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# Cost Effectiveness of Ibutilide With Prophylactic Magnesium in the Treatment of Atrial Fibrillation

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## Abstract

**Background:** In the Treatment with Ibutilide and Magnesium Evaluation (TIME) study, a retrospective multicentre cohort trial, prophylactic magnesium was found to improve the antiarrhythmic efficacy of ibutilide as demonstrated by an increase in the rate of successful chemical conversion and reduction in the need for direct current cardioversion (DCC).

**Objective:** The primary objective of this piggyback cost-effectiveness analysis of the TIME study was to compare the cost per successful conversion of atrial fibrillation (AF) for ibutilide in the presence and absence of magnesium prophylaxis. A secondary objective was to determine whether specific factors predict costs in the conversion of AF.

**Method:** The study was conducted from the US hospital-payer perspective. Direct medical costs ($US, 2002 values) including drugs, intravenous admixture and administration, DCC, electrocardiographs and physicians' fees were obtained directly from the provider. Nonparametric bootstrapping was conducted to calculate confidence intervals for the incremental cost-effectiveness ratios. One-way sensitivity analysis was conducted varying efficacy, and drug, hospital and physician costs. Multivariate analysis was conducted to determine whether specific baseline factors were predictors of total cost.

**Results:** Total costs per patient were lower in the ibutilide plus magnesium group compared with ibutilide alone ($US1075 vs $US1201); however, the difference was not statistically significant ($p = 0.116$). Patients receiving ibutilide plus magnesium had lower DCC costs compared with those receiving ibutilide alone ($US261 vs $US399; $p = 0.036$), but higher magnesium-associated costs ($US0.50 vs $US0; $p < 0.001$). Bootstrapping revealed that the ibutilide plus magnesium strategy would result in lower costs and greater efficacy 93.4% of the

time. These results remained robust to changes in both cost and efficacy. No baseline factors were found to be independent predictors of total costs.

**Conclusion:** Our data suggest that adding prophylactic magnesium to ibutilide may be cost effective, from a US hospital-payer perspective, for the acute conversion of patients in AF or flutter compared with ibutilide alone.

Data from clinical trials indicate that ibutilide, a class III antiarrhythmic agent, is effective in converting 31–57% of patients from atrial fibrillation (AF) to normal sinus rhythm. Similar response rates have been observed in general practice.[1-4] The efficacy of ibutilide is highly dependent on the duration of AF.[3,4] For example, conversion rates decrease from 61% to 14% when AF is >15 days in duration.[3]

Studies suggest that ibutilide is cost-saving compared with direct current cardioversion (DCC) for the acute conversion of AF.[3,5] However, when the efficacy of ibutilide was only 24%, DCC was a less expensive option compared with ibutilide.[6]

Ibutilide is well tolerated although Torsade de Pointes, a rapid polymorphic ventricular arrhythmia, may occur in approximately 4% of patients.[7] Magnesium is commonly used to treat Torsade de Pointes.[7,8] To date, no study has attempted to reduce the incidence of ibutilide-induced Torsade de Pointes with prophylactic magnesium therapy. In an animal investigation, magnesium prophylaxis significantly reduced the incidence of Torsade de Pointes when given with the class III antiarrhythmic agent clofilium.[9] Since ibutilide is also a class III antiarrhythmic the effect should be similar. The Treatment with Ibutilide and Magnesium Evaluation (TIME) study was conducted to assess this.

The cost effectiveness of routine magnesium administration prior to ibutilide infusion is also currently unknown. The routine use of magnesium will increase cost due to the drug, pharmacy cost for preparing the infusion and nursing administration time. However, magnesium may enhance successful chemical conversion which may lower costs by reducing the need for other therapies such as rate controllers, DCC and agents to treat AF-induced haemodynamic instability.[8] In addition, if magnesium prevents Torsade de Pointes, there may be cost savings associated with not using DCC, cardiac pacing, or drugs such as lidocaine to treat the ventricular arrhythmia.

This study is a piggyback cost-effectiveness analysis of the TIME study. The primary objective was to compare the cost per successful conversion, from the hospital perspective, of ibutilide in the presence and absence of magnesium prophylaxis for the conversion of AF. A secondary objective was to determine whether specific factors predict costs in the conversion of AF.

## Methods

### The Treatment with Ibutilide and Magnesium Evaluation Study

The TIME study was a multicentre, retrospective, cohort study conducted at Hartford Hospital (Hartford, Connecticut, USA), Medical University of South Carolina Medical Center (Charleston, South Carolina, USA), and Texas Tech University Medical Center (Lubbock, Texas, USA).[10] Billing and medical records of all patients receiving ibutilide for acute chemical conversion of AF or flutter from August 1996 to December 2001 were reviewed for inclusion. Patients receiving magnesium within 2 hours of ibutilide administration, not intended for the treatment of Torsade de Pointes, served as the active group. Patients who did not receive magnesium either before or during ibutilide therapy served as the control patients.

#### *Cost-Effectiveness Analysis*

A piggyback cost-effectiveness analysis of the TIME cohort study was conducted from a hospital perspective. Standardised costs from a single institution (Hartford Hospital) were used, with all costs

 

adjusted to 2002 US dollars and obtained directly from the provider. The following costs were included in the analysis: ibutilide, magnesium, intravenous administration (including nursing time) and admixture, physician fees, electrocardiography, and adverse events. The costs of adverse events (Torsades de Pointes only) were calculated and included the following: drug therapy such as magnesium, phenytoin, lidocaine and isoprenaline; conversion; pacing; and physician fees for conversion and management of adverse events.

The incremental cost-effectiveness ratio (ICER) for treatment with ibutilide plus magnesium versus ibutilide alone was calculated by using the following formula:[11]

Equation 1:

$$\text{ICER} = \frac{\text{cost}_{\text{Ibutilide + Mg}} \quad \text{cost}_{\text{Ibutilide alone}}}{\text{Conversion rate}_{\text{Ibutilide + Mg}} \quad \text{conversion rate}_{\text{Ibutilide alone}}}$$

where: Mg is magnesium.

### Statistical Analysis

In order to determine an estimate of the uncertainty of the ICER, the nonparametric bootstrap method was used. Bootstrapping has been found to provide accurate estimates of group differences in healthcare costs.[12-14] Actual patient-level data for both costs and effects were treated as an empirical probability distribution that is repeated with random components many times. Data were resampled in such a manner that all'cost- effect' pairings were equally likely to be selected in each successive redraw.[12]

In this study the data were resampled 25 000 times. The resultant incremental cost-effectiveness estimates were then plotted upon the cost-effectiveness plane and used to estimate confidence intervals.[12] The plane is divided into four regions (see figure 1) which illustrate the probability of a new therapy being greater or less effective, as well as greater or less costly, than its competitor:

- region (I) would be more effective and more costly
- region (II) less effective and more costly (inferior)
- region (III) less effective and less costly
- region (IV) more effective and less costly, and therefore dominant.

Data are presented as proportions or means ± SDs. Categorical variables were compared using $\chi^2$ analysis or Fischer's exact test, where appropriate. The unpaired t-test was used to compare continuous data.[11] A p-value of <0.05 was considered statistically significant.

In a previous study,[1] ibutilide was effective in converting atrial fibrillation or flutter to normal sinus rhythm in 50% of patients. Assuming an $\alpha$-level of 0.05, 80% power, and that a 50% change in efficacy induced by administration of intravenous magnesium sulphate would be considered clinically significant, a sample size of 112 patients would be necessary to detect significant differences between groups. However, it was decided *a priori* to include all eligible patients at the three participating institutions in our analysis of efficacy and the cost-effectiveness analysis. This study was approved by the institutional review boards of all three participating institutions.

Multivariate linear regression was conducted to determine whether specific baseline factors were predictors of total cost. Univariate analysis was conducted, correlating the dependant variable total cost with the following independent variables: age, gender, weight, magnesium level, corrected QT interval, AF or atrial flutter, magnesium prophylaxis and adverse events. Upon completion of the univariate analysis, any independent variable with a p-value <0.2 was judged as a candidate for multivariate analysis.

The choice of p-value for entry into the multivariate regression model is somewhat arbitrary, as is the choice of $p < 0.05$ for statistical significance. Lowering the p-value to $p < 0.1$ would likely results in fewer variables being entered into the multivariate model. In previous trials to which we have conducted multivariate regression[15,16] the p-value of <0.2 was chosen upon request of the journals. A review of the literature was also done prior to analysing these data revealing a number of other articles using similar methodology.[17] Consequently, $p < 0.2$ was chosen for this regression analysis.

**Table I.** Demographics of patients included in the Treatment with Ibutilide and Magnesium Evaluation study

| Characteristic | Ibutilide plus magnesium (n = 107) | Ibutilide alone (n = 214) |
|---|---|---|
| Gender (% male) | 59.8 | 61.7 |
| Age (years)[a] | 66.0 ± 14.8 | 67.2 ± 14.1 |
| Weight (kg)[a,b] | 82.1 ± 19.9 | 84.9 ± 20.6 |
| Type of atrial arrhythmia (% AF) | 57.0 | 65.9 |
| Magnesium level (mg/dL)[a,c] | 2.04 ± 0.30 | 2.15 ± 0.38 |
| Ibutilide dose (mg)[a] | 1.56 ± 0.51 | 1.55 ± 0.54 |

a Mean ± SD.

b Data available on 249 patients.

c Data available on 150 patients.

**AF** = atrial fibrillation.

Variable selection was conducted using the 'ENTER' option. The model was evaluated further by examining tolerance, variance inflation factor and partial regression plots of each variable. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) version 11.0 (SPSS, Chicago, Illinois, USA) and ICEplane 2001.08 (Pharmaceutical Manufacturers of America, Indianapolis, Indiana, USA).

### Sensitivity Analysis

A one-way sensitivity analysis was conducted to determine whether alterations in key parameters will alter the results of the cost-effectiveness analysis.[13] In the sensitivity analysis, efficacy was varied by the 95% CI while the costs of ibutilide, magnesium, intravenous administration and admixture, DCC, physician fees, electrocardiographs and adverse events were varied by ±50%.

## Results

From the three study sites, a total of 321 patients were identified. One hundred and seven patients received intravenous magnesium (mean ± SD = 2.2 ± 1.0g) within 2 hours of ibutilide administration. Baseline demographics were similar between the two groups (average age 66.8 ± 14.3 years, 61.1% male, 62.9% had AF, ibutilide dose 1.55 ± 0.53mg) except for the baseline plasma magnesium level which was slightly lower in the ibutilide plus magnesium group (2.04 mg/dL ± 0.30) compared with the ibutilide only group (2.15 mg/dL ± 0.38) [see table I].

An approximate 19% relative increase in the rate of successful chemical conversion (defined as conversion within 6 hours of ibutilide administration), and a 34% reduction in the need for subsequent DCC was observed in patients receiving magnesium compared with those not receiving prophylaxis (p = 0.040 and 0.045, respectively) [see table II]. The improvement in conversion rate was both statistically (OR = 1.69 95% CI to 1.02, 2.80; ARR 11.7% 95% CI 0.5%, 21.8%; p = 0.04) and clinically significant. In addition, although not statistically significant, a 33% relative reduction in the incidence of ventricular arrhythmias (defined as ventricular arrhythmia occurring within 6 hours of ibutilide administration and documented by a rhythm strip or cardiologist note) was observed in the magnesium group. However, the study was not powered to evaluate this endpoint.[10]

Total per patient costs were 10.5% lower in the ibutilide plus magnesium group compared with ibutilide alone; however, this difference was not statistically significant (p = 0.116). This was driven primarily by a 34.6% reduction in the cost of DCC (including fees for DCC, electrocardiographs, anaesthesiologist and cardiologist) in the ibutilide plus magnesium group versus ibutilide alone (p = 0.036). Not surprisingly, the ibutilide plus magnesium group had higher magnesium acquisition costs (p < 0.001).

Costs associated with treatment of adverse events (Torsades de Pointes) were minimal and similar between both groups. In most cases ventricular ar-

**Table II.** Conversion-associated costs ($US, 2002 values) and efficacy of ibutilide plus magnesium compared with ibutilide alone

| | Ibutilide plus magnesium (n = 107) [mean ± SD] | Ibutilide alone (n = 214) [mean ± SD] | p-Value |
|---|---|---|---|
| Drug costs | | | |
| Ibutilide acquisition | $US285 ± 92 | $US280 ± 98 | 0.711 |
| Magnesium acquisition | $US0.50 ± 0.23 | $US0 ± 0 | <0.001 |
| Intravenous admixture | $US1.57 ± 0.51 | $US1.55 ± 0.50 | 0.711 |
| Nursing administration | $US527 ± 171 | $US520 ± 181 | 0.711 |
| Drug cost total | $US814 ± 263 | $US802 ± 279 | 0.711 |
| Direct current cardioversion (DCC) costs | | | |
| DCC | $US76 ± 148 | $US117 ± 170 | 0.036 |
| Electrocardiograph | $US8 ± 15 | $US12 ± 17 | 0.036 |
| Anaesthesiologist fee | $US101 ± 197 | $US155 ± 225 | 0.036 |
| Cardiologist fee | $US76 ± 148 | $US116 ± 169 | 0.036 |
| DCC cost total | $US261 ± 508 | $US399 ± 580 | 0.036 |
| ADR costs | | | |
| Magnesium acquisition | $US0.01 ± 0.04 | $US0.01 ± 0.05 | 1.00 |
| ADR cost total | $US0.01 ± 0.04 | $US0.01 ± 0.05 | 1.00 |
| Incidence of TdP | 2.8% | 4.2% | 0.533 |
| Total costs | $US1075 ± 605 | $US1201 ± 712 | 0.116 |
| Efficacy[a] (95% CI) | 72.0% (62–79%) | 60.3% (53–67%) | 0.040 |

a Data reported as percent of patients who underwent successful chemical conversion from AF.

**ADR** = adverse drug reaction; **AF** = atrial fibrillation; **TdP** = Torsade de Pointes.

rhythmias resolved spontaneously or were treated with intravenous magnesium. No patient in either group required defibrillation or pacing to treat Torsade de Pointes.

The results of the bootstrap analysis are depicted in figure 1. The figure plots the first 1000 resamplings of the ICER comparing ibutilide plus magnesium with ibutilide alone. Of the 25 000 total resamplings, 4.5%, 0.5%, 1.6% and 93.4% fall in regions I, II (inferior), III and IV (dominant), respectively.

When the efficacy of ibutilide plus magnesium and ibutilide alone were increased or lowered by the 95% CIs, ibutilide plus magnesium remained cost effective compared with ibutilide alone. Similarly, the findings were robust when the costs of ibutilide, magnesium, intravenous administration and admixture, DCC, physician fees, electrocardiographs and adverse events were varied by ±50% (table III).

During univariate analysis, age, weight, AF or atrial flutter and magnesium prophylaxis correlated with total costs ($p < 0.2$). However, in the multivariate linear regression model, no baseline factors were found to be independent predictors of total conversion-related costs.

## Discussion

To our knowledge, this is the first economic analysis comparing ibutilide plus magnesium prophylaxis with ibutilide alone for the acute conversion of AF or flutter. Our analysis suggests that magnesium prophylaxis within 2 hours of ibutilide administration is more efficacious and less costly than ibutilide alone in >93% of patients with little chance of inferior results (see figure 1). One-way sensitivity analysis revealed our findings remained robust to changes in cost and effectiveness.

In each of three pharmacoeconomic evaluations, ibutilide was compared with first-line DCC for the treatment of AF. Two of the three evaluations found that ibutilide was cost effective; however, the results were highly sensitive to variations in conversion rate, which ranged from 24% to 65%, and was likely related to the varying length of time the study populations remained in AF (<15 days to >3–4 weeks) prior to the chemical conversion attempt.[3,5,6] De-

creases in conversion rate resulted in the increased need for DCC and the high medical cost associated with the procedure.[10]

Our study had three main strengths which included, the use of data from three sites in different parts of the US, a relatively large study population, and the use of nonparametric bootstrapping. The utilisation of the bootstrap method has been increasing in recent years due to the availability of patient-level data for pharmacoeconomic analysis and the ease to which the results can be interpreted by decision-makers.[12,14] The utilisation of bootstrapping has been recommended in addition to more common statistical analysis approaches and sensitivity analysis.[14] Bootstrapping does not require the investigator to make unrealistic assumptions about the parametric distribution of data.[12-14] Cost data is often widely skewed and associated with large standard deviations.[14] In addition, while sensitivity analysis can be used to test uncertainty associated with the generalisability of results and methodological concerns, it does not adequately test assumptions related to sampling variation.[14]

Limitations of our analysis include that this was a piggyback cost-effectiveness analysis of a retrospective, cohort study. As such, it was not powered to detect significant differences in total costs between the groups. A prospective evaluation of magnesium should be conducted to provide more firm evidence of its efficacy and cost effectiveness when utilised as a strategy for conversion of AF. However, given the generic availability of intravenous magnesium and the extensive study population that would be required, it is unlikely that such a trial would ever be conducted. In situations such as these, modelling studies may be a reasonable alternative.[18] An additional limitation of our study includes the lack of QOL data. It is possible that a decrease in the occurrence of Torsades de Pointes would have a positive impact on quality of life. For future evaluations broadening of the study perspective to include QOL data should be considered. The absence of multivariate sensitivity analysis and the fact that all costs used in this investigation were standardised costs from Hartford Hospital and applied to patients at other institutions, are also limitations. To account for the latter, one-way sensitivity analysis was conducted to examine the potential effects of any significant inter-institutional variations in costs that may be present.[13]

## Conclusion

Our study suggests that ibutilide plus magnesium may be cost effective, from a US hospital-payer perspective, for the acute conversion of patients in AF or flutter, compared with ibutilide alone. During

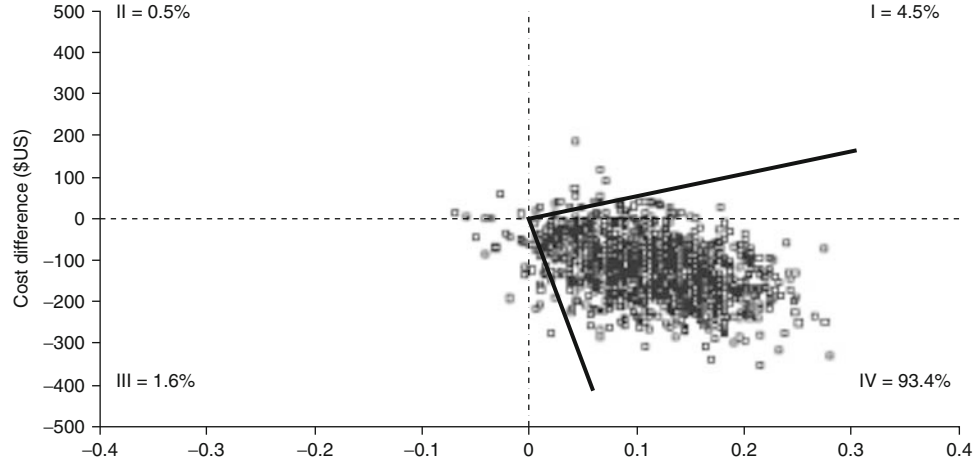


**Fig. 1.** Cost-effectiveness plane depicting the results of the Bootstrap analysis. The figure plots the first 1000 resamplings of the ICER comparing ibutilide plus magnesium with ibutilide alone. The bold lines mark the 95% CI for the ICER.

**Table III.** Results of one-way sensitivity analysis ($US, 2002 values)

| Variable | ACER | |
|---|---|---|
| | ibutilide plus magnesium | ibutilide alone |
| Ibutilide (max) | 1765 | 2223 |
| Ibutilide (min) | 1296 | 1758 |
| Magnesium (max) | 1494 | 1992 |
| Magnesium (min) | 1493 | 1992 |
| ADE (max) | 1493 | 1992 |
| ADE (min) | 1493 | 1992 |
| IV admixture time (max) | 1494 | 1993 |
| IV admixture time (min) | 1493 | 1992 |
| Nursing time (max) | 1860 | 2223 |
| Nursing time (min) | 1128 | 1561 |
| DCC (max) | 1547 | 2088 |
| DCC (min) | 1547 | 1894 |
| EKG (max) | 1296 | 1758 |
| EKG (min) | 1489 | 1892 |
| Anaethesiologist fee (max) | 1564 | 2119 |
| Anaethesiologist fee (min) | 1424 | 1862 |
| Cardiologist (max) | 1546 | 2088 |
| Cardiologist (min) | 1440 | 1896 |
| Efficacy: ibutilide alone (max) | 1493 | 1793 |
| Efficacy: ibutilide alone (min) | 1493 | 2266 |
| Efficacy: magnesium prophylaxis (max) | 1361 | 1991 |
| Efficacy: magnesium prophylaxis (min) | 1734 | 1991 |

**ACER** = average cost-effectiveness ratio; **ADE** = adverse drug event; **DCC** = direct current cardioversion; **EKG** = electrocardiograph; **IV** = intravenous.

one-way sensitivity analysis, the results of our evaluation were found to be robust to changes in both costs and efficacy and are therefore expected to have excellent external validity.

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