

Meta-Analysis of Magnesium Therapy for the Acute Management of Rapid Atrial Fibrillation

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The profile of electrophysiologic effects of magnesium on the heart suggests that magnesium might be effective in the treatment of atrial fibrillation (AF) in terms of rhythm and rate control. We aimed to investigate the efficacy of magnesium administration in the acute treatment of rapid AF. Randomized controlled trials comparing intravenous magnesium versus placebo or antiarrhythmic agents for the acute management of rapid AF were included. Nine electronic databases were searched for relevant trials from the earliest possible dates through June 2005, as were abstract books from 8 cardiovascular meetings held in the past 10 years. We analyzed all outcomes using a fixed-effect model because of the low number of trials in each comparison. The results were expressed as relative risks (RRs) or odds ratios (ORs) for dichotomous outcomes and weighted mean differences for continuous outcomes, along with their 95% confidence intervals (CIs). Data were pooled for 4 trials (n = 303) and 8 trials (n = 476), respectively, for rate control (<100 beats/min) and rhythm control. Magnesium was effective in achieving rate control (OR 1.96, 95% CI 1.24 to 3.08) or rhythm control (OR, 1.60, 95% CI 1.07 to 2.39). An overall response was achieved in 86% and 56% of patients in the magnesium and control groups, respectively (OR 4.61 95% CI 2.67 to 7.96). Time to response (in hours) was significantly shorter in the magnesium group (weighted mean difference, -6.98; 95% CI -9.27 to -4.68). The risk of having a major adverse effect in the magnesium group was similar to that in the placebo group (RR 0.85, 95% CI 0.44 to 1.61). In conclusion, the present meta-analysis of published data suggests that intravenous magnesium administration is an effective and safe strategy for the acute management of rapid AF. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99:1726-1732)

Major cardiac effects of magnesium are prolongation of atrial¹⁻⁴ and atrioventricular nodal^{1,4-6} refractory periods, which may facilitate rate and rhythm control in atrial fibrillation (AF). In addition, hypomagnesemia is relatively common in patients presenting with AF, which could be detected in 20% to 53% of cases.⁷⁻⁹ Hypomagnesemia and AF are common after cardiac surgery,¹⁰ and prophylactic magnesium use has resulted in a significant reduction in the incidence of postoperative AF.¹¹ Numerous clinical trials were performed to evaluate efficacy of magnesium for the treatment of AF. Most of these trials were small and underpowered. We therefore conducted a systematic review and meta-analysis of randomized clinical trials (RCTs) on the effectiveness of magnesium therapy for the acute management of rapid AF.

Methods

We included studies that (1) included adult patients presenting with non-postoperative AF; (2) included patients with

chronic or paroxysmal AF with rapid ventricular rate; (2) were RCTs of a parallel or crossover design; (3) included intervention that consisted of intravenous magnesium compared with routine care or placebo or antiarrhythmic drugs; and (4) adequately reported data on ventricular rate or rhythm control. Double-blind and nonblinded studies were included. In crossover trials, only the first phase of the study was considered for meta-analysis.

The search strategy was carried out according to recommendations of the Cochrane Collaboration, with the following electronic databases from the earliest possible dates through June 2005: (1) Medline; (2) "old" Medline; (3) EMBASE; (4) CENTRAL; (6) Web of Science; (7) ISI Proceedings; (8) Biosis Previews; (9) CINAHL; and (10) HealthSTAR. No language, date, RCT filter, or other restrictions were applied. The following strategy was used to search MEDLINE and adapted appropriately for other databases. The capitalized terms are controlled terms: (1) "ATRIAL FIBRILLATION"; (2) "ATRIAL FLUTTER"; (3) "TACHYCARDIA, SUPRAVENTRICULAR"; (4) "(atrial or atrium or auricul\$) adj6 (fibrillat\$ or flutter\$)"; (5) "(atrial or atrium or auricul\$) adj6 (arrhythmi\$ or tachycardi\$ or tachyarrhythmi\$)"; (6) or/1-5; (7) "MAGNESIUM"; (8) "MAGNESIUM COMPOUNDS"; (9) "magnesi\$"; (10) or/7-9; and (11) 6 and 10.

Abstracts from the American Heart Association, American College of Cardiology, European Society of Cardiol-

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Table 1
Sifting steps for determination of relevant randomized controlled trials

Step	No. of studies
First step of sifting	
Initial number of articles	1,113
Duplicated articles	552
Nonrelevant articles: editorials, letters, replies, reviews, meta-analyses, experimental studies, articles about cardiac or noncardiac surgeries and other types arrhythmias etc.	525
Second step of sifting	
Initial number of articles	36
Non randomized prospective studies	5
Noncomparative	6
Retrospective studies	4
Case series	3
Review	1
Abstracts of full-text articles	3
Third step of sifting	
Initial no. of articles	14
Oral magnesium	1
Chronic AF patients with normal ventricular rate	1
Glucose-insulin-potassium-magnesium solution used	1
In SVT patients, no data on AF patients	1
Various arrhythmias (only 1 AF case)	1
RCTs considered for review (n=9)	
Magnesium vs placebo	4
Magnesium vs verapamil	2
Magnesium vs diltiazem	1
Magnesium vs amiodarone	1
Magnesium vs ajmaline	1

SVT = supraventricular arrhythmia.

ogy, Hearth Rhythm Society (formerly North American Society of Pacing and Electrophysiology), Europace, Cardiotim, World Congress on Cardiac Pacing and Electrophysiology, and Asian-Pacific Symposium on Cardiac Pacing and Electrophysiology meetings held in the past 10 years were hand-searched or electronically searched for relevant studies. Additional publications were examined with the reference lists of identified articles and published reviews about acute management of AF.

The selection of studies was assessed independently by 3 assessors (OO, AD, AC); disagreement was resolved by discussion and, when necessary, in consultation with a third person (EC, IL, CL). The quality of each included trial was assessed by 2 reviewers (OO, AD) using the standard Jadad score based on the adequacy of randomization, blinding, and withdrawals, with a maximum score of 5 points.¹²

Primary outcomes were success in achieving rate control, rhythm control, and rate or rhythm control (i.e., overall response) when available. Secondary outcomes were time to response in hours and the risk of having a major adverse effect. We defined adverse effects as major if they required an additional intervention, treatment discontinuation, or withdrawal from study; caused death; or were considered significant in the article or by reviewers.

Data were pooled and analyzed using the Cochrane Collaboration software RevMan (version 4.2.8). Heterogeneity of treatment effect was estimated by Cochrane Q test, with $p < 0.1$ considered as significant and presented in Forrest plots. We analyzed all outcomes with the Mantel-Haenszel

Table 2
Baseline characteristics of studies

	Jadad Score	Blinding	Study Arms	Mean Age (yr)	Men (%)	N, Mg/C	Duration of Arrhythmia Mg/C	Mean Baseline Mg level (mmol/L)	Ventricular Rate (beats/min)		Time to Outcome Measure (h)
									Inclusion Criteria	Mean Mg/C	
Gullestad et al ¹³	3	SB	MgSO ₄ vs verapamil	61/64	65/65	21/24	<7/<7 day Mean: 39/23 hour	0.85/0.82	>100	NA	0.5
Brodsky et al ¹⁴	2	DB	MgSO ₄ vs placebo	59/56	50/53	10/8	<7/<7 day Mean: 4/6 day	1.1/0.9	100-200	133/131	24
Hays et al ¹⁵	3	DB	MgSO ₄ vs placebo	67/59	43/50	7/8	NA/NA	0.77/0.78*	>100	140/135	4
Joshi et al ^{16†}	2	NB	MgSO ₄ vs verapamil	36/39	34/36	41/45	NA/NA	0.84/0.84*	>160	NA	≈0.5
Moran et al ¹⁷	2	NB	MgSO ₄ vs amiodarone	67	52/71	21/21	≥1/≥1 hour‡	0.84/1.02	>120	151/153	24
Walker et al ¹⁸	3	DB	MgSO ₄ vs placebo	NA	NA	21/20	<48/<48 hour	NA	>100	144/145	6
Chiladakis et al ¹⁹	1	SB	MgSO ₄ vs diltiazem	61/64	52/57	23/23	<12/<12 hour	NA	>100	142/136	6
Davey et al ²⁰	5	DB	MgSO ₄ vs placebo	72/73§	45/46	102/97	NA/NA	0.85/0.88	>120	142/143	2.5
Dluzniewski et al ²¹	1	NB	MgSO ₄ vs ajmaline	NA	NA	30/40	>30/>30 min¶	NA	>140	NA	<0.5

* Basal magnesium levels were converted from milligram per deciliter to millimole per liter with a conversion factor of 0.411.

† This study was excluded from pooled analysis due to presence of significant clinical heterogeneity compared with other trials.

‡ Duration of arrhythmia was >6 months in 3 and 5 patients in the magnesium and amiodarone groups, respectively.

§ Median value.

¶ Duration of symptoms was <24 hours, ≥24 hours and unknown in 62%, 24%, and 14% of participants, respectively.

|| All patients had ≥3 episodes of paroxysmal AF in the last 2 months.

C = control; DB = double blind; Mg = magnesium; NA = nonavailable; NB = non-blind; SB = single blind.

Table 3
Underlying conditions

	Heart Disease (%)				HTN (%) (Mg/C)	Pulmonary Disease (%) (Mg/C)	Other (%) (Mg/C)	LAD (mm) (Mg/C)
	Any (Mg/C)	CHD (Mg/C)	Valvular (Mg/C)	CMP (Mg/C)				
Gullestad et al ¹³	77/61	50/48	12/3	15/10	–	15/6	–	36/39 [‡]
Brodsky et al ¹⁴	10/38	0/1	10/25	–	50/38	10/13	30/13	42/45
Hays et al ¹⁵	57/50	–	57/50	–	43/50	–	–	NA
Joshi et al ¹⁶	90/91	10/4	80/87	–	–	10/9	–	NA
Moran et al ¹⁷	24/43	–	–	–	–	24/29	–	NA
Chiladakis et al ¹⁹	9/22	9/22	–	–	35/52	4/4	30/22	37/38
Davey et al ²⁰	45/48	NA	NA	NA	NA	NA	8/10	NA
Walker et al ¹⁸	NA	NA	NA	NA	NA	NA	NA	NA
Dluzniewski et al ^{21*}	NA	NA	NA	NA	NA	NA	NA	NA
Total [†]	50/55	8/10	18/20	2/1	7/8	7/6	8/7	–

* Patients with structural heart disease or ischemia were excluded.

† Values are based on 7 studies with reported data on underlying conditions.

‡ Echocardiography was performed in half of the patients.

CHD = coronary heart disease; CMP = cardiomyopathy; HTN = hypertension; LAD = left atrial diameter; NA = not available; other abbreviations as in Table 2.

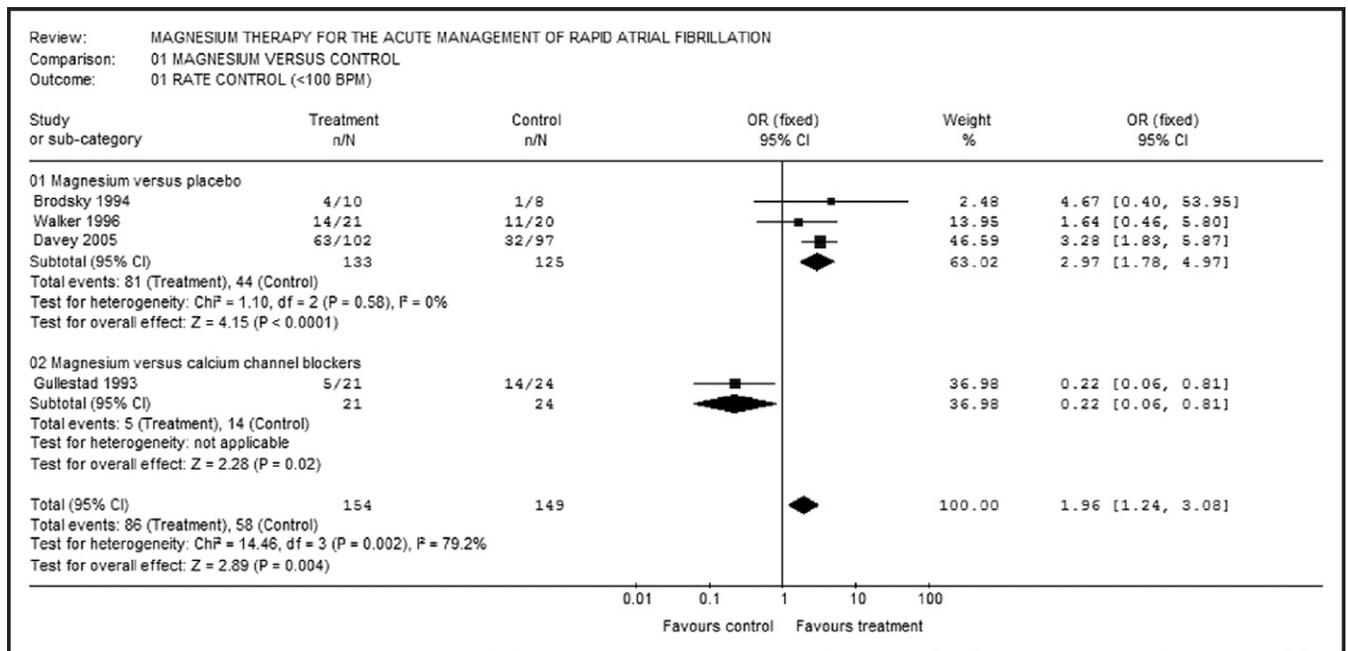


Figure 1. Intravenous magnesium therapy and rate control. N = number of patients; n = number of events.

fixed-effect model because of the low number of trials in each comparison. The results were expressed as relative risk (RR) or odds ratio (OR) for dichotomous outcomes and weighted mean difference for continuous outcomes, along with their 95% confidence intervals (CIs). Analysis was based on the intent-to-treat principle.

Results

Table 1 represents literature search and elimination process. Overall, of 1,113 initial hits, 9 randomized trials were identified.^{13–21}

The most important baseline characteristics of included studies are shown in Table 2. All studies excluded hemodynamically unstable patients, but 1 study was conducted in

patients in an intensive care unit.¹⁷ Reported underlying heart diseases across all studies are presented in Table 3. In 1 verapamil controlled study,¹⁶ most the included patients had rheumatic heart disease (Table 3). The age of this study population was also significantly younger than those in other studies (Table 2). Therefore, this study was excluded from further analysis. The remaining 8 trials, which included 476 patients, were considered for analysis. Five trials (n = 348) included only patients with AF.^{14,15,19–21} Two studies (n = 86) included patients with AF in addition to those with atrial flutter.^{13,18} The remaining study included 30 patients with AF or flutter and 12 patients with other supraventricular tachycardias.¹⁷ Overall, the type of arrhythmia was AF or atrial flutter in 97.5% of cases (464 of 476).

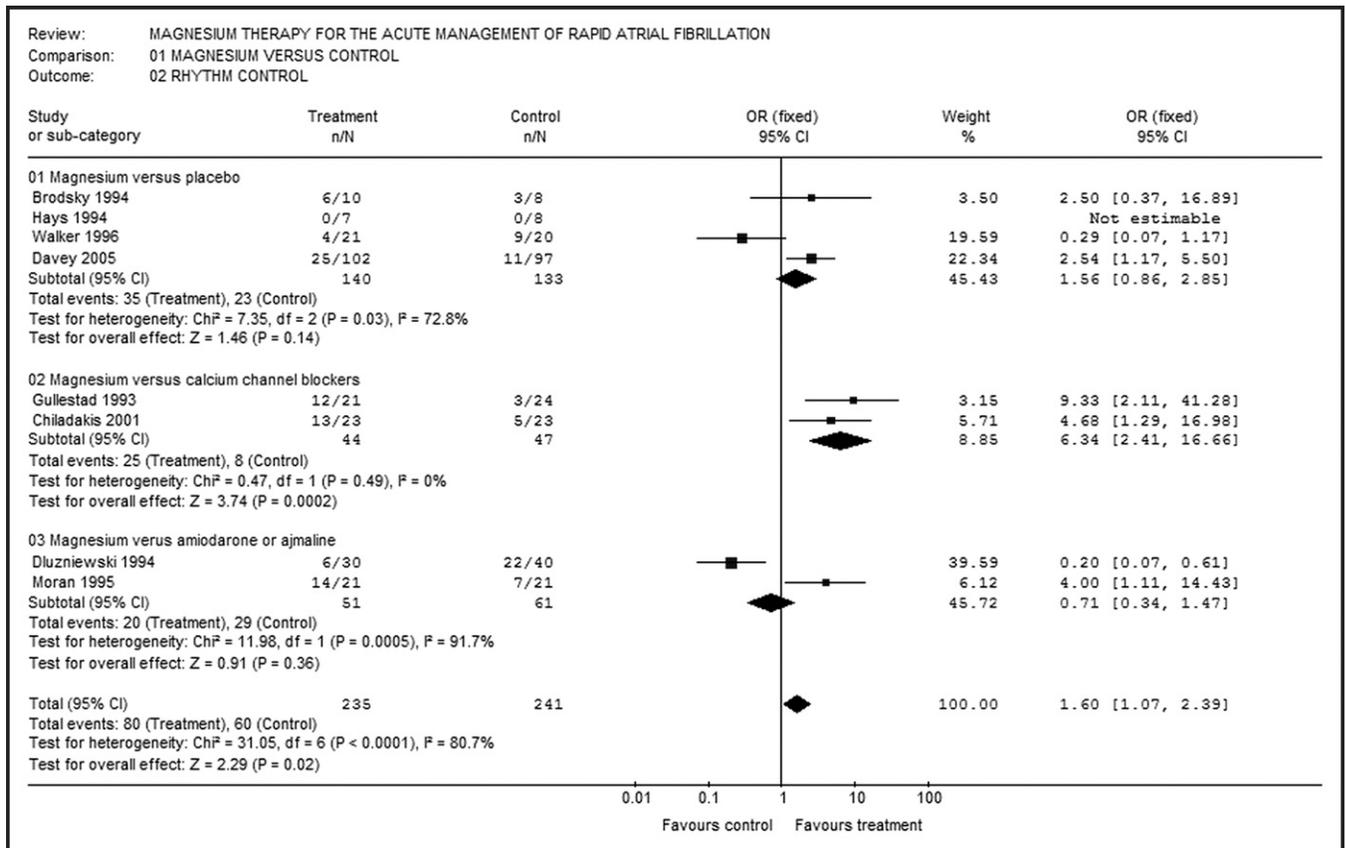


Figure 2. Intravenous magnesium therapy and rhythm control. Abbreviations as in Figure 1.

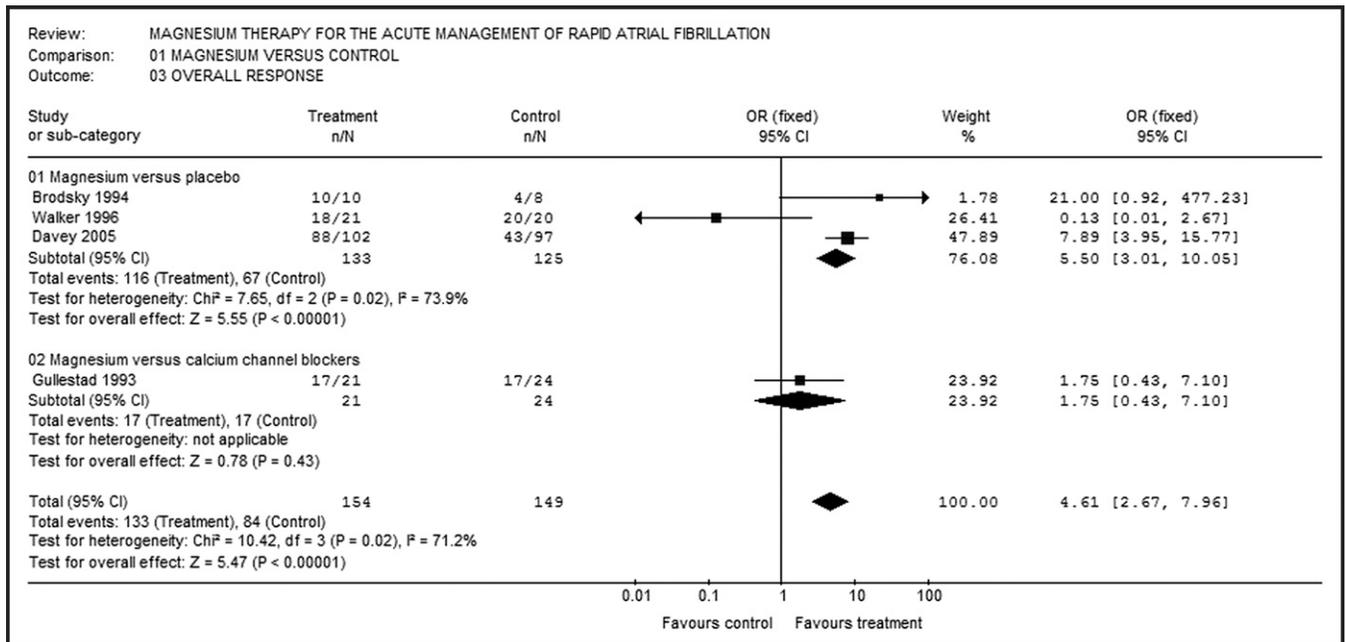


Figure 3. Intravenous magnesium therapy and overall response. Abbreviations as in Figure 1.

All studies evaluated intravenous magnesium sulfate administration. Magnesium was compared with placebo,^{14,15,18,20} verapamil,¹³ diltiazem,¹⁹ amiodarone,¹⁷ and ajmaline.²¹ Total dose of magnesium was in the range of 1.2 to 10 grams in

7 studies.^{13–16,18–21} The dose of magnesium was based on plasma creatinine level or presence of continuous venous–venous hemofiltration in 1 study.¹⁷ An initial dose of 1.2- to 5-grams magnesium was administered in all of these stud-

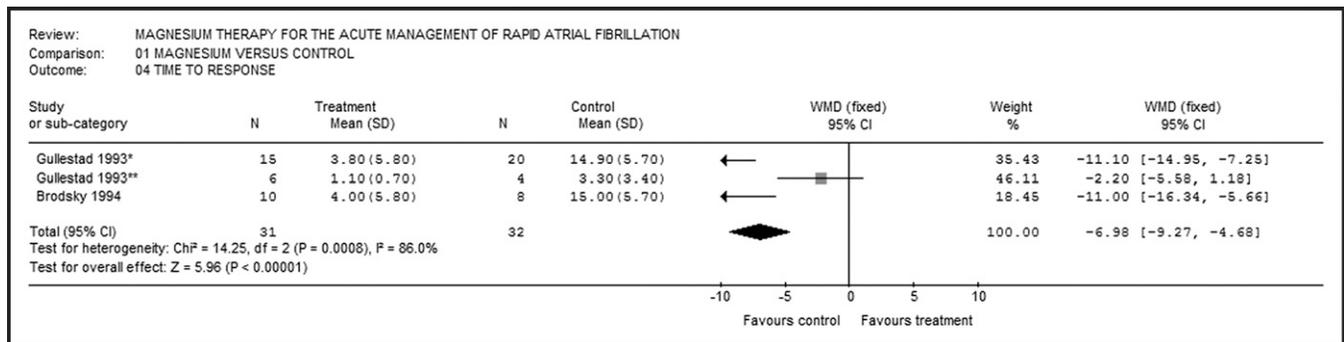


Figure 4. Time to response in treatment groups. SDs were imputed for the study of Brodsky et al¹⁴ to pool data. *Patients with atrial fibrillation; **patients with atrial flutter. WMD = weighted mean difference; other abbreviations as in Figure 1.

ies over 1 to 30 minutes.^{13–15,18–21} In 1 study, a second dose similar to the first was administered if a positive response was not achieved after 10 minutes.¹³ Magnesium infusion was continued for an additional 2 to 6 hours in 4 studies.^{14,15,19,20} In 1 study, intravenous digoxin was given in both groups simultaneously with the first dose of magnesium or placebo.¹⁴ In another placebo-controlled trial,²⁰ both treatments were given in addition to usual care, including digoxin, β blockers, and verapamil in 79%, 10%, and 3% of patients, respectively. Time to outcome measure was ≤ 24 hours for all studies. In 2 studies, patients who did not respond to first therapy were switched to alternate therapy.^{13,21} Only the first phase of these studies was considered for analysis.

Seven trials reported outcome of rate control (Figure 1). Four trials (n = 303) used a predefined criterion for rate control: a ventricular rate <100 beats/min in 3 trials^{13,18,20} and <90 beats/min in 1 trial.¹⁴ Magnesium sulfate was compared with placebo^{14,18,20} or verapamil¹³ in these studies. Comparing with placebo, sufficient rate control was achieved in a significantly larger proportion of the patients in the magnesium group (61% vs 35%; OR 2.97, 95% CI 1.78 to 4.97). Magnesium was also more effective in achieving rate control compared with placebo or verapamil (OR 1.96, 95% CI 1.24 to 3.08). In the remaining 3 studies, data on rate control were presented in different formats, making them unsuitable for pooling.^{15,17,19} In 1 placebo-controlled study, ventricular rate did not change significantly in the placebo group during the first 30 minutes of treatment, whereas the magnesium group showed an average of $16 \pm 7\%$ decrease in ventricular rate within 5 minutes (p < 0.02), and it was sustained during the first 30 minutes.¹⁵ In 2 studies, data on rate control are presented as trend graphs.^{17,19} Magnesium and diltiazem¹⁹ had a similar significant reduction in ventricular rate at the first hour of treatment, with a tendency toward a further decrease during infusion times of 6 hours (p < 0.001). In another study, magnesium was compared with amiodarone in 42 severely ill patients in an intensive care unit.¹⁷ Intravenous magnesium was as effective as amiodarone in slowing ventricular rate during 24-hour follow-up. There was a mean 19 beats/min decrease in ventricular rate within 30 minutes (p = 0.0001) and another 10 beats/min decrease between 30 minutes and 24 hours in both groups.

All studies reported conversion rates (Figure 2). Overall, in 8 trials (n = 476), magnesium-treated patients had a

Table 4

Available data on baseline serum magnesium (Mg) status and response to treatment

	Outcome	Mean Serum Mg Level (mmol/L)		p Value
		Response (+)	Response (-)	
Gullestad et al ¹³	Rhythm control	0.88	0.82	<0.05
Moran et al ^{17*}	Rhythm control	NA	NA	NA
Davey et al ^{20*}	Rhythm control	NA	NA	NA
Dluzniewski et al ^{21†}	Rhythm control	0.65	0.74	NA

* No association was found between baseline serum magnesium levels and response to treatment.

† Basal magnesium levels were converted from milligram per deciliter to millimole with a conversion factor of 0.411. Abbreviation as in Table 2.

higher chance to regain sinus rhythm than the control group (OR 1.60, 95% CI 1.07 to 2.39). In 6 studies including 364 patients, magnesium was more effective than placebo or calcium channel blockers in restoration of sinus rhythm (OR 2.34, 95% CI 1.42 to 3.87).^{13–15,18–20}

Data on overall response (rate or rhythm control) were pooled for 4 trials that included 303 patients (Figure 3). Overall, rate or rhythm control were achieved in 86% and 56% of magnesium-treated patients and control subjects, respectively (OR 4.61, 95% CI 2.67 to 7.96).

Time to rate control was available in 1 study separately for cases of AF and atrial flutter (Figure 4). In another study, time to overall response was available. Time to response (in hours) was significantly shorter in the magnesium group than in the control group (weighted mean difference, -6.98, 95% CI -9.27 to -4.68).

Data on the relation between baseline serum magnesium levels and response to treatment were available in 4 studies.^{13,17,20,21} Two studies found no association between baseline serum magnesium levels and response to treatment (Table 4). Mean baseline serum magnesium levels were significantly higher in patients with a positive response in 1 study (p < 0.05). In another study, baseline serum magnesium levels were 0.65 and 0.74 mmol/L, respectively, in responders and nonresponders (p value not available).

The most common side effects reported during magnesium administration were transient sensation of warmth and flushing. Reported numbers of withdrawals for any reason across all studies were 10 (4%) and 13 (5%) in the magne-

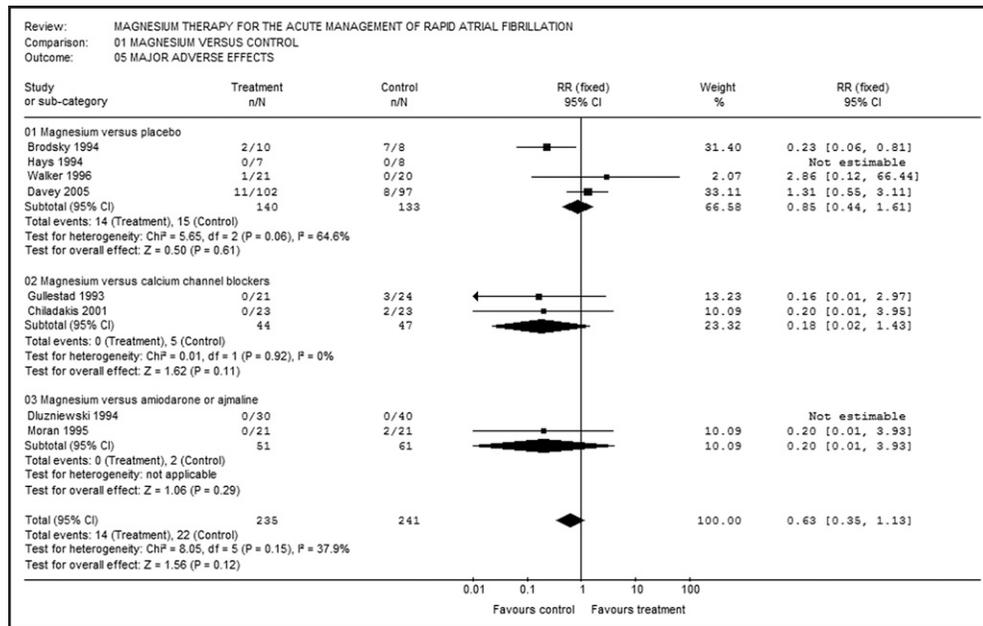


Figure 5. Major adverse effects in treatment groups. Abbreviations as in Figure 1.

Table 5
Summary of pooled effect of intravenous magnesium versus control treatment on the outcomes

Outcomes	Studies (n)	Participants (n)	Statistical Measure	Effect Size
Rate control (<100 beats/min)	4	303	OR, 95% CI	1.96 (1.24 to 3.08)
Rhythm control	8	476	OR, 95% CI	1.60 (1.07 to 2.39)
Overall response	4	303	OR, 95% CI	4.61 (2.67 to 7.96)
Time to response	2	63	WMD, 95% CI	-6.98 (-9.27 to -4.68)
Major adverse effects	8	476	RR, 95% CI	0.63 (0.35 to 1.13)

WMD = weighted mean difference.

sium and control groups, respectively. The corresponding figures for major adverse effects were 14 (6%) and 22 (9%). The risk of having a major adverse effect (Figure 5) in the magnesium group was similar to that in the placebo group (RR 0.85, 95% CI 0.44 to 1.61). Overall, there was a strong trend toward less major side effects in magnesium-treated patients (RR 0.63, 95% CI 0.35 to 1.13). No deaths were reported in magnesium-treated patients. The effects of intravenous magnesium on outcomes are listed in Table 5.

Discussion

To our knowledge, this is the first meta-analysis of previous publications for available evidence of the effectiveness of magnesium therapy in the acute management of non-post-operative AF. Data from 8 RCTs were pooled, with total populations of 235 patients in the magnesium group and 241 patients in the control group. Magnesium was more effective than control treatments with respect to rate control (OR 1.96, 95% CI, 1.24 to 3.08) and rhythm control (OR 1.60, 95% CI 1.07 to 2.39). The overall response rate was significantly higher in the magnesium group than in the control group (86% vs 56%; OR 4.61, 95% CI 2.67 to 7.96). Time to response (in hours) was significantly shorter in the magnesium group than in the control group (weighted mean difference, -6.98, 95% CI -9.27 to -4.68). The risk of

having a major adverse effect in the magnesium group was similar to that in the placebo group (RR 0.85, 95% CI 0.44 to 1.61).

Shortening of the atrial effective refractory period with loss of its rate dependency and prolongation of atrial conduction times are the most characteristic features of atrial electrical remodeling.^{22,23} Consistent with these findings, drug-induced prolongation of the atrial effective refractory period is the most widely accepted mechanism for termination of AF.²⁴ In addition, atrioventricular nodal conduction properties are the main determinant of ventricular rate in AF. From an electrophysiologic perspective, magnesium increases atrial¹⁻⁴ and atrioventricular nodal^{1,4-6} refractory periods, PA,² PR, and atrio-His intervals.¹⁻⁶ Therefore, magnesium may modulate those electrophysiologic substrates that lead to perpetuation of AF and acceleration of its ventricular rate in patients with AF. Consistent with this, data from the present meta-analysis favor the efficacy of magnesium compared with the control group in the achievement of rate control. In addition, magnesium was found to be as effective as amiodarone and diltiazem, well-known rate-controlling agents in AF, with respect to rate control. Intravenous magnesium administration was also more effective than control treatments in restoration of sinus rhythm in the present review.

Rhythm and rate control alleviate symptoms in patients with rapid AF. Therefore, a rate or rhythm control strategy may be suitable for most patients treated acutely for rapid AF. An overall response were achieved in 133 of 154 patients (86%) and 84 of 149 patients (56%), respectively, in the magnesium and control groups.

In addition to the plausibility of the reported findings, as a result of the physiologic effects of magnesium, its depletion in a significant proportion of cases of AF may play an important role. Hypomagnesemia was in as many as 50% of patients presenting with AF,⁷⁻⁹ and patients with hypomagnesemia required more intravenous digoxin doses for the control of symptomatic AF.⁹ Available limited data from this review are conflicting with regard to baseline serum magnesium status and response to magnesium treatment in patients with AF and rapid ventricular rate.^{13,17,20,21}

Numerous safety limitations interfere with AF management in emergency room settings. Most of these limitations are related to the safety profile of antiarrhythmic drugs. Magnesium can be used safely in most patients in whom other antiarrhythmic drugs are contraindicated or considered harmful.^{25,26}

Magnesium has a relatively wide toxic/therapeutic window, and the most common reported side effects are transient sensation of warmth and flushing. When administered intravenously, magnesium has a rapid action, which may be useful in controlling symptoms. Mean time to response was available in 2 studies.^{13,14} Time to conversion (3.8 vs 14.9 hours) in 1 study¹³ and mean time to overall response (4 vs 15 hours) in another study¹⁴ were significantly shorter in patients who received magnesium. Finally, magnesium is inexpensive, easy to use and titrate, and widely available for immediate use in every clinical unit.^{27,28}

Several limitations potentially influence the applicability of the findings presented in this review. Although a highly sensitive search strategy was carried out in several electronic databases and printed materials, only a few relevant studies with small sample sizes were found. In addition, based on the adequacy of randomization, blinding, and withdrawals, most of the included trials have medium quality. Negative studies are usually under-reported; therefore, meta-analysis may overestimate the clinical efficacy of magnesium.

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