Original Article

Efficacy of Intravenous Magnesium in Facilitating Cardioversion of Atrial Fibrillation

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Background—Low serum magnesium (Mg) levels are associated with an increased risk of atrial fibrillation. Some studies have shown a benefit of Mg in facilitating pharmacological cardioversion. The role of an intravenous infusion of Mg alone in facilitating electric cardioversion is not clear.

Methods and Results—In a prospective, randomized, double-blind, placebo-controlled trial, we enrolled patients with atrial fibrillation who were scheduled for electric cardioversion. Patients were randomized to receive Mg or placebo before cardioversion using a step-up protocol with 75, 100, 150, and 200 J biphasic shocks. Patients with hypokalemia, hypermagnesemia, or postcardiac surgery atrial fibrillation were excluded. Patients on antiarrhythmic drugs were included as long as they were at steady state. All patients were monitored for 1 hour post procedure for the maintenance of sinus rhythm. A total of 261 patients (69% male, mean age 65.5±11.1 years) were randomized (132 and 129 patients receiving Mg and placebo, respectively). Baseline characteristics were similar between both the groups. There was no statistically significant difference in the success rate of cardioversion between the 2 groups (86.4% versus 86.0%; P=0.94), cumulative amount of energy required for successful cardioversion (123.3±55.5 versus 129.5±52.6 J; P=0.40), or the number of shocks required to convert to sinus rhythm (2.25±1.24 versus 2.41±1.22, P=0.31). No adverse events were noted in either group.

Conclusions—In patients undergoing electric cardioversion for persistent atrial fibrillation, Mg infusion does not increase the rate of successful cardioversion.

Clinical Trial Information—URL: https://clinicaltrials.gov. Unique identifier: NCT01597557.

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Key Words: atrial fibrillation ■ electric countershock ■ magnesium

Patients with atrial fibrillation (AF) may require electric cardioversion, either because of intolerable symptoms related to AF or as part of a rhythm control strategy.

See Editorial by Kotecha

Electric cardioversion using a biphasic waveform has a procedural success rate of 86% to 94%, sometimes requiring multiple shocks.[1–3] The success of electric cardioversion depends on the duration of AF, transthoracic impedance, delivered energy, and the type of electric shock used.[1] Pharmacological cardioversion using antiarrhythmic drugs (AADs) has a lower success rate and may take a few hours to days to achieve sinus rhythm.

Magnesium (Mg) is an abundant mineral in the body, present in bone, the heart, and the central nervous system. In the heart, Mg modulates potassium (slow-activating delayed rectifier K channel, I_{Ks}) and calcium channels (L-type) in both the atria and the ventricles.[4,5] Mg has been shown to have membrane-stabilizing properties within the atrium.[4] This membrane-stabilizing property may be particularly helpful in rhythm control of AF. Data from the Framingham offspring and Atherosclerosis Risk in Communities (ARIC) prospective cohorts have linked low serum Mg levels to AF.[6,7] Studies on pharmacological cardioversion have shown increased success of cardioversion when Mg is used along with an AAD.[8,9] A recent study on electric cardioversion showed that the infusion of a K–Mg electrolyte solution was successful in facilitating electric cardioversion of AF.[3] On the basis of data suggesting an association of low Mg levels with the incidence of AF and the membrane-stabilizing property of Mg in the atrium with the modulation of I_{K+} and I_{Ca2+} currents, we postulated that administration of Mg alone would be useful in increasing the success of cardioversion. The purpose of this study was to investigate the benefit of intravenous

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WHAT IS KNOWN

- Low serum magnesium levels have been associated with the increased prevalence of atrial fibrillation in prospective cohorts.
- Administration of intravenous magnesium sulfate and potassium chloride together has been reported to increase the success rate of electric cardioversion of atrial fibrillation.
- Administering intravenous magnesium sulfate along with antiarrhythmic agents such as ibutilide and dofetilide increases the success of pharmacological cardioversion in atrial fibrillation.

WHAT THE STUDY ADDS

- Administering intravenous magnesium sulfate alone before electric cardioversion does not increase the rate of successful cardioversion of atrial fibrillation.

Mg infusion on the success of achieving sinus rhythm with electric cardioversion and in decreasing the amount of energy required for cardioversion of AF.

Methods

Study Design

Recruitment

This study was a prospective, randomized, double-blind, placebo-controlled trial to study the effects of intravenous Mg administered before cardioversion. All patients with AF who were >18 years of age and scheduled for elective cardioversion were eligible for participation in the study. Patients on AADs were included as long as they had received at least 5 doses of the AAD (3 weeks in the case of amiodarone) before cardioversion in order for the drug to have achieved steady state. Patients were anticoagulated effectively for at least 3 weeks with warfarin or one of the newer oral anticoagulants before cardioversion or underwent transesophageal echocardiography to rule out a left atrial appendage thrombus. All patients were anticoagulated for at least 4 weeks after cardioversion.

Baseline characteristics including age, sex, body mass index (BMI), time since diagnosis of AF, duration of the current AF episode, medications, history of cardioversion or ablation, comorbid conditions, and echocardiographic data including left ventricular ejection fraction and left atrial size were collected. In most cases, duration of the current AF episode and the time since the diagnosis of AF were based on the patient's history. In some cases, corroborative data in the form of pacemaker interrogations or ECG/Holter monitor recordings were available. On the basis of the duration of the AF episode, we classified AF as paroxysmal (≤7 days) or persistent (>7 days). Blood was drawn for serum K, Mg, creatinine, and thyroid function. Patients with hypokalemia (K <3.5 mg/dL), hypermagnesemia (>3 mg/dL), hyperthyroidism (thyroid stimulating hormone <0.5), or serum creatinine >2 mg/dL were excluded, as were pregnant women and patients with AF postcardiac surgery. Patients who required emergent cardioversion and those who had a recent acute myocardial infarction (<6 weeks) were also excluded. Patients were enrolled at 4 local hospitals within the University at Buffalo system. All patients were enrolled after their written informed consent was obtained. The protocol was approved by the Institutional Review Board at the University at Buffalo. The study was monitored by an independent data and safety monitoring board, which overlooked the conduct of the study and patient safety outcomes. (Clinicaltrials.gov number, NCT01597557).

Randomization, Study Treatment, and Monitoring

All study participants were randomized by the pharmacy at the local sites into the study group or the placebo group in a 1:1 ratio. A computer-generated randomization log was used in a double-blind fashion. Baseline serum creatinine, potassium, and Mg levels before cardioversion were recorded. Patients were then given either 2 g of IV Mg sulfate ($MgSO_4$) or placebo over 30 minutes, no more than 1 hour before cardioversion. Because the study involved a bolus administration of $MgSO_4$, a dose of 2 g was chosen, as it was readily available in most hospitals and was the bolus dose used in many trials.[8,10,11] $MgSO_4$ (Hospira, Inc) 2 g vials were reconstituted with normal saline into a 50-mL infusion, which was administered over 30 minutes through a peripheral intravenous line. A 50 mL infusion of normal saline was used as the placebo. Heart rate, blood pressure, and rhythm were monitored before and after administration of the study drug. Patients were sedated using propofol before the procedure. Propofol was administered intravenously using

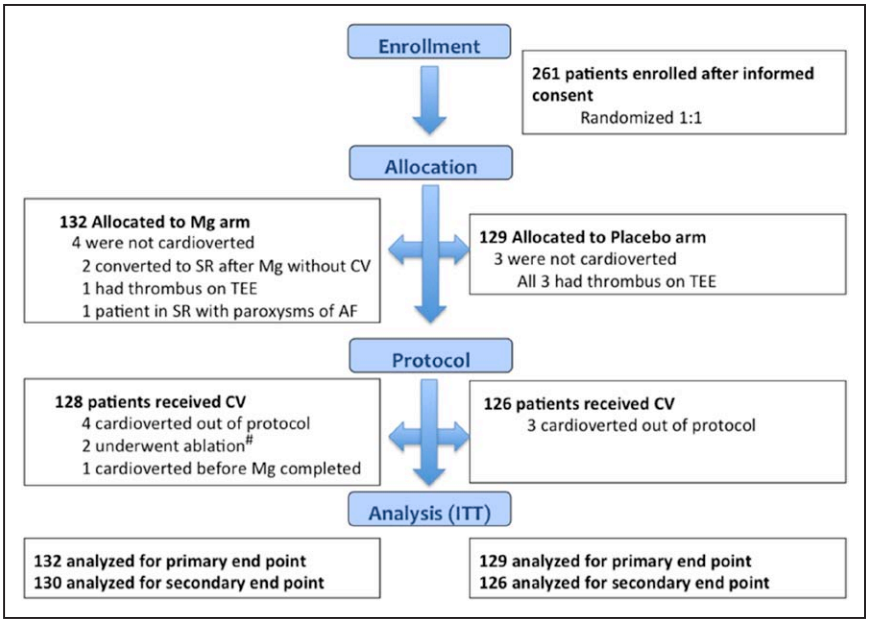

Figure 1. Study enrollment and randomization. CV indicates cardioversion; ITT, intention-to-treat; SR, sinus rhythm; and TEE, transesophageal echocardiogram. #Two patients had atrial fibrillation (AF) with atypical flutter and underwent ablation of both rhythms rather than cardioversion.

bolus doses as needed to achieve deep sedation. Cardioversion was performed using a biphasic defibrillator (Zoll M-Series). Patches were applied in an anterior–posterior position. Cardioversion was performed using a step-up protocol starting with a biphasic shock at 75 J, followed by 100, 150, and then 200 J in an incremental manner if cardioversion was unsuccessful at the lower energy. The protocol was stopped when the patient achieved sinus rhythm. At 200 J, if cardioversion was unsuccessful in restoring sinus rhythm, the patient was considered to have failed cardioversion for study purposes and further management, including more shocks or medications, was based on physician preference. All patients were monitored for 1 hour after cardioversion while in recovery to detect early recurrence of AF. Any early recurrence of AF was considered as a failed cardioversion.

End Points

The primary efficacy end point was successful cardioversion of AF to sinus rhythm lasting at least 1 hour. The secondary end point was the cumulative amount of energy required for successful cardioversion of AF to sinus rhythm that lasted at least 1 hour.

The primary safety end point was the incidence of a severe hypotensive episode defined as a systolic blood pressure of <90 mm Hg with a >20 mm Hg drop after the infusion of the study drug.

Statistical Analysis

We based our sample size analysis on the results of Sultan et al,[3] which showed a 96% cardioversion success rate in patients administered a K/Mg solution before cardioversion compared with an 86% success rate in a control group. Using these parameters in a 1-tailed Fisher's exact test and assuming an α level of 0.05 and a β level of 0.20, we estimated that a total sample size of 224 patients was required. We increased this estimate to 240 (120 patients per group) to account for participant attrition and possible protocol violations. Although we used a 1-tailed test to estimate our sample size, on examination of our data distribution we decided that a 2-tailed test would be more appropriate. Given the same parameters as described above, a 2-tailed test with 120 patients per group would result in 72% power as opposed to 80%. With 261 enrolled patients, the achieved power is 81%. Two-tailed tests were subsequently used for all efficacy and safety analyses.

All patients who were randomized into either treatment arm were considered to be in the intention-to-treat sample (N=261). Seven patients were not cardioverted (Figure 1) including 2 patients who converted to sinus rhythm spontaneously after Mg infusion before any shocks were delivered. Ten patients experienced protocol violations (Figure 1) during the cardioversion procedure. All other patients for whom the protocol was followed were included in a per protocol sample (N=244). All analysis was conducted in both intention-to-treat and per protocol sample.

Descriptive statistics (eg, means, SD, and percentages) were used to summarize the baseline characteristics of the entire sample. T tests and χ^2 analyses were used to determine whether there were any statistical differences between the 2 treatment groups with respect to continuous and categorical baseline characteristics, respectively. α levels were set at 0.05 for the primary and secondary analyses. The Bonferroni correction procedure was used in the subgroup analyses to control for multiple comparisons. χ^2 analyses were used for both the intention-to-treat and per protocol samples to test the primary efficacy end point. Logistic regression was used to test for any significant interactions between treatment and selected subgroups with respect to the rate of successful cardioversion. For the secondary efficacy end point, *t* tests were used to determine whether the amount of energy and the total numbers of shocks required for successful cardioversion were significantly lower for Mg infusion compared with placebo. Only the per protocol sample was included in these secondary end point analyses. All analyses were performed using SPSS version 22.

Results

Study Participants

A total of 261 patients were randomized, of whom 254 patients received cardioversion. Figure 1 shows the enrollment details. Four patients had thrombus on a transesophageal echocardiogram. One had been on dabigatran for only a week, whereas the other three were on warfarin with subtherapeutic international normalized ratios (INRs). Two patients converted to sinus rhythm after Mg infusion.

Baseline characteristics (Table 1) were similar between both the groups. Patients were mostly in persistent AF (85.1%) with a similar duration of AF episode between the groups (111.5±231.7 versus 85.2±114.9 days, *P*=0.25). Time since

Table 1. Baseline Characteristics*

	Magnesium (n=132)	Placebo (n=129)
Age, y	65.4±10.4	65.6±11.9
Sex, % male	67.4	70.5
Race, % white	92.4	96.9
BMI, kg/m^2	31.3±6.8	32.6±7.0
Time since AF diagnosis, y	3.3±5.2	3.4±4.7
Duration of current AF episode, d	111.5±231.7	85.2±114.9
Persistent AF (>7 d)	86.4%	83.7%
Previous cardioversion	50.0%	47.3%
Previous ablation	21.2%	20.9%
Antiarrhythmic drugs	53.0%	48.1%
LA size, cm	4.8±0.7	4.8±0.7
LV ejection fraction, %	52.6±11.5	51.2±11.4
Creatinine, mg/dL	1.05±0.28	1.06±0.30
K, mmol/dL	4.28±0.43	4.31±0.39
Mg, mg/dL	2.05±0.25	2.06±0.22
β-Blockers	71.2%	73.6%
Calcium channel blockers	35.6%	37.2%
ACE inhibitors/ARB	41.7%	47.3%
Digoxin	16.7%	10.9%
Statin	47.0%	45.0%
Spironolactone	3.0%	3.9%
Flecainide	14.4%	11.6%
Propafenone	4.5%	5.4%
Sotalol	11.4%	7.0%
Amiodarone	15.2%	15.5%
Dofetilide	4.5%	7.0%
Dronedarone	3.0%	1.6%
Warfarin	38.6%	38.8%
Dabigatran	25.8%	29.5%
Rivaroxaban	24.2%	23.3%
Apixaban	2.3%	1.6%

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blockers; BMI, body mass index; LA, left atrium; and LV, left ventricle

*There are no significant differences between the groups in any of the characteristics.

diagnosis of AF was also similar in the 2 groups (3.3±5.2 versus 3.4±4.7 years, *P*=0.83). Both groups had the same mean left atrial size (4.8±0.7 cm, *P*=0.60) and had a similar mean BMI (31.3±6.8 versus 32.6±7.0 kg/m^2, *P*=0.13). Nearly half the patients were on AADs and had a previous cardioversion. The most common AADs used were amiodarone and flecainide.

Outcomes

The primary outcome of achieving sinus rhythm occurred in 114 patients in the Mg group compared with 111 patients in the placebo group (86.4% versus 86.0%, *P*=0.94) in the intention-to-treat analysis. The results were similar in the per protocol analysis (86.8% versus 88.6%, *P*=0.66). In the intention-to-treat analysis, there was no statistically significant difference between the groups in the mean amount of energy required for successful cardioversion (123.3±55.5 J in the Mg group versus 129.5±52.6 J in the placebo group, *P*=0.40) or the mean number of shocks required for successful cardioversion (2.25±1.24 in the Mg group versus 2.41±1.22 in the placebo group, *P*=0.31). No statistically significant difference was observed in the mean amount of energy or total number of shocks in the per protocol analysis also. Figure 2 shows the success rate of cardioversion at various energy levels in both the groups. Interestingly, 2 patients in the Mg group spontaneously converted to sinus rhythm without cardioversion after Mg infusion. One patient in the Mg group reverted back to AF within 30 minutes of cardioversion and was considered as a treatment failure for study purposes. No adverse effects were noted in either group, including no significant hypotension in any patient. There was no significant change in blood pressure or heart rate after study drug administration in either the Mg or placebo groups (Table 2).

Subgroup analysis as shown in Figure 3 did not reveal any statistically significant differences in outcomes between the groups, including patients on or off AADs. The results should be interpreted with caution because some of the subgroups were relatively small in size.

Discussion

In this study, Mg was not found to be superior to placebo in facilitating cardioversion of AF. It also did not show any benefit in reducing the energy required for cardioversion. Electric cardioversion is a commonly used procedure for rhythm control of AF, and under the best circumstances, it is 86% to 94% successful in converting AF to sinus rhythm.[1–3] When cardioversion is unsuccessful, a variety of approaches have been used to facilitate cardioversion. Use of biphasic waveforms over monophasic shocks has increased the success of cardioversion at comparatively lower energy levels.[1,2] Some studies have shown that a change in patch location, especially to an anterior-posterior position, helps to increase the success of cardioversion.[12,13] Pharmacological facilitation of cardioversion using ibutilide has been shown to improve the success of cardioversion.[14] However, there is still a proportion of patients who remain in AF despite our best efforts at cardioversion, and so alternative approaches are desirable.

Mg has many direct effects in the heart. It acts as a cofactor for the Na–K ATPase pump in the myocardium[15] and has membrane-stabilizing properties in both the atria and the ventricles.[4,16,17] Mg decreases I_{K+} and I_{Ca2+}, thereby modulating the membrane action potential and stabilizing cardiac muscle contraction.[16,18] Inhibition of L-type calcium (Ca) channels prevents Ca overload and cell toxicity. Mg acts as a physiological antagonist of calcium within the cardiac myocyte by interfering with its binding with calmodulin and troponin C. It also affects the Na^+–Ca^{2+} exchanger and SERCA (sarcoendoplasmic reticulum calcium ATPase) activity, thereby decreasing Ca availability.[19] Mg increases sinus node recovery time, atrioventricular node conduction time, and the atrioventricular node refractory period, and thereby may decrease the ventricular rate during atrial arrhythmias.[20,21] The electrophysiological properties of Mg combined with its excellent safety profile would seem to make Mg a good target for use in facilitating electric cardioversion.

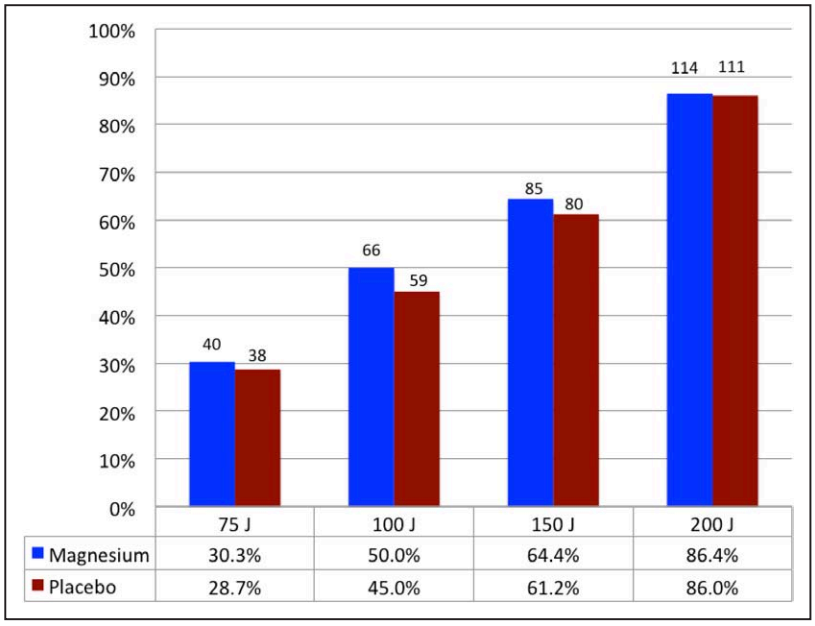

Figure 2. Cardioversion success at 1 h using various energy levels.

Table 2. Blood Pressure and Heart Rate at Baseline and at the End of the Study Drug Administration

	Systolic BP Before, mm Hg	Systolic BP After, mm Hg	Diastolic BP Before, mm Hg	Diastolic BP After, mm Hg	Heart Rate Before, beat per minute	Heart Rate After, beat per minute
Magnesium	131.3±18.7	132.4±19.0	80.5±14.0	79.8±13.6	87.7±18.4	84.7±20.3
Placebo	128.4±17.0	129.3±16.8	78.1±13.6	79.9±13.1	91.8±18.7	87.9±20.8

BP indicates blood pressure.

Previous studies have shown a benefit of Mg in patients with AF by increasing the success of pharmacological cardioversion and by decreasing the incidence of postoperative AF.[8,9,22,23] Facilitation of cardioversion by Mg has been studied more commonly in pharmacological cardioversion, in which Mg also has the benefit of decreasing adverse events, such as torsades de pointes.[8,9] However, there is a paucity of data on the role of Mg alone in facilitating electric cardioversion.

A study conducted by Sultan et al[3] on the role of a K–Mg electrolyte solution at much smaller doses of Mg showed a 12% increase in the success of cardioversion of AF.[3] There are a few important differences between their study and ours. Our study included patients mostly with persistent AF with a mean duration of the episodes being 3 to 4 months compared with 90 hours in their study. Nearly 50% of our patients were on AADs compared with <20% in their study. The doses of magnesium used were different (196 mg of elemental Mg in our study versus 34.1 mg in the study by Sultan et al[3]). We did not use K in our study, while they gave 2.774 mEq of K, a very small dose compared with a commonly used clinical dose of 40 mEq. The mean serum K in their study was around 3.6±0.6 mmol/dL versus 4.3±0.4 mmol/dL in our study. It is unclear whether K supplementation is beneficial in normokalemic patients, and in any event, it is highly unlikely that such a small dose could have had an impact on the success rate of cardioversion.

For the most part, our patients had persistent AF, mean BMI in the obese range, multiple earlier failed AADs, moderate LA dilatation, and previous cardioversion, all of which may have decreased the success of cardioversion in general. With 50% of our patients on AADs, there may have been difficulty showing an incremental benefit with Mg infusion.

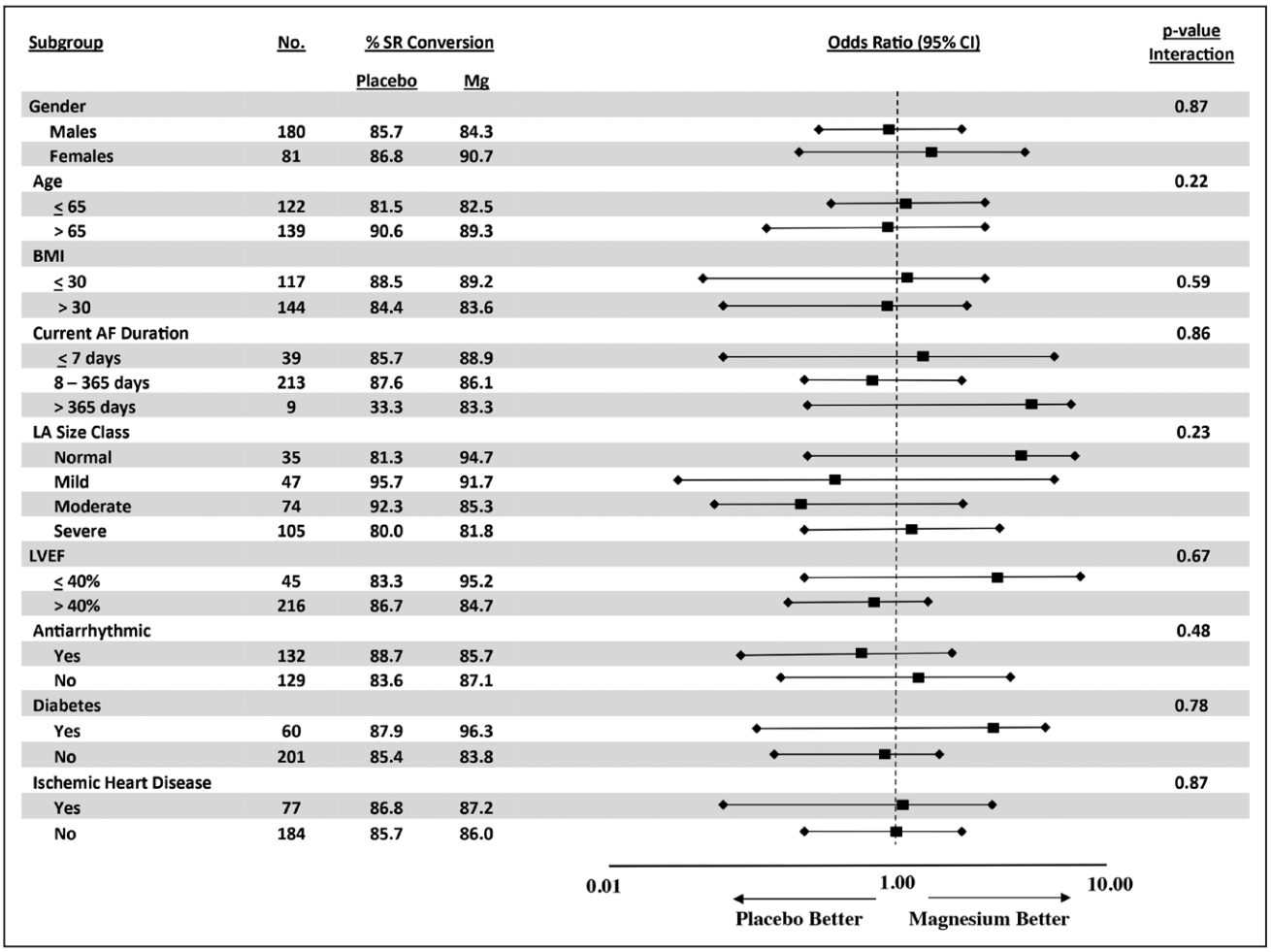

Figure 3. Forest plot showing the primary efficacy end point among subgroups. AF indicates atrial fibrillation; BMI, body mass index; LA, left atrial; LVEF, left ventricular ejection fraction; and SR, sinus rhythm.

We conclude that there is no benefit in routinely administering an intravenous infusion of Mg preprocedure to facilitate cardioversion of AF.

Limitations

Our study had very few patients in paroxysmal AF and hence the benefit of Mg in facilitating cardioversion in this population is not known. A majority of the study population had failed earlier rhythm control strategies, thereby making them a potentially resistant group in which it would be more difficult to show any incremental benefit from Mg infusion. Our study was not adequately powered to see whether Mg infusion benefits patients who have not attempted any previous rhythm control strategies. We are not able to comment on any potential interaction of Mg infusion with individual AADs in facilitating electric cardioversion, as this was beyond the scope of this study. Only one dose of Mg infusion was tested, although the dose we tested was substantially higher than in a previous study that showed an apparent benefit with a K–Mg electrolyte infusion.[3] Our study monitored patients for only 1 hour post cardioversion. It is unclear whether the success rate of cardioversion with Mg during a longer follow-up period would be any different.

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Disclosures

Dr Kim is in advisory board of Medtronic, Inc and Boston Scientific. He received honoraria from St. Jude Medical. Dr Switzer is in advisory board of Medtronic, Inc. Dr Curtis is a consultant of Medtronic, Inc and received honoraria from the same. She is in the advisory board of St. Jude Medical and Daiichi Sankyo and received honoraria from St. Jude Medical.

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