Magnesium for Atrial Fibrillation: Myth or Magic?

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DOI:
10.1161/CIRCEP.116.004521

Document Version
Peer reviewed version

Citation for published version (Harvard):
Kotecha, D 2016, 'Magnesium for Atrial Fibrillation: Myth or Magic?', *Circulation Arrhythmia and Electrophysiology*, vol. 9, no. 9. https://doi.org/10.1161/CIRCEP.116.004521

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Running title: Magnesium for Atrial Fibrillation: Myth or Magic?

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Journal subject terms

Arrhythmia and Electrophysiology: Atrial Fibrillation

Quality and Outcomes: Health Services

Word count: 927

Key words: Atrial fibrillation; Magnesium, Cardioversion; Prevention

Low magnesium levels have been implicated as a risk factor for the development of atrial fibrillation.[1] 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.[2] Not only is AF prevalent in the general population (approximately 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.[3, 4] Identifying practical and effective methods for managing AF is a clinical imperative.

The attention on magnesium as a potential anti-arrhythmic agent is founded on a small number of physiological assessments in human and animal models.[5] 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.[6, 7] However, although low serum magnesium levels were associated with incident AF in the Atherosclerosis Risk in Communities (ARIC) study, dietary levels were not [8], 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.[9]

In this issue of *Circulation: Arrhythmia and Electrophysiology*, Rajagopalan and colleagues add to the growing evidence-base on this issue by performing a randomized, double-blind, placebo-controlled trial of intravenous magnesium prior to electrical cardioversion of AF.[10] 261 patients were enrolled with normal magnesium levels at baseline (2.1 ± 0.2 mg/dL).

Their key finding was that one-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? Figure 1 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 electrical cardioversion.[10-14] 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 endpoint of numerous pathologies.[15] Future trials, in this and other areas, should target patients better in order 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 anti-arrhythmic drug use. Nonetheless this data, in addition to other studies discussed, would suggest that magnesium is not a useful clinical therapy to improve the success rates of electrical 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.[16-18]

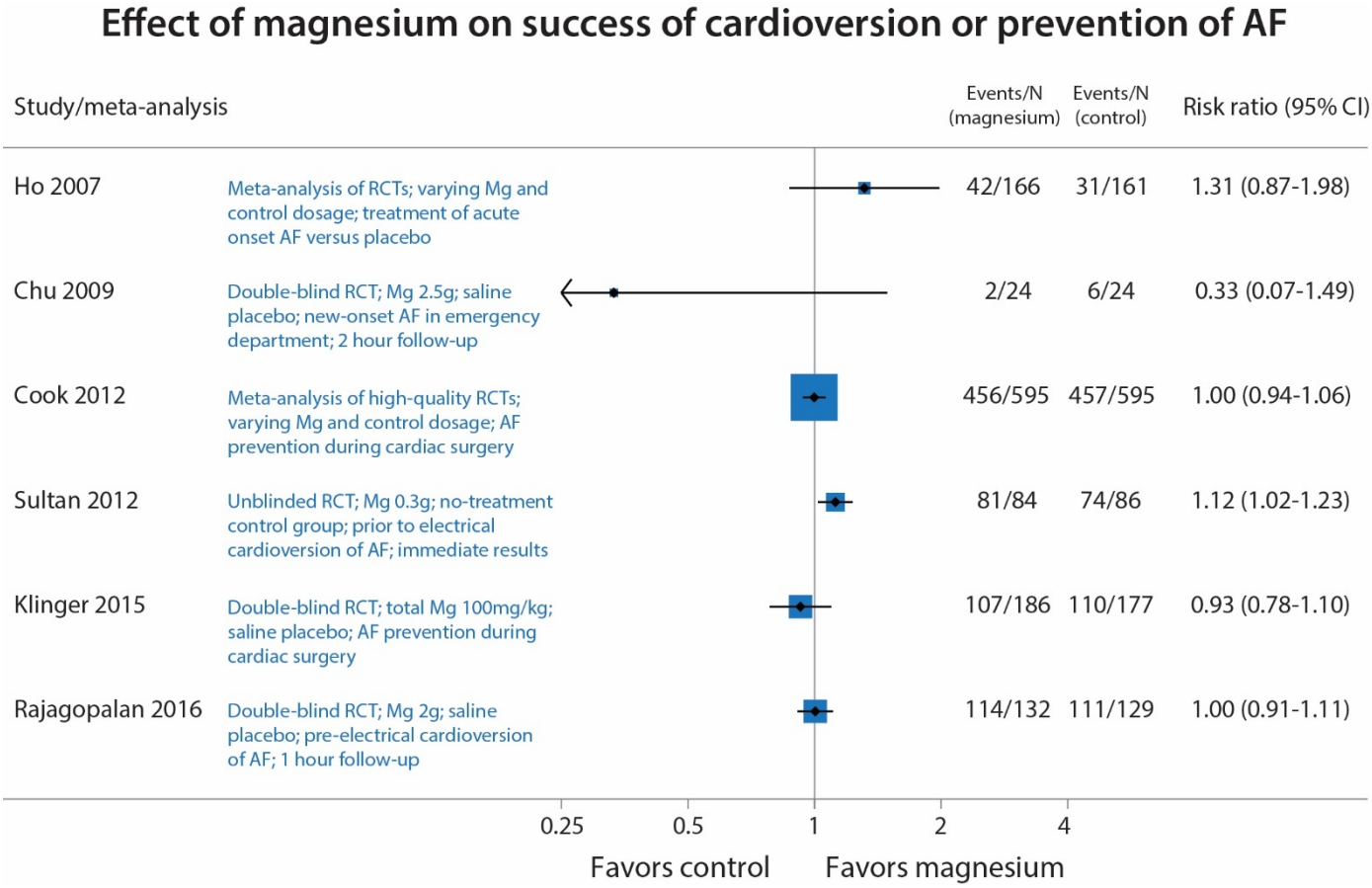
Magnesium has also been noted as a potential drug for complementing a rate control

approach. In meta-analysis of five randomized trials (n=380), patients receiving magnesium were three times as likely to reach a heart rate <100 beats/minute compared to placebo, mostly with digoxin as background therapy.[13] 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/minute at two hours (relative risk 1.89; 95% CI 1.38-2.59).[19] While 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 beta-blockers, verapamil and diltiazem.[2]

The authors of this study are congratulated on recognizing the importance of study design and choosing to employ a randomized and blinded approach. Magnesium has shown potential benefits in observational studies, and has an inherent physiological association due to 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.[20] Although observational data are useful for determining epidemiological patterns, 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 (NCT00965874). Currently recruiting is a double-blind placebo-controlled trial in Thailand of 128 patients to assess sinus rhythm conversion and rate control over 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 AF patients. However at present, the available data would suggest that magnesium, as an adjunct to electrical cardioversion or for prevention, is more myth than a practical, easy (or magical) solution to the growing problem of AF.

Figure 1



Legend: Selected studies and meta-analyses of randomized controlled trials of magnesium for facilitating cardioversion or preventing AF.[10-14] An 'event' is a successful cardioversion to sinus rhythm, or the absence of AF on follow-up. AF = atrial fibrillation; CI = confidence interval; Mg = magnesium; N = total number of patients; RCT = randomized controlled trial.

Conflict of Interest Disclosures

DK has received research grants from Menarini, speaker fees from Atricure and professional development support from Daiitchi Sankyo.

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