Editorial

Magnesium for Atrial Fibrillation, Myth or Magic?

Dipak Kotecha, MD, PhD, FESC, FHEA

Low magnesium levels have been implicated as a risk factor for the development of atrial fibrillation (AF).[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] 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.[3,4] Identifying practical and effective methods for managing AF is a clinical imperative.

See Article by Rajagopalan et al

The attention on magnesium as a potential antiarrhythmic 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 ARIC study (Atherosclerosis Risk in Communities), 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 et al[10] 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.[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 end point of numerous pathologies.[15] 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.[16–18]

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.[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 per minute at 2 hours (relative risk, 1.89; 95% confidence interval, 1.38–2.59).[19] 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

From the Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom & Monash Centre of Cardiovascular Research and Education in Therapeutics, Monash University, Melbourne, Australia.

Correspondence to Dipak Kotecha, MD, PhD, FESC, FHEA, University of Birmingham, Institute of Cardiovascular Sciences, The Medical School, Vincent Dr, Birmingham, B15 2TT, United Kingdom. E-mail d.kotecha@bham.ac.uk

(*Circ Arrhythm Electrophysiol*. 2016;9:e004521. DOI: 10.1161/CIRCEP.116.004521.)

***Circ Arrhythm Electrophysiol* is available at http://circep.ahajournals.org**

DOI: 10.1161/CIRCEP.116.004521

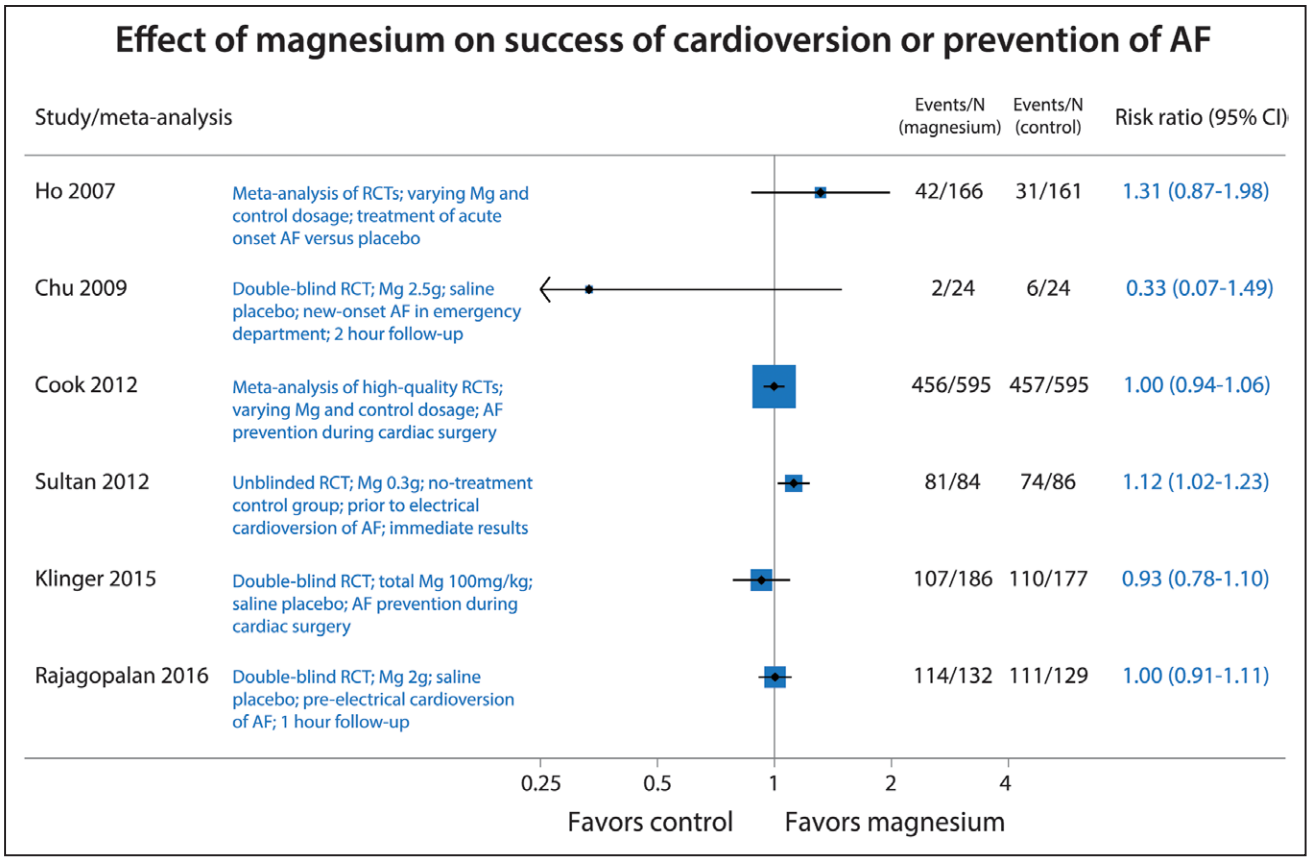

Figure. Selected studies and meta-analyses of randomized controlled trials (RCTs) of magnesium (Mg) for facilitating cardioversion or preventing atrial fibrillation (AF).[10–14] An event is a successful cardioversion to sinus rhythm or the absence of AF on follow-up. CI indicates confidence interval; and N, total number of patients.

a randomized and blinded approach. 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.[20] 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.

Disclosures

Dr Kotecha has received research grants from Menarini, speaker fees from Atricure and professional development support from Daiichi Sankyo.

References

1. Khan AM, Lubitz SA, Sullivan LM, Sun JX, Levy D, Vasan RS, Magnani JW, Ellinor PT, Benjamin EJ, Wang TJ. Low serum magnesium and the development of atrial fibrillation in the community: the Framingham Heart Study. *Circulation*. 2013;127:33–38. doi: 10.1161/CIRCULATIONAHA.111.082511.
2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella Pericas M, Diener H, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Endorsed by the European Stroke Organisation (ESO). *Eur Heart J*. 2016. doi: 10.1093/eurheartj/ehw210.
3. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? *Eur Heart J*. 2015;36:3250–3257. doi: 10.1093/eurheartj/ehv513.
4. Steinberg BA, Zhao Y, He X, Hernandez AF, Fullerton DA, Thomas KL, Mills R, Klaskala W, Peterson ED, Piccini JP. Management of postoperative atrial fibrillation and subsequent outcomes in contemporary patients undergoing cardiac surgery: insights from the Society of Thoracic Surgeons CAPS-Care Atrial Fibrillation Registry. *Clin Cardiol*. 2014;37:7–13.
5. Delva P. Magnesium and cardiac arrhythmias. *Mol Aspects Med*. 2003;24:53–62.

6. Bara M, Guiet-Bara A, Durlach J. Regulation of sodium and potassium pathways by magnesium in cell membranes. *Magnes Res*. 1993;6:167–177.
7. Kulick DL, Hong R, Ryzen E, Rude RK, Rubin JN, Elkayam U, Rahimtoola SH, Bhandari AK. Electrophysiologic effects of intravenous magnesium in patients with normal conduction systems and no clinical evidence of significant cardiac disease. *Am Heart J*. 1988;115:367–373.
8. Misialek JR, Lopez FL, Lutsey PL, Huxley RR, Peacock JM, Chen LY, Soliman EZ, Agarwal SK, Alonso A. Serum and dietary magnesium and incidence of atrial fibrillation in whites and in African Americans–Atherosclerosis Risk in Communities (ARIC) study. *Circ J*. 2013;77:323–329.
9. Markovits N, Kurnik D, Halkin H, Margalit R, Bialik M, Lomnicky Y, Loebstein R. Database evaluation of the association between serum magnesium levels and the risk of atrial fibrillation in the community. *Int J Cardiol*. 2016;205:142–146. doi: 10.1016/j.ijcard.2015.12.014.
10. Rajagopalan B, Shah Z, Narasimha D, Bhatia A, Kim CH, Switzer DF, Gudleski GH, Curtis AB. Efficacy of intravenous magnesium in facilitating cardioversion of atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2016;9:e003968. doi: 10.1161/CIRCEP.116.003968.
11. Chu K, Evans R, Emerson G, Greenslade J, Brown A. Magnesium sulfate versus placebo for paroxysmal atrial fibrillation: a randomized clinical trial. *Acad Emerg Med*. 2009;16:295–300. doi: 10.1111/j.1553-2712.2009.00360.x.
12. Cook RC, Yamashita MH, Kearns M, Ramanathan K, Gin K, Humphries KH. Prophylactic magnesium does not prevent atrial fibrillation after cardiac surgery: a meta-analysis. *Ann Thorac Surg*. 2013;95:533–541. doi: 10.1016/j.athoracsur.2012.09.008.
13. Ho KM, Sheridan DJ, Paterson T. Use of intravenous magnesium to treat acute onset atrial fibrillation: a meta-analysis. *Heart*. 2007;93:1433–1440. doi: 10.1136/hrt.2006.111492.
14. Sultan A, Steven D, Rostock T, Hoffmann B, Müllerleile K, Servatius H, Drewitz I, Lüker J, Meyer P, Salukhe T, Willems S. Intravenous administration of magnesium and potassium solution lowers energy levels and increases success rates electrically cardioverting atrial fibrillation. *J Cardiovasc Electrophysiol*. 2012;23:54–59. doi: 10.1111/j.1540-8167.2011.02146.x.
15. Fabritz L, Guasch E, Antoniades C, Bardinet I, Benninger G, Betts TR, Brand E, Breithardt G, Bucklar-Suchankova G, Camm AJ, Cartlidge D, Casadei B, Chua WW, Crijns HJ, Deeks J, Hatem S, Hidden-Lucet F, Kääb S, Maniadakis N, Martin S, Mont L, Reinecke H, Sinner MF, Schotten U, Southwood T, Stoll M, Vardas P, Wakili R, West A, Ziegler A, Kirchhof P. Expert consensus document: Defining the major health modifiers causing atrial fibrillation: a roadmap to underpin personalized prevention and treatment. *Nat Rev Cardiol*. 2016;13:230–237. doi: 10.1038/nrcardio.2015.194.
16. Coleman CI, Sood N, Chawla D, Talati R, Ghatak A, Kluger J; Dofetilide and Intravenous Magnesium Evaluation (DIME) Investigators. Intravenous magnesium sulfate enhances the ability of dofetilide to successfully cardiovert atrial fibrillation or flutter: results of the Dofetilide and Intravenous Magnesium Evaluation. *Europace*. 2009;11:892–895. doi: 10.1093/europace/eup084.
17. Kalus JS, Spencer AP, Tsikouris JP, Chung JO, Kenyon KW, Ziska M, Kluger J, White CM. Impact of prophylactic i.v. magnesium on the efficacy of ibutilide for conversion of atrial fibrillation or flutter. *Am J Health Syst Pharm*. 2003;60:2308–2312.
18. Tercius AJ, Kluger J, Coleman CI, White CM. Intravenous magnesium sulfate enhances the ability of intravenous ibutilide to successfully convert atrial fibrillation or flutter. *Pacing Clin Electrophysiol*. 2007;30:1331–1335. doi: 10.1111/j.1540-8159.2007.00866.x.
19. Davey MJ, Teubner D. A randomized controlled trial of magnesium sulfate, in addition to usual care, for rate control in atrial fibrillation. *Ann Emerg Med*. 2005;45:347–353. doi: 10.1016/j.annemergmed.2004.09.013.
20. Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GY, Steeds RP, Townend J, Kotecha D. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. *BMJ*. 2015;351:h4451.

KEY WORDS: Editorials ■ atrial fibrillation ■ cardioversion ■ magnesium ■ prevention & control