The Cost-Effectiveness of Ibutilide Versus Electrical Cardioversion in the Conversion of Atrial Fibrillation and Flutter to Normal Rhythm

Gary A. Zarkin, PhD; Mohan V. Bala, PhD; Brian Calingaert, MA; and James T. VanderLugt, MD

Abstract

Atrial fibrillation and atrial flutter are cardiac rhythm disorders that are often symptomatic and may interfere with the heart's function, limiting its effectiveness. These arrhythmias are responsible for a large number of hospitalizations at a significant cost to the healthcare system. Electrical cardioversion (EC) is the most common nonpharmacologic intervention used to convert atrial fibrillation and atrial flutter to normal rhythm. Electrical cardioversion is highly successful in converting patients to normal rhythm; however, it is more traumatic and resource intensive than pharmacologic treatment. Recently, a new rapid-acting drug, ibutilide, was approved for the conversion of atrial fibrillation and atrial flutter. Ibutilide is administered through intravenous infusion and does not require anesthetization of the patient, as is required for EC. A decision-tree model was developed to estimate the cost-effectiveness of ibutilide therapy compared with EC therapy. Clinical outcomes were based on a phase III trial of ibutilide, and resource use was based on the literature and physician clinical judgment. A stepped conversion regimen of first-line ibutilide followed by EC for patients who fail to convert is less expensive and has a higher conversion rate than first-line EC. Sensitivity analysis shows that our results are robust to changes in cost and effectiveness estimates.

(Am J Man Care 1997;3:1387-1394)

From the Center for Economics Research, Research Triangle Institute, Research Triangle Park, NC (G.A.Z. and M.V.B.); the Department of Biostatistics, University of North Carolina—Chapel Hill, Chapel Hill, NC (B.C.); and Pharmacia & Upjohn Co., Kalamazoo, MI (J.T.V.).

Address correspondence to: Gary A. Zarkin, PhD, Center for Economics Research, Research Triangle Institute, 3040 Cornwallis Road, Research Triangle Park, NC 27709-2194; e-mail: gaz@rti.org.

This research was supported by a contract from The Upjohn Company. The opinions expressed herein are exclusively those of the authors and do not represent the opinions of Research Triangle Institute or Pharmacia & Upjohn Co.

Atrial fibrillation (AF) and atrial flutter (AFL) are the most common cardiac arrhythmias seen in clinical practice. Atrial fibrillation is the most common arrhythmia requiring hospitalization, and together AF and AFL account for more than 35% of hospital admissions for patients with a primary diagnosis of cardiac arrhythmia.[1] Both AF and AFL cause patients to experience symptoms such as palpitations, weakness, dyspnea, and decreased exercise tolerance.[2] Treatment focuses on controlling the ventricular response rate, preventing stroke, or restoring and maintaining normal sinus rhythm; anticoagulation therapy is administered in appropriate cases. Several pharmacologic agents, including digoxin, beta-blockers, and calcium antagonists, are used in treating AF and AFL to control the ventricular response rate. Electrical cardioversion (EC) is the most common nonpharmacologic intervention used to treat AF and AFL. Although EC is highly successful in converting patients to normal sinus rhythm almost immediately,[3,4] it requires anesthesia and induces stress and apprehension in patients.

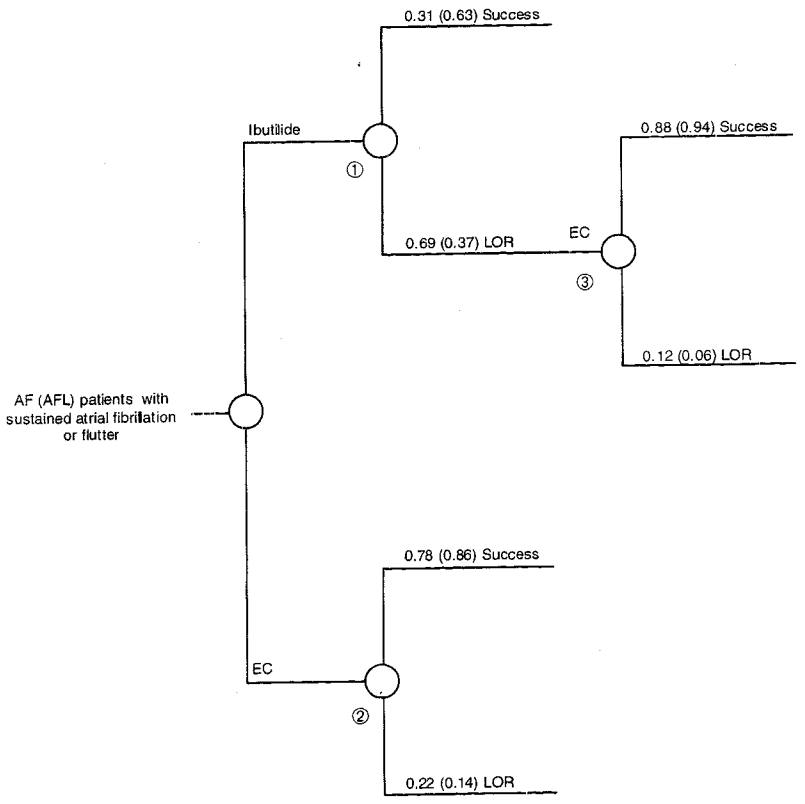
Recently, ibutilide fumarate (ibutilide), a new intravenous rapid-acting class III antiarrhythmic agent, was approved by the FDA for conversion of AF and AFL to normal rhythm. In a phase III clinical trial, ibutilide was found to rapidly terminate AF and AFL in 31% and 63% of patients, respectively.[5] When ibutilide therapy was successful, average time to conversion was 27 minutes after initiation of infusion.[5] Because ibutilide is fast acting and does not require anesthesia, patients whose AF and AFL are successfully converted incur lower physician and hospital costs than those treated with EC. In addition, ibutilide may result in less stress and discomfort to patients because it avoids the trauma of electrical shock. However, as with other class III agents, ibutilide may cause serious side effects, such as polymorphic ventricular tachycardia (PVT), in some patients.

··· DATA AND METHODS ···

Clinical outcomes were based on a double-blind, placebo-controlled randomized dose-response clinical trial of the effectiveness of intravenous ibutilide.[5] The study cohort was limited to hemodynamically stable patients who had exhibited AF or AFL for over 3 hours and less than 45 days. Class I or class III antiarrhythmic medications were discontinued at least five half-lives before study enrollment. Patients were stratified based on arrhythmia type (AF or AFL) and were randomized to receive either placebo or ibutilide treatment as first-line therapy. Intravenous ibutilide was administered in two 10-minute doses 10 minutes apart. The initial dose was 1 mg, and the second dose was either 1 mg or 0.5 mg. Conversion to normal rhythm with EC or, in a few cases, other drugs was attempted for those who failed to respond to the first-line therapy. All adverse events were recorded for a 72-hour period after infusion with ibutilide or placebo.

Although the clinical trial compared the efficacy of ibutilide with that of placebo, this comparison has little clinical relevance to practicing cardiologists. A more clinically relevant comparison is between ibutilide and EC. Hence, our decision-tree model (Figure 1) compared two first-line conversion options—ibutilide (node 1) and EC (node 2)—and their associated outcomes: success and lack of response. Because AF and AFL have the same therapy options and outcomes, we used the same decision-tree model to describe both diseases. However, note that the outcome probabilities are different for the two diseases, resulting in different cost and cost-effectiveness estimates.

Figure 1. Atrial Fibrillation and Atrial Flutter Decision Tree with Probabilities



Probabilities of each of the outcomes were obtained from a phase III clinical trial.[5] Probabilities for atrial flutter are in parentheses.
AF = atrial fibrillation; AFL = atrial flutter; EC = electrical cardioversion; LOR = lack of response

For ibutilide therapy, success was defined in the clinical trial as termination of AF or AFL for any length of time within 1.5 hours of the initial infusion; lack of response was defined in the clinical trial as failure to terminate AF or AFL within 1.5 hours of the initial infusion. For EC, success was defined as the immediate termination of AF or AFL as a result of EC; lack of response was defined as failure to terminate AF or AFL immediately. As with the majority of patients in the clinical trial, patients in our model who failed to respond to ibutilide treatment received EC as a second-line treatment.

The time horizon for our decision-tree model was from the first attempt at conversion to normal rhythm until either conversion or an additional 3 days

after the first attempt at conversion, which is the time period for which patients were followed in the clinical trial. Although patients may have experienced AF and AFL subsequent to initial termination during the trial, our model addressed only acute conversion of AF and AFL and did not address costs associated with prevention of recurrence or recurrence itself beyond the trial.

The outcome probabilities for first-line ibutilide therapy (node 1) were estimated directly from results of the clinical trial.[5] The probabilities associated with first-line EC (node 2) were estimated on the basis of clinical trial patients who failed to respond to placebo and were subsequently treated with EC. The outcome probabilities for second-line EC (node 3) were taken directly from the clinical trial results of patients who received EC after a lack of response to first-line ibutilide. The ibutilide success rates (0.31 for AF and 0.63 for AFL) were lower than those of first-line EC (0.78 for AF and 0.86 for AFL). However, the second-line EC success rates (0.88 for AF and 0.94 for AFL) were greater than the EC first-line success rates. The overall success rate for the ibutilide arm, S_{ib}, was computed by using the following equation:

$$S_{ib} = S_{ib,first} + (1 - S_{ib,first}) * S_{EC,second},$$

where $S_{ib,first}$ is the success rate of first-line ibutilide and $S_{EC,second}$ is the success rate of second-line EC. S_{ib} is equal to 0.92 for AF and 0.98 for AFL.

Resource Use and Cost

The resource use estimates in our model are based on a physician-generated clinical practice model. The model was developed by a cardiologist and validated in discussion with other experts. The clinical practice model was used to estimate the resource use associated with converting AF and AFL to normal rhythm, as well as the resource use associated with treating adverse events. Table 1 shows the resource use assumptions for first-line ibutilide as well as first- and second-line EC for AF and AFL.

We identified cost data for three primary resource categories: physician, hospital, and drugs. We obtained the cost of the physician component of treatment from the 1993 calendar-year national averages for physician charges by procedure (CPT code) submitted for Medicare reimbursement according to the Health Care Financing Administration, which administers Medicare. Although Medicare data are limited to patients over the age of 65, these data are appropriate to estimate the physician cost of treating AF and AFL because those suffering from these disorders tend to be elderly. We obtained the cost of the hospital component of treatment from charge data adjusted by cost-to-charge ratios appropriate for each cost center from Duke University Hospital. We used wholesale drug prices reported in the *Red Book*[6] to estimate drug costs. All costs were adjusted to 1996 dollars based on the inflation rate for medical expenditures obtained from the Bureau of Labor Statistics. Table 2 shows the unit cost assumptions for each resource.

Adverse Events

The most significant potential adverse events resulting from ibutilide therapy are induced ventricular arrhythmias requiring acute treatment. Among the

Table 1 Resource Use for Converting Atrial Fibrillation and Atrial Flutter

Resource	First-Line Ibutilide	Ibutilide Failures Second-Line EC (Incremental Resource Use)		First-Line EC	First-Line EC Failures (Incremental Resource Use)
		Success	Failure		
Intermediate Care Room	1		2	1	2
IV Access Kit	1			1	
Ibutilide	1				
Midazolam		1	1.6	1	0.6
Quinidine			6		6
Physician—Moderate Complexity (days)	1		1	1	1
Anesthesiologist		1	1.6	1	0.6
Complete Blood Count	1			1	
Electrolytes and Renal Function	1			1	
EC		1	1.6	1	0.6
ECG	2	2	4	2	2

EC = electrical cardioversion; ECG = electrocardiogram; IV = intravenous

ibutilide-treated patients, 1.7% experienced sustained PVT.[5] In the event of sustained PVT, we assumed that the patient was treated with EC. Patients with sustained PVT were also charged for an extra day of hospitalization, an extra hour of physician time, and a dose of magnesium. The additional cost of PVT for ibutilide-treated patients was computed as the product of the extra cost of treating PVT and the probability of experiencing PVT. Significant adverse events were not experienced by patients receiving EC.

Analysis

After estimating outcomes and costs associated with each treatment option, we computed the expected cost and expected success for each treatment. The expected cost of a treatment was obtained by summing the product of the probability of experiencing an outcome and the cost of that outcome over all possible outcomes. The expected success rate was computed in a similar fashion. We then compared the differences in costs and success rates across the alternative treatment options and computed cost-effectiveness ratios.

After computing the baseline cost-effectiveness results, we conducted sensitivity analysis to determine whether our results were robust to changes in the model parameters. We examined the effect of changes in the cost and resource use parameters, as well as the effect of changes in the effectiveness estimates, on the cost-effectiveness results. First, we examined the effect of changing the key cost components, which were identified to be the number of days hospitalized and the cost of the EC procedure. Next, we examined the effect of changes in the effectiveness estimates by conducting a Monte Carlo simulation using the probability distribution around each effectiveness estimate to construct distributions around the overall cost and success rates of the two treatment options. Based on the methodology developed by Doubilet et al[7] and implemented previously by Zarkin et al,[8] we drew a vector of random effectiveness probabilities for each treatment. We then recomputed the success rate and associated cost for each treatment using this vector of probabilities. We repeated the probability draws 1,000 times. We used the distribution of costs of the two treatments to construct a 95% confidence interval around the cost difference. This 95% confidence interval allowed us to determine whether the cost difference was significantly different from zero. In addition, we also used the distribution of costs and effectiveness rates to estimate the probability that ibutilide followed by EC is cheaper than first-line EC.

Finally, as noted above in the equation, the overall success rate of ibutilide followed by second-line EC depends on both the ibutilide success rate and the second-line EC success rate. To evaluate how changes in these key parameters affect the cost-effectiveness of ibutilide, we performed Monte Carlo simulation by making 1,000 draws of both the ibutilide success rate and second-line EC success rate (assuming independence) and computed the associated cost for each therapy arm. In these simulations, the first-line EC success rate was fixed at its baseline value. We then plotted the results of the simulated cost-effectiveness analysis and estimated the probability that ibutilide is both more successful and less expensive than first-line EC.

Table 2. Unit Cost of Resources

Resource	Cost per Unit (1996 Dollars)
Ibutilide	$65
Intermediate Room with Telemetry (days)	$755
IV Access Kit	$3
Complete Blood Count	$31
Electrolytes and Renal Function	$45
ECG	$46
Physician—Moderate Complexity (hour)	$78
Physician—Continued Care (hour)	$39
EC	$297
Anesthesiologist	$139
Midazolam (5 mg)	$11
Magnesium	$3
Quinidine (324 mg)	$1

EC = electrical cardioversion; ECG = electrocardiogram; IV = intravenous

··· RESULTS ···

The results of the cost-effectiveness analysis for AF and AFL are presented separately in Table 3. We compared two treatment options—first-line EC and ibutilide followed by EC. Under the baseline scenario for AF, the expected cost per patient for EC ($1,881) is greater than that for ibutilide followed by EC ($1,621). Because the expected success rate for ibutilide followed by EC (0.92) is greater than that for first-line EC (0.78), ibutilide followed by EC is both cheaper and more successful than just EC for AF. This is true also for AFL, because ibutilide followed by EC is both more successful (0.98 vs. 0.86) and less expensive ($1,330 vs. $1,725) than first-line EC.

Hence, from the perspective of cost-effectiveness analysis, ibutilide followed by EC is better than first-line EC treatment for both AF and AFL.

Table 3 also presents the results of our sensitivity analysis. In the first part of our sensitivity analysis, the two scenarios examine the effects of changes in the key cost components. In scenario 1, we reduced the number of days of hospitalization required for patients that failed to respond to treatment from 2 days to 1 day. In scenario 2, we reduced the cost of the EC procedure (including anesthesia) by 25%, because this is the main cost component for the EC arm of the decision tree. The sensitivity analysis indicates that our results are robust to changes in resource use and cost assumptions and that ibutilide followed by EC is still cheaper than first-line EC for both the scenarios examined.

In the second part of our sensitivity analysis, we constructed confidence intervals around the cost estimates and cost differences based on a Monte Carlo simulation. Note that the 95% confidence intervals for the cost difference for the baseline as well as the two scenarios for AF include zero. This indicates that the cost difference is not significantly different from zero at the 5% level. However, the probability that the cost of ibutilide followed by EC is less than the cost of first-line EC is greater than 90% in all cases. For AFL, the 95% confidence interval does not include zero for the baseline as well as the two scenarios; the probability that the ibutilide treatment followed by EC is less expensive than the EC treatment is 100% in all cases.

Figures 2 and 3 examine the effect of changes in the ibutilide and second-line EC success rates on the cost-effectiveness of ibutilide followed by EC therapy. For all combinations of success rates on the solid line, the cost of ibutilide followed by EC is equal to the cost of first-line EC (isocost line), and for all combinations of success rates on the dotted line the effectiveness of ibutilide followed by EC is equal to that of first-line EC (isoeffectiveness line). These two curves divide the graph into four regions: (i) ibutilide followed by EC is both more successful and less expensive than first-line EC; (ii) ibutilide followed by EC is more successful, but more expensive, than first-line EC; (iii) ibutilide followed by EC is less

Table 3. Costs of Converting Atrial Fibrillation and Atrial Flutter to Normal Rhythm

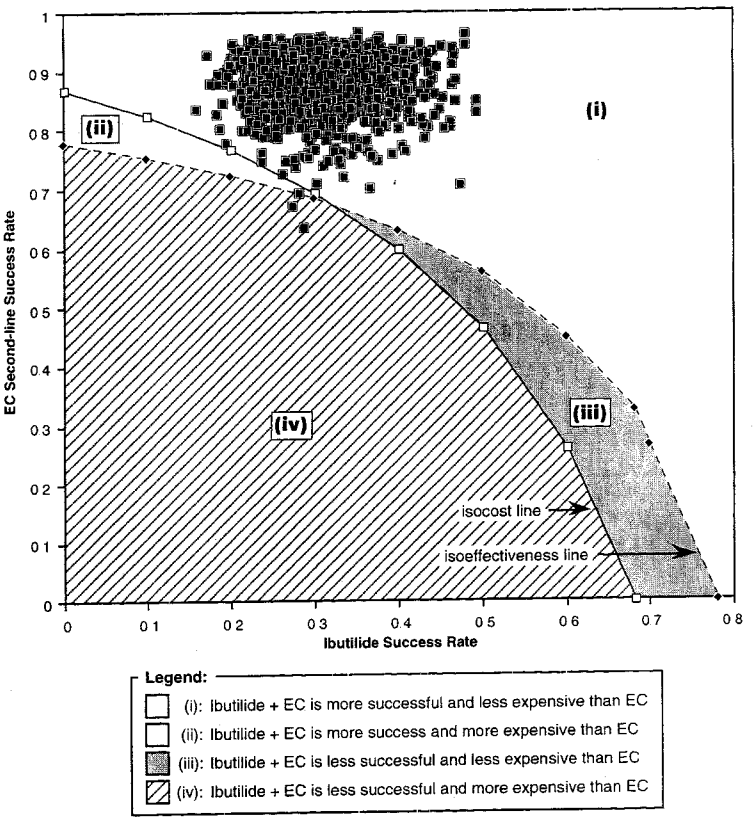
Disorder	Cost per Patient (95% Confidence Interval)*			*P* (difference < zero)*
	EC	Ibutilide + EC	Difference	
AF				
Baseline	$1,881 ($1,654, $2,232)	$1,621 ($1,488, $1,797)	-$260 (-$658, $27)	0.96
Scenario 1: Reduce days of hospitalization for patients who failed to respond to treatment from 2 to 1	$1,715 ($1,576, $1,931)	$1,559 ($1,456, $1,677)	-$156 (-$400, $28)	0.95
Scenario 2: Reduce cost of EC procedure by 25%	$1,758 ($1,539, $2,097)	$1,539 ($1,421, $1,703)	-$219 (-$595, $57)	0.93
AFL				
Baseline	$1,725 ($1,572, $1,989)	$1,330 ($1,253, $1,441)	-$395 (-$685, -$206)	1
Scenario 1: Reduce days of hospitalization for patients who failed to respond to treatment from 2 to 1	$1,619 ($1,525, $1,781)	$1,315 ($1,246, $1,395)	-$304 (-$488, -$177)	1
Scenario 2: Reduce cost of EC producedure by 25%	$1,606 ($1,459, $1,862)	$1,287 ($1,221, $1,338)	-$319 (-$596, -$138)	1

AF = atrial fibrillation; AFL = atrial flutter; EC = electrical cardioversion.
*The 95% confidence intervals and the probability that the cost difference is negative were calculated by using Monte Carlo methods as described in the text.

successful, and less expensive, than first-line EC; and (iv) ibutilide followed by EC is both less successful and more expensive than first-line EC. The figures plot 1,000 draws of ibutilide and second-line EC success rates obtained from a Monte Carlo simulation. Of the 1,000 draws for AF, 99.7% (99.9% for AFL) fall in region i, 0.1% (0% for AFL) fall in region ii, 0% (0.1% for AFL) fall in region iii, and 0.2% (0% for AFL) fall in region iv.

Figures 2 and 3 can also be used to examine for a given ibutilide success rate the range of second-line EC success rates for which the stepped therapy is cheaper and more successful than first-line EC. For example, if we draw a vertical line through 0.31 on the X axis (the baseline success rate for ibutilide) in Figure 2, it intersects the isoeffectiveness line at a Y value of 0.68 and the isocost line at a Y value of about 0.69. This means that if the first-line success rate of ibutilide is 0.31, as long as the second-line EC success rate is larger than 0.69, treatment with ibutilide followed by EC will be cheaper and more successful than first-line ibutilide therapy.

Figure 2. Simulated Cost-Effectiveness Results for Atrial Fibrillation



Each data point on the figure corresponds to one random draw of the ibutilide success rate and the second-line EC success rate (the first-line EC success rate was fixed at the baseline level). The line labeled "isocost line" shows the combinations of the ibutilide success rate and second-line EC success rate for which the cost of ibutilide followed by EC therapy is equal to the cost of first-line EC. Similarly, the line labeled "isoeffectiveness line" shows the combinations of the two parameters such that the effectiveness of the two treatment arms are equal.
EC = electrical cardioversion.

··· DISCUSSION ···

In today's healthcare environment, health decision makers require evidence on both the effectiveness and cost-effectiveness of new medications before they approve them for widespread use by clinicians. In this study, we combined data from a phase III clinical trial[5] with resource use information to develop a decision-tree model of the costs and cost-effectiveness of a new antiarrhythmia drug, ibutilide, compared with EC for the conversion of AF and AFL to normal rhythm.

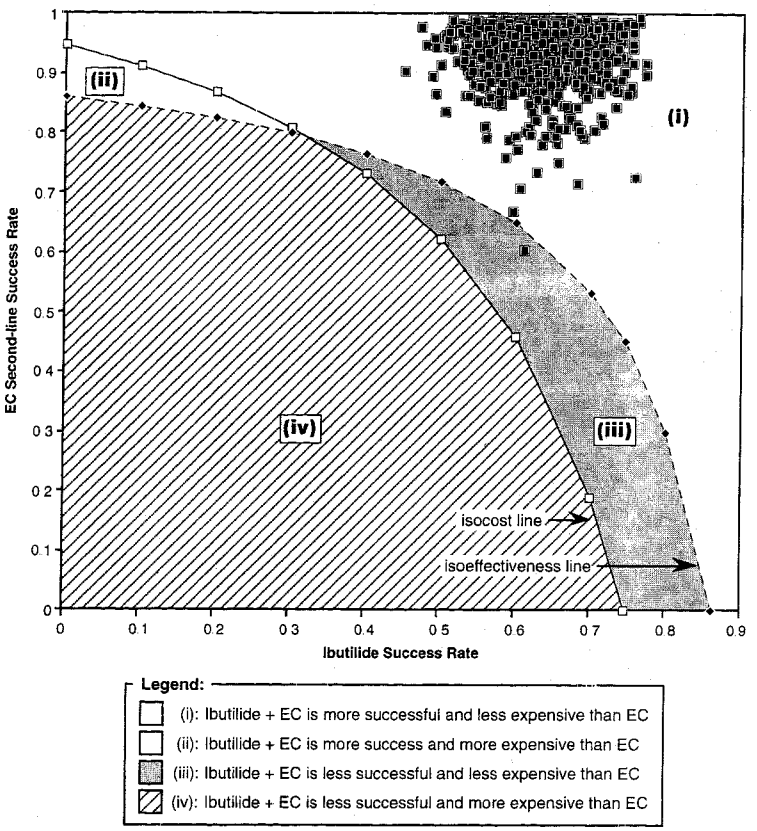
Our decision analysis shows that the expected costs of AF and AFL therapy with first-line EC are $1,881 and $1,725, respectively. However, we estimate that $260 per AF patient and $395 per AFL patient might be saved if these patients were first given ibutilide, and patients failing to respond to ibutilide were treated with EC. Besides reducing patient discomfort and yielding a higher success rate, this stepped treatment regimen would save substantial resources compared with first-line EC. Our sensitivity analysis indicates that our results are robust to changes in assumptions regarding the number of days of hospitalization and the cost of the EC procedure. The Monte Carlo analysis

showed that even when we allowed the success rates to vary randomly, ibutilide followed by EC was both more successful and less expensive than first-line EC, with a probability in excess of 90% in all cases.

Two important parameters in our model are the first-line and second-line success rates of EC. The baseline conversion rate for AF with first-line EC found in the trial (0.78) is within the range of values reported in the literature.[9] Note that our second-line success rate (0.88) is higher than the first-line success rate. This result might seem counterintuitive, because second-line EC is used for patients who do not respond to ibutilide, and the success rate of EC for these patients might be expected to be lower than that of first-line EC. However, some prior evidence suggests that administration of antiarrhythmic drugs improves the conversion rate for patients receiving EC.[9] Thus, the finding in this study that patients who received ibutilide had a higher conversion rate with second-line EC (even if this difference is not statistically significant) is consistent with past findings in the literature.

It is important to recognize some limitations of our study. First, our decision-tree model was based on a phase III clinical trial of ibutilide.[10] As a result, the first-line treatment options for AF and AFL are limited to ibutilide and EC. In clinical practice, several other antiarrhythmic drugs, such as quinidine or procainamide, may be chosen for patients with AF or AFL before first-line EC. Thus, our model does not represent the entire range of first-line choices that clinicians have at their disposal for treating arrhythmias. However, ibutilide's rapid action—when ibutilide therapy is successful, conversion to normal rhythm occurs within 1.5 hours—may be an important clinical and cost advantage over quinidine (although the use of quinidine has been decreasing because of the incidence of proarrythmias) and other drugs used to convert patients from AF and AFL. Other pharmacologic agents act more slowly, requiring up to 48 hours for determination of their effectiveness. Thus, 2 days are required to determine whether an attempted conversion has failed and second-line EC is necessary. Because ibutilide failures are identified within 1.5 hours, second-line EC conversion can be attempted as soon as 2 hours after the initial ibutilide conversion attempt.

Figure 3. Simulated Cost-Effectiveness Results for Atrial Flutter



Each data point on the figure corresponds to one random draw of the ibutilide success rate and the second-line EC success rate (first-line EC success rate was fixed at the baseline level). The line labeled "isocost line" shows the combinations of the ibutilide success rate and the second-line EC success rate for which the cost of ibutilide followed by EC therapy is equal to the cost of first-line EC. Similarly, the line labeled "isoeffectiveness line" shows the combinations of the two parameters such that the effectiveness of the two treatment arms are equal.
EC = electrical cardioversion.

Our reliance on a phase III clinical trial also limits our ability to model resource use for either first-line or second-line EC failures, because data on failure to respond to EC therapy were not available. Including drug or additional EC therapy for patients who fail to respond to EC would increase the cost of the EC arm by a larger amount than the ibutilide arm, which would further increase the estimated cost differential.

A second limitation of our study is that our model covers a relatively short time period. Following the clinical trial protocol,[5] the success rates in our study for both ibutilide and EC are based on conversion to normal rhythm during a short time frame after therapy initiation (1.5 hours for ibutilide and immediate conversion for EC) and do not include maintenance of sinus rhythm. Further, we do not include long-term cost of maintenance therapy, as well as the cost of treating recurrence of AF and AFL. Including long-term outcomes and costs is likely to make the stepped treatment regimen even more cost-effective compared with treatment with just EC because of the higher success rate of the stepped therapy, as long as the recurrence rates are similar in the two populations. Because our focus was on acute conversion, we did not include long-term outcomes and costs.

A third limitation of our study is that, because resource use data were not collected in the trial, our resource use estimates were derived from a clinical practice algorithm. Ideally, phase III clinical trials should include prospective collection of economic data. When economic data are not available, decision makers may find it useful to develop models that supplement clinical trial data. To enable development of better estimates of resource use, we hope future phase III clinical trials of new antiarrhythmia medications include prospective collection of economic data.

Although several articles have appeared on the cost-effectiveness of alternative antiarrhythmic therapies (eg, Kupperman et al[11]; Larsen et al[12]; Hogenhuis et al[13]; Roberts et al[14]; Kupersmith et al[15]; Hlatky[16]), we know of no previous study that estimated the cost and cost-effectiveness of a drug compared with EC for the conversion of AF and AFL to normal rhythm. Our results indicate that the cost-effective strategy is to first attempt conversion with ibutilide and then treat patients that fail to respond to ibutilide with EC. Patients who convert from AF and AFL to normal rhythm with first-line ibutilide treatment will save the additional resources required for EC conversion.

Acknowledgments

We gratefully acknowledge James Jollis, MD, of Duke University Medical Center, for his contribution to this paper.

··· REFERENCES ···

1. Bialy D, Lehman MH, Schumacher DN, et al. Hospitalization for arrhythmias in the United States: Importance of atrial fibrillation. *J Am Coll Cardiol* 1992;19(suppl A): 41A. Abstract.
2. Geraets DR, Kienzle MG. Therapy reviews: Atrial fibrillation and atrial flutter. *ClinPharm* 1993;12(October):721-735.
3. van Gelder IC, Crijns HJ, Van Gilst WH, et al. Prediction of uneventful cardioversion and maintenance of sinus rhythm from direct-current electrical cardioversion of chronic atrial fibrillation and flutter. *Am J Cardiol* 1991; 68:41-46.
4. Lown B. Electrical reversion of cardiac arrhythmias. *Br Heart J* 1967;29:469-489.
5. Stambler BS, Wood MA, Ellenbogen KA, et al. Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. *Circulation* 1996;94:1613-1621.
6. *1995 Drug Topics® Red Book*. Montvale, NJ: Medical Economics Data, Inc; 1995.
7. Doubilet P, Begg CB, Weinstein MC, et al. Probabilistic sensitivity analysis using Monte Carlo simulation. *Med Decis Making* 1985;5:157-177.
8. Zarkin GA, Bala MV, Wood LL, et al. Estimating the cost effectiveness of atovaquone versus intravenous pentamidine in the treatment of mild-to-moderate *Pneumocystis carinii* pneumonia. *Pharmacoeonomics* 1996;9:525-534.
9. van Gelder IC, Crijns HJGM, Lie, KI. Characteristics of patients with chronic atrial fibrillation and the prediction of successful DC electrical cardioversion. In: Kingma JH, et al, eds. *Atrial Fibrillation, A Treatable Disease?* Netherlands: Kluwer; 1992:67-86.
10. Stambler BS, Portnow AS, Wood MA, et al. Proven efficacy of repeated dose intravenous ibutilide, a class III antiarrhythmic drug, for rapid termination of chronic atrial flutter or fibrillation: Results of a multicenter placebo-controlled study. *J Am Coll Cardiol* 1995;25:230A. Abstract 754-4.
11. Kupperman M, Luce BR, McGovern B, et al. An analysis of the cost effectiveness of the implantable defibrillator. *Circulation* 1990;81:91-100.
12. Larsen GC, Manolis AS, Sonnenberg FA, et al. Cost-effectiveness of the implantable cardioverter defibrillator: Effect of improved battery life and comparison with amiodarone therapy. *J Am Coll Cardiol* 1992;19:1323-1334.
13. Hogenhuis W, Stevens SK, Wang P, et al. Cost-effectiveness of radio frequency ablation compared with other strategies in Wolff-Parkinson-White syndrome. *Circulation* 1993;88:II-437-II-446.
14. Roberts SA, Diaz C, Nolan PE, et al. Effectiveness and costs of digoxin treatment for atrial fibrillation and flutter. *Am J Cardiol* 1993;72:567–573.
15. Kupersmith J, Hogan A, Guerrero P, et al. Evaluating and improving the cost-effectiveness of the implantable cardioverter-defibrillator. *Am Heart J* 1995;130:507-515.
16. Hlatky MA. Cost and efficacy analysis in the ESVEM trial: Implications for diagnosis and therapy for ventricular tachyarrhythmias. *Prog Cardiovasc Dis* 1996;38:371-376.