Low magnesium levels have been implicated as a risk factor for the development of atrial fibrillation (AF). However, like many interventions before it, supplementing magnesium levels does not necessarily lead to a successful cardioversion or better prevention of AF in high-risk groups. This issue is clinically important in view of the high burden that AF poses, the increasing incidence of AF, and the association of AF with adverse long-term clinical outcomes. AF is not only prevalent in the general population (≈3%, with much higher rates in older patients) but also a frequent comorbidity and risk factor in patients with a range of cardiovascular conditions, including heart failure and after cardiac surgery. Identifying practical and effective methods for managing AF is a clinical imperative.

The attention on magnesium as a potential antiarrhythmic agent is founded on a small number of physiological assessments in human and animal models. Intravenous magnesium directly affects myocardial potassium channels, has voltage-dependent and indirect effects on calcium and sodium channels, prolongs the PR interval, and increases the refractory period of antegrade atrioventricular node conduction. However, although low serum magnesium levels were associated with incident AF in the ARIC study (Atherosclerosis Risk in Communities), dietary levels were not, suggesting a causal disconnect. This was demonstrated in another large community cohort where the association of hypomagnesemia with incident AF was identified in long-term follow-up, but not present within the first 90 days.

In this issue of Circulation: Arrhythmia and Electrophysiology, Rajagopalan et al add to the growing evidence-base on this issue by performing a randomized, double-blind, placebo-controlled trial of intravenous magnesium before electric cardioversion of AF. A total of 261 patients were enrolled with normal magnesium levels at baseline (2.1±0.2 mg/dL; 0.86±0.08 mmol/L). Their key finding was that 1-hour conversion to sinus rhythm was similar in both the magnesium-treated patients and the placebo group (86.4% magnesium versus 86.0% placebo). They also found no difference in biphasic energy requirement or the number of shocks needed in a ramping energy protocol.

Where does this fit in with other studies? The Figure displays trials and meta-analyses that have randomized patients to magnesium in a range of situations, including treatment of acute AF, prevention of AF during cardiac surgery, and facilitation of electric cardioversion. Although varying with respect to population and magnesium dosage, they share common features of a small sample size, short follow-up, and disappointing treatment effect.

It is likely that patient selection is a major issue—AF is not just a single condition, but the end point of numerous pathologies. Future trials, in this and other areas, should target patients better to optimize the likelihood of demonstrating treatment effects. Another key problem is the length of follow-up. The possibility of a longer-term benefit of magnesium supplementation is unknown from the current literature.

Sample size is also important. Demonstrating the effect of a treatment is challenging when immediate success rates are so high. This study, and others, may actually be underpowered when considering the heterogeneity of patients included, particularly with respect to antiarrhythmic drug use. Nonetheless these data, in addition to other studies discussed, would suggest that magnesium is not a useful clinical therapy to improve the success rates of electric cardioversion. Although there are data to support the use of magnesium for facilitating pharmacological cardioversion, this is largely based on retrospective analyses in patients receiving ibutilide or dofetilide as antiarrhythmic drug therapy.

Magnesium has also been noted as a potential drug for complementing a rate control approach. In meta-analysis of 5 randomized trials (n=380), patients receiving magnesium were 3× as likely to reach a heart rate <100 beats per minute compared with placebo, mostly with digoxin as background therapy. In 199 patients receiving rate control for rapid AF (again mostly with digoxin), those randomized to intravenous supplemental magnesium were more likely to reach a rate of <100 beats per minute at 2 hours (relative risk, 1.89; 95% confidence interval, 1.38–2.59). Although these results are encouraging, magnesium has not been widely adopted as a rate control strategy, as more effective agents are available for acute ventricular rate control, such as β-blockers, verapamil, and diltiazem.2

The authors of this study are congratulated on recognizing the importance of study design and choosing to use
### Effect of magnesium on success of cardioversion or prevention of AF

<table>
<thead>
<tr>
<th>Study/meta-analysis</th>
<th>Events/N (magnesium)</th>
<th>Events/N (control)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho 2007</td>
<td>42/166</td>
<td>31/161</td>
<td>1.31 (0.87-1.98)</td>
</tr>
<tr>
<td>Chu 2009</td>
<td>2/24</td>
<td>6/24</td>
<td>0.33 (0.07-1.49)</td>
</tr>
<tr>
<td>Cook 2012</td>
<td>456/595</td>
<td>457/595</td>
<td>1.00 (0.94-1.06)</td>
</tr>
<tr>
<td>Sultan 2012</td>
<td>81/84</td>
<td>74/86</td>
<td>1.12 (1.02-1.23)</td>
</tr>
<tr>
<td>Klinger 2015</td>
<td>107/186</td>
<td>110/177</td>
<td>0.93 (0.78-1.10)</td>
</tr>
<tr>
<td>Rajagopalan 2016</td>
<td>114/132</td>
<td>111/129</td>
<td>1.00 (0.91-1.11)</td>
</tr>
</tbody>
</table>

**Figure.** Selected studies and meta-analyses of randomized controlled trials (RCTs) of magnesium (Mg) for facilitating cardioversion or preventing atrial fibrillation (AF). An event is a successful cardioversion to sinus rhythm or the absence of AF on follow-up. CI indicates confidence interval; and N, total number of patients.

Magnesium has shown potential benefits in observational studies and has an inherent physiological association because of its effects on membrane potentials and ion transport. This exemplifies the problems in assigning causality and disentangling the issue of confounding in observational studies, which we recently highlighted for digoxin use in AF. Although observational data are useful for determining epidemiological patterns, any decision on treatment effects should be restricted to randomized controlled trials, where selection and performance biases can be addressed.

More trials of magnesium are in process. Completed but yet to report is a 300-patient study in Tunisia randomizing to high- or low-dose magnesium infusion, to assess effects on rate and rhythm control in emergency department patients with rapid AF. Currently recruiting is a double-blind, placebo-controlled trial in Thailand of 128 patients to assess sinus rhythm conversion and rate control >6 hours (NCT01049464), and a Norwegian single-blind trial of 218 patients with paroxysmal AF or flutter, with outcomes of cardioversion success at 24 hours and also 3-month AF follow-up (NCT01818583).

Further trial data may shed light on whether there is any role for magnesium in improving the management of patients with AF. However at present, the available data would suggest that magnesium, as an adjunct to electric cardioversion or for prevention, is more myth than a practical, easy (or magical) solution to the growing problem of AF.

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**References**


Key Words: Editorials ◼ atrial fibrillation ◼ cardioversion ◼ magnesium ◼ prevention & control
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