based atrial fibrillation guidelines and decision-making tools.[20,21,29,30,47,50] This uncertainty led to differences in atrial fibrillation guidelines, with some advocating preference-based therapy, at least in low-risk patients,[13,15,20,21,29,30,47] and others recommending warfarin therapy[51–54] but sometimes accompanied by the caution that "patients' preferences are of utmost importance."[14] Our analysis confirms the relevance of quality of life in the choice of antithrombotic therapy.

We found that a treatment strategy based on patient preferences could improve 10-year projections of quality-adjusted survival and medical expenditures in 65- or 75-year-old low-risk patients. On average, preference-based therapy could extend the quality-adjusted survival by 0.05 QALY and save $670 per low-risk 65-year-old patient compared with warfarin-for-all therapy. Although this average gain in QALYs for the cohort was modest, certain patients gained greater than 0.40 QALY with the preference-based approach (Figure 2). The benefit from preference-based therapy arose from the heterogeneity in patients' aversion to stroke and to stroke prophylaxis (Table 2). The heterogeneity caused 14 (20%) of 69 low-risk patients to have a greater quality-adjusted survival with aspirin therapy. This finding should not be surprising: In low-risk patients, warfarin therapy reduces the absolute probability of stroke or death by less than 1% per annum compared with aspirin therapy,[5,8] and warfarin therapy requires life-long international normalized ratio monitoring and daily attention to what one eats and drinks. Because low-risk patients' expected length of life is similar with warfarin or aspirin therapy, their optimum therapy hinges on their personal preferences, especially on their utility for warfarin therapy.[12,15,20,21,47]

When combined with related work, our analysis also supports incorporating preferences when prescribing antithrombotic therapy in medium-risk patients. In these patients, preference-based therapy could improve quality-adjusted survival by 0.02 QALY and save $90. Although the benefits expected in this population may seem modest, they are comparable to the benefits of reducing the risk of stroke by screening for hypertension in middle-aged patients.[55] Furthermore, there may be additional health benefits of assessing

patients' preferences that were not included in our analysis. Longitudinal studies have demonstrated that physician encouragement of patients' active participation in treatment decisions improves outcomes: a participatory decision-making style facilitated reduction of glycosylated hemoglobin in diabetics,[56,57] blood pressure in hypertensive patients,[58] and pain in arthritic patients.[59] Furthermore, involving patients in their choice of therapy improves their knowledge,[30] mental health,[60,61] satisfaction,[62] and compliance.[63,64] Improvement in compliance could be a significant advantage of preference-based therapy, because compliance with warfarin therapy is less than 90%, even in clinical trials whose average duration was less than 2 years.[1–8]

In comparison to our findings in low- and medium-risk patients, our analysis provides little support for the formal incorporation of preferences into the treatment decision of high-risk patients. Their average gain in quality-adjusted survival would be only 0.01 QALY at a cost of $110, and only 6 (9%) of every 69 high-risk patients would benefit from preference-based therapy. There are other important reasons to involve patients in the choice of therapy, as just discussed, but the present analysis provides minimal additional support for preference-based therapy in high-risk patients.

Our finding, in sensitivity analyses, that inclusion of a no-therapy option would not increase quality-adjusted survival significantly for any risk group has important implications for public health. Specifically, we can now estimate the fraction of anticoagulation candidates that should be prescribed antithrombotic therapy for their atrial fibrillation. Sixty-eight of the 69 patients had a greater projected quality-adjusted survival with antithrombotic therapy; one patient would have a greater projected quality-adjusted survival with no therapy, but only if he were at low-risk of stroke. Because most of the atrial fibrillation population is at medium or high risk of stroke,[65,66] we estimate that over 99% of anticoagulation candidates would have a greater projected quality-adjusted survival with antithrombotic therapy. In contrast to this finding, fewer than 70% of anticoagulation candidates receive antithrombotic therapy for their atrial fibrillation.[31,33–35,37,38,65,67–69] Thus, there is substantial opportunity to improve the future health of this growing population. Our finding that essentially all anticoagulation candidates would benefit from antithrombotic therapy implies that atrial fibrillation decision aids that now focus on the choice between warfarin and no therapy[30,70,71] should be refocused on the choice between warfarin and aspirin therapy.

Our analysis has several limitations. First, most of the volunteers for our study came from the Veterans Affairs Palo Alto Health Care System, and the benefits of incorporating patient preferences may be different in other populations. However, because more diverse populations may have even greater variability in their preferences, preference-flexible therapy may be more important in other settings. Second, the efficacy of warfarin therapy relative to that of aspirin is uncertain for low-risk patients. If the advantage of warfarin over aspirin is greater than we assumed, then we would have overestimated the benefit of preference-based therapy in low-risk patients. Third, our assessments of preference-based and warfarin-for-all therapy are based on projected outcomes. A prospective trial comparing the two approaches would provide a more rigorous evaluation. Fourth, we only considered variability in the preferences for (ischemic and hemorrhagic) strokes and for stroke prophylaxis. Including variability in preferences for other events, such as gastrointestinal hemorrhage, could have increased the benefits of preference-based approach. Finally, we have only a limited understanding of how patients' preferences change over time. To the extent that patients' preferences change, a therapy selected at one time may later become inappropriate.[72] Longitudinal assessment of patients' preferences would help us to evaluate the importance of this problem.[73]

Our analysis is the first demonstration that preference-based atrial-fibrillation therapy may both improve health outcomes and reduce expenditures. Related work indicates that patient participation in other medical decisions can be cost saving or cost-effective. For example, decision-making programs for selecting treatment of benign prostatic hyperplasia can improve satisfaction and can be cost-saving (because some prostatectomy candidates elect to forego the operation, choosing medical therapy instead).[74] Nease and Owens[16] found that preference-based antihypertensive therapy could be cost-effective. McNeil and colleagues'[75] analysis of treatment desires for laryngeal carcinoma found that approximately 20% of participants would opt for radiation therapy—the therapy associated with a shorter life expectancy—because it would avoid an invasive surgery that would decrease quality of life by preventing normal speech. That patient preferences influence optimal treatment decisions has been the rule rather than the exception.[76]

How should the present analysis affect clinical practice? First, the finding that the no-therapy option lowered quality-adjusted survival should encourage us to prescribe antithrombotic therapy. Second, the finding that preference-based therapy prolonged quality-adjusted survival and reduced costs should encourage us to consider preferences when prescribing antithrombotic therapy in low- and medium-risk patients. Although it is likely that physicians already tailor therapy in part based on patients' preferences, the extent to which they do so is unknown. To the extent that physicians tailor therapy based on preferences rather than adopt a warfarin-for-all approach, some of the benefit we estimate for tailored therapy may already have been realized in clinical practice.

How we should assess patients' preferences is unclear because any method that incorporates individual preferences has advantages and disadvantages: traditional physician-patient conversation is well accepted but may not actively involve patients in the choice of therapy; flip-charts promote patient involvement but may not maximize quality-adjusted survival; and utility-based methods may maximize quality-adjusted survival but are unfamiliar. Utility-based methods have the strongest theoretical basis[77] as an approach for maximizing patient utility. Our study, however, did not directly compare one approach with another; instead, it indicated that health benefit is attainable from therapy tailored to the individual's preferences. Further study of all alternative methods for preference assessment will help determine which methods are most practical and efficacious.

In conclusion, previous work found that the optimal antithrombotic therapy for patients who have nonvalvular atrial

fibrillation depends on their risks of stroke[5,8,15,78] and of hemorrhage.[5,20,22] Our analysis demonstrates that the optimal antithrombotic therapy also depends on individual preference. Our findings provide quantitative support for the emphasis on patients' preferences in recent atrial fibrillation guidelines and should encourage clinicians to consider patients' preferences when they make recommendations for therapy. Our findings do not suggest that clinicians should substitute patients' preferences for clinical judgment, but rather that clinicians should incorporate their patients' views about quality of life (as well as their patients' risks of stroke and of hemorrhage) when prescribing antithrombotic therapy. For low- and medium-risk patients, preference-based therapy offers greater health benefits and lower medical expenditure than would warfarin-for-all therapy.

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