Intravenous magnesium for acute myocardial infarction (Review)

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ABSTRACT

Background
Mortality and morbidity from acute myocardial infarction (AMI) remain high. Intravenous magnesium started early after the onset of AMI is thought to be a promising adjuvant treatment. Conflicting results from earlier trials and meta-analyses warrant a systematic review of available evidence.

Objectives
To examine the effect of intravenous magnesium versus placebo on early mortality and morbidity.

Search strategy
We searched CENTRAL (*The Cochrane Library* Issue 3, 2006), MEDLINE (January 1966 to June 2006) and EMBASE (January 1980 to June 2006), and the Chinese Biomedical Disk (CBM disk) (January 1978 to June 2006). Some core Chinese medical journals relevant to the cardiovascular field were hand searched from their starting date to the first-half year of 2006.

Selection criteria
All randomized controlled trials that compared intravenous magnesium with placebo in the presence or absence of fibrinolytic therapy in addition to routine treatment were eligible if they reported mortality and morbidity within 35 days of AMI onset.

Data collection and analysis
Two reviewers independently assessed the trial quality and extracted data using a standard form. Odds ratio (OR) were used to pool the effect if appropriate. Where heterogeneity of effects was found, clinical and methodological sources of this were explored.

Main results
For early mortality where there was evidence of heterogeneity, a fixed-effect meta-analysis showed no difference between magensium and placebo groups (OR 0.99, 95%CI 0.94 to 1.04), while a random-effects meta-analysis showed a significant reduction comparing magnesium with placebo (OR 0.66, 95% CI 0.53 to 0.82). Stratification by timing of treatment (< 6 hrs, 6+ hrs) reduced heterogeneity, and in both fixed-effect and random-effects models no significant effect of magnesium was found. In stratified analyses, early mortality was reduced for patients not treated with thrombolysis (OR=0.73, 95% CI 0.56 to 0.94 by random-effects model) and for those treated with less than 75 mmol of magnesium (OR=0.59, 95% CI 0.49 to 0.70) in the magnesium compared with placebo groups.

Meta-analysis for the secondary outcomes where there was no evidence of heterogeneity showed reductions in the odds of ventricular fibrillation (OR=0.88, 95% CI 0.81 to 0.96), but increases in the odds of profound hypotension (OR=1.13, 95% CI 1.09 to 1.19) and bradycardia (OR=1.49, 95% CI 1.26 to 1.77) comparing magnesium with placebo. No difference was observed for heart block (OR=1.05, 95% CI 0.97-1.14). For those outcomes where there was evidence of heterogeneity, meta-analysis with both fixed-effect and random-effects models showed that magnesium could decrease ventricular tachycardia (OR=0.45, 95% CI 0.31 to 0.66 by fixed-effect model; OR=0.40, 95% CI 0.19 to 0.84 by random-effects model) and severe arrhythmia needing treatment or Lown 2-5 (OR= 0.72, 95% CI 0.60 to 0.85 by fixed-effect model; OR=0.51, 95% CI 0.33 to 0.79 by random-effects model) compared with placebo. There was no difference on the effect of cardiogenic shock between the two groups.

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Authors' conclusions

Owing to the likelihood of publication bias and marked heterogeneity of treatment effects, it is essential that the findings are interpreted cautiously. From the evidence reviewed here, we consider that: (1) it is unlikely that magnesium is beneficial in reducing mortality both in patients treated early and in patients treated late, and in patients already receiving thrombolytic therapy; (2) it is unlikely that magnesium will reduce mortality when used at high dose (>=75 mmol); (3) magnesium treatment may reduce the incidence of ventricular fibrillation, ventricular tachycardia, severe arrhythmia needing treatment or Lown 2-5, but it may increase the incidence of profound hypotension, bradycardia and flushing; and (4) the areas of uncertainty regarding the effect of magnesium on mortality remain the effect of low dose treatment (< 75 mmol) and in patients not treated with thrombolysis.

PLAIN LANGUAGE SUMMARY

In some countries, intravenous (IV) magnesium is administered to heart attack patients in order to limit damage to the heart muscle, prevent serious arrhythmias and reduce the risk of death. Several small trials appeared to support the practice. But the authors of this review found that other trials went unpublished once they produced unfavorable results. A controversy erupted in 1995, when a large well-designed trial with 58,050 participants did not demonstrate any beneficial effect to IV magnesium, contradicting earlier meta-analyses of the smaller trials. This review includes 26 clinical trials that had randomly assigned heart attack patients to receive either IV magnesium or an inactive substance (placebo). Their results were mixed: IV magnesium reduced the incidence of serious arrhythmias, but this treatment also increased the incidence of profound hypotension, bradycardia and flushing. However, any apparent beneficial effects of magnesium may simply reflect various biases in these trials. Additionally, there was a lack of uniformity in these trials in terms of dosage and the timing of the IV magnesium regimen, which in some trials also included anti-clotting drugs. The evidence produced by this review does not support continued use of IV magnesium. Other effective treatments (aspirin, beta-blockers) should be used to treat heart attack.

BACKGROUND

Cardiovascular disease remains the leading cause of death in developed countries, and acute myocardial infarction accounts for a large proportion of these deaths. The major determinant of mortality and morbidity of acute myocardial infarction is infarct size. Many early deaths are due to ventricular fibrillation but in patients who survive the first few hours, the outcome is largely determined by the extent of myocardial damage.

Magnesium probably functions as an inorganic calcium channel blocker and there are several plausible mechanisms for a beneficial effect in acute myocardial infarction (Woods 1991). Research on animals and humans has shown that magnesium is a peripheral (Mroczek 1977) and coronary vasodilator (Vigorito 1991). It can increase the threshold for depolarization of cardiac myocytes, thereby reducing the likelihood of cardiac arrhythmia caused by injury currents near ischaemic or infarcted tissue (Haverkamp 1988; Tzivoni 1990). Magnesium decreases reperfusion injury by preventing or lessening mitochondrial calcium overload in ischaemic myocardial cells during the first few minutes of reperfusion (Ferrari 1986) (namely, the restoration of blood flow to an organ or tissue) and preserving intracellular ATP and creatine phosphate reserves (Borchgrevink 1989), and inhibits platelet function, perhaps indirectly by release of prostacyclin (Watson 1986). Thus, magnesium infusion started early after the onset of myocardial ischaemia might limit infarct size, prevent serious arrhythmias, and reduce mortality.

However, the clinical role of magnesium is still uncertain. The role of intravenous magnesium therapy in patients with acute myocardial infarction is controversial. The results from previous clinical trials are not in agreement. Several trials and pooled analyses of their results demonstrated a mortality rate reduction with magnesium treatment (Egger 1994; Horner 1992; Teo 1991; Yusuf 1993), but were later contradicted by one large trial, ISIS-4 (ISIS-4 1995).

Proposed explanations for the lack of consistency between the mega-trial ISIS-4 and the meta-analyses of the small trials, including LIMIT-2 (Woods 1992), are related to the timing of treatment, the dose of magnesium used, the duration of treatment, concomitant thrombolysis and methodological problems (i.e. publication bias, statistical models used).

- Timing of intravenous magnesium regimen and thrombolytic treatment

The magnesium in ISIS-4 was, on average, given later than in LIMIT-2, and was started after (rather than before or within) the initial 'lytic' phase of fibrinolytic therapy (ISIS-4 1995; Woods 1992).

- The dose of magnesium given in the first 24 hours

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Examination of the dose effect in a meta-analysis of eight studies (Horner 1992), LIMIT-2 (Woods 1992) and ISIS-4 (ISIS-4 1995), showed that the dose of intravenous magnesium given in the first 24 hours was related to the relative risk (RR) of death in the magnesium group versus placebo (Galloe 1994). A curvilinear correlation indicated a significant correlation between dose and effect. Mortality decreases following administration of between 0 mmol and 55 mmol magnesium. The optimum reduction in mortality (RR 0.36) was obtained at a dose of 55 mmol magnesium. Mortality increased between 55 mmol and 75 mmol, but the relative risk of death was still below 1 (the benefit was larger than any harm). Over 75 mmol magnesium, any beneficial treatment effect appeared to be lost (RR of death was more than 1). In ISIS-4 the initial 8 mmol bolus was given over approximately 15 minutes with a 24-hour infusion dose of 72 mmol compared with initial 8 mmol bolus given in approximately 5 minutes with a 24-hour infusion dose of 65 mmol in LIMIT-2. Therefore it has been (Galloe 1994) proposed that the absence of effect in ISIS-4 could be related to the dose used in the first 24 hours which might resulted in a higher prevalence of hypotension, II-III degree atrioventricular block, heart failure and cardiac shock.

- The duration of magnesium regimen

For most of the small trials, the intravenous magnesium infusion continued for 48 hours (rather than 24 hours in LIMIT-2 and ISIS-4) before showing any benefit (especially an antiarrhythmic effect), therefore the optimal duration of magnesium treatment remains to be clarified.

- Concomitant treatment

The proportion of patients who did not receive thrombolysis was 65% in LIMIT-2, more than twice the proportion not given thrombolysis in ISIS-4 (30%), therefore the use of thrombolysis might overlap or obscure any potential beneficial actions of magnesium when both drugs are used in combination. Besides, other drugs such as aspirin, β-blockers, nitrate, heparin and angiotensin-converting-enzyme inhibitors, etc could also influence the effect of magnesium.

- Bias in conducting meta-analysis

Egger et al (Egger 1995; Egger 1997) studied the value of funnel plots (plots of effect estimates against sample size) in detecting bias in meta-analysis and found that the funnel plots for magnesium and acute myocardial infarction were not symmetrical which indicated the possible presence of publication bias.

- Statistical models used in previous meta-analysis

Use of specific statistical models may affect outcome. When ISIS-4 is added to the earlier RCTs, the fixed effect model that assumes homogeneity among the trials indicates no beneficial effect of magnesium (OR = 1.02, 95%CI 0.96 to 1.08, P = 0.48), whereas the random effects model that takes into account the heterogeneity among these trials suggests that magnesium may reduce mortality (OR = 0.59, 95%CI 0.39 to 0.90, P = 0.014) (Antman 1995a; Antman 1996).

Considering the conflicting results of previous meta-analyses and later large trials, and the possibility of bias in these meta-analyses, we propose that further clarification of the effect of magnesium on the mortality and morbidity of acute myocardial infarction is warranted.

OBJECTIVES

In patients suffering acute myocardial infarction:

- To examine the effect of intravenous magnesium versus control on early mortality (primary objective), stratified by time since onset of symptoms (< 6 hours, 6+ hours), use of thrombolysis (used, not used), dose of magnesium used (< 75 mmol, 75+ mmol);

- To examine the effect of intravenous magnesium versus control on early morbidity (secondary objective), including ventricular fibrillation and tachycardia, atrioventricular block, bradycardia, heart failure, cardiogenic shock, hypotension, severe arrhythmia needing treatment or Lown 2-5, and flushing.

Early outcomes are defined as mortality and morbidity occurring in hospital during the acute admission phase or within 35 days of onset of MI. Lown 2-5 is defined as frequent or complex ventricular arrhythmia based on 24-hour electrocardiogram (ECG) recordings and analyses of ventricular arrhythmias (Hedblad 1997).

Since the definition of clinical events such as heart failure, cardiogenic shock, bradycardia and hypotension varied in different trials, the presence of these clinical events was based on the investigators' judgement.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomized controlled trials that compared intravenous magnesium with placebo in the presence or absence of thrombolytic therapy in addition to routine treatment were eligible if they reported mortality and clinical events within 35 days of acute myocardial infarction onset, published in any language.

Types of participants

All patients with first-time acute myocardial infarction or suspected myocardial infarctionin the preceding 24 hours diagnosed by clinical symptoms, enzymes and ECG, regardless of age, gender, infarct size and location, and without contraindication to magnesium.

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Types of intervention

- Experimental treatment: intravenous magnesium plus routine treatment in the presence or absence of thrombolytic therapy
- Control treatment: routine treatment in the presence or absence of thrombolytic therapy

Types of outcome measures

The following outcomes within the first 5-week were considered:

- Primary outcome: within 5-week total mortality
- Secondary outcomes: ventricular fibrillation and tachycardia, atrioventricular block, bradycardia, heart failure, cardiogenic shock, hypotension, severe arrhythmia needing treatment or Lown 2-5, flushing

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Heart Group methods used in reviews.

We searched the Cochrane Centreal Register of Controlled Trials (CENTRAL) on *The Cochrane Library (*Issue 3, 2006), MEDLINE (January 1966 to June 2006), EMBASE (January 1980 to June 2006), and the Chinese Biomedical Disk (CBM disk) (January 1978 to June 2006). No language restrictions were applied.

Since CENTRAL does not cover most Chinese medical journals and the index of randomized controlled trials in the Chinese Biomedical Disk is not complete, therefore some core Chinese medical journals relevant to the cardiovascular area were hand searched from their starting date to the first-half year of 2006, including Chinese Journal of Cardiology, Chinese Circulation Journal, Chinese Journal of Interventional Cardiology, Chinese Journal of Hypertension, and Journal of Clinical Cardiology. The bibliographies of the randomised trials were reviewed and the authors, and known experts in the field, were contacted to identify additional published or unpublished data.

The electronic search of CENTRAL was performed using the following specific terms, similar terms were used to search MEDLINE, EMBASE and CBM:
#01MYOCARDIAL-ISCHEMIA*:ME
#02CORONARY-ARTERY-BYPASS*:ME
#03(ISCHEMI* near HEART)
#04(ISCHAEMI* near HEART)
#05(CORONARY near DISEASE*)
#06(CORONARY near BYPASS)
#07(CORONARY near THROMBO*)
#08(CORONARY near ANGIOPLAST*)
#09(MYOCARD* near ISCHEMI*)
#10(MYOCARD* near ISCHAEMI*)
#11(MYOCARD* near INFARCT*)
#12(HEART near INFARCT*)
#13ANGINA
#14(((((((#1 or #2) or #3) or #4) or #5) or #6) or #7) or #8)
#15((((#9 or #10) or #11) or #12) or #13)
#16(#14 or #15)
#17MAGNESIUM*:ME
#18MAGNESIUM-COMPOUNDS*:ME
#19MAGNESI*
#20((#17 or #18) or #19)
#21(#16 and #20)

METHODS OF THE REVIEW

Study selection
Two members of the review team independently reviewed the abstracts of randomized controlled trials to identify the trials that met the eligibility criteria. English and Chinese trials were reviewed. However, all English abstracts of non-English, non-Chinese language publications were also reviewed to collect available data of interests.

Trials were only rejected on initial screen if the reviewer could determine from the title and abstract that the trial was not a report of a randomized controlled trial or the trial did not address the effect of intravenous magnesium on the mortality and morbidity of acute myocardial infarction.

When a title/abstract could not be rejected with certainty, the full text of the article was obtained for further evaluation. An inclusion/exclusion form was used to assist the selection of the trials.

Methodological quality assessment
The methodological quality was assessed by taking into account the method of randomization, allocation concealment, blinding of participants and investigators, and completeness of follow-up. The allocation concealment was graded as A: adequate, B: unclear, C: inadequate and D: unknown.

Data extraction
A data extraction form was used to extract information from the eligible trials, regarding participants, interventions, outcomes, study quality and pre-tested using a random sample of studies. The key information of each section of the data extraction form was as following:

1. Participants: inclusion and exclusion criteria, baseline characteristics as age, gender and comorbid conditions, etc.
2. Intervention: dose, length of intravenous magnesium, timing of magnesium with thrombolytic therapy, concomitant treatment and treatment of control group, etc.
3. Outcomes: number of outcome events including mortality and morbidity (ventricular fibrillation and tachycardia, atrioventricular block, bradycardia, heart failure, cardiogenic shock, hypotension, flushing).

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Two reviewers (Jing Li, and either Qing Zhang or Mingming Zhang) independently conducted the selection of studies, assessment of methodological quality of included studies and data extraction. Disagreement was resolved by discussion and, when necessary, in consultation with a third person. Whenever there was uncertainty, authors were contacted to clarify the details.

Data analysis

Review Manager 4.2 (RevMan) software was used for the statistical analysis. The odds ratio (OR) was used as the effect measure. Heterogeneity was assessed and a fixed-effect model (assumes that the true effect of treatment is the same value in every study, namely fixed across studies) and/or a random-effects model (assumes that the effects being estimated in the different studies are not identical, but follow some distribution) was used, as appropriate as determined by heterogeneity, to summarize the evidence. Estimates of the relative rates of the outcomes were pooled using standard methods for combining odds ratios for early mortality stratified by time since onset of symptoms (< 6 hours, 6+ hours), use of thrombolysis (used, not used), dose of magnesium used (< 75 mmol, 75+ mmol) and clinical events of intravenous magnesium versus control . Ninety-five percent confidence interval was used for all effect size estimates for both individual trials and pooled estimates.

Heterogeneity was assessed using the the chi-squared test with significance set at $P < 0.10$. Whenever there was heterogeneity and it was considered feasible to pool the data, both fixed effect model and random effects model were used.

Sensitivity analysis for the primary outcome was performed based on the adequate of concealment of allocation. Publication bias and other biases were examined using a funnel plot.

DESCRIPTION OF STUDIES

See Table entitled "Characteristics of included studies"

Included studies

Forty-eight potentially relevant studies were identified after extensive searching and selection, of these, 26 RCTs with a total of 73363 participants were included in the review (Abraham 1987; Bhargava 1995; Ceremuzynski 1989; Chen 1991; Feldstedt 1991; Gyamlani 2000; Ising 1990; ISIS-4 1995; MAGIC 2000; Morton 1984; Nakashima 2004; Nameki 2004; Parikka 1999; Raghu 1999; Rasmussen 1986; Santoro 2000; Shechter 1990; Shechter 1991; Shechter 1995; Singh 1990; Smith 1986; Thogersen 1995; Urek 1996; Woods 1992; Wu 1992; Zhu 2002).

Participants

The 26 trials varied in sample size (ranging from 40 to 58,050 participants), characteristics of patients (eight trials with suspected acute myocardial infarction patients (Feldstedt 1991; ISIS-4 1995; Rasmussen 1986; Shechter 1995; Singh 1990; Smith 1986; Thogersen 1995; Woods 1992) and the other 18 with proven acute myocardial infarction patients). Of these, 22 trials (72,476 participants) contributed to the information on mortality, 11 trials (62,392 participants) on ventricular fibrillation, 9 trials (1187 participants) on ventricular tachycardia, 9 trials (67,338 participants) on II-III degree heart block, 14 trials (68,140 participants) on heart failure, 5 trials (60,668 participants) on profound hypotension, 12 trials (62,334 participants) on cardiogenic shock, 10 trials (7353 participants) on severe arrhythmia needing treatment, 4 trials (60,574 participants) on bradycardia, and 5 trials (58,744 participants) on flushing.

Interventions

The 26 trials varied in dose of magnesium within the first 24 hours (sulphate, chloride or aspartate) ranging from 8 mmol to 80 mmol. Duration of treatment ranged from 5 hours to 14 days.

Outcomes

The 26 trials provided different outcomes and the follow-up period varied from 24 hours to 5 weeks. The definition and measurement of outcomes were different in different trials. Adverse effects of bradycardia and flushing were reported in four trials (Bhargava 1995; ISIS-4 1995; Rasmussen 1986; Woods 1992) and five trials (Abraham 1987; Gyamlani 2000; ISIS-4 1995; Raghu 1999; Santoro 2000) respectively.

Excluded studies

Five papers were additional publications to studies already included. Twelve studies were excluded for the following reasons: (1) compared magnesium with other drugs such as propranolol (Abraham 1994; Balkin 1994); (2) only abstracts, without available data (Petri 1985; Smith 1985; Su 1997; Xu 1990); (3) long-term effect of magnesium in acute myocardial infarction (Rasmussen 1988; Shechter 2003; Woods 1994); (4) pilot study of ISIS-4 (Flather 1994); (5) not a randomized controlled trial (Leone 1991; Sun 1990).

Studies awaiting assessment

Five trials published in language other than English or Chinese (Pereira 1990; Rekosz 1996; Spisak 1994; Yavelov 1995a; Yavelov 1995b). Translation is needed to assess eligibility and collect the available data.

METHODOLOGICAL QUALITY

Thirteen trials provided the methods to generate randomization sequence (Abraham 1987; Bhargava 1995; Feldstedt 1991; Gyamlani 2000; ISIS-4 1995; MAGIC 2000; Morton 1984; Raghu 1999; Santoro 2000; Shechter 1995; Thogersen 1995; Woods 1992; Zhu 2002). Sixteen trials stated use of double blinding (Abraham 1987; Feldstedt 1991; Gyamlani 2000; MAGIC 2000; Morton 1984; Parikka 1999; Raghu 1999; Rasmussen 1986; Shechter 1990; Shechter 1991; Shechter 1995; Singh 1990; Smith 1986; Thogersen 1995; Urek 1996; Woods 1992); two stated use

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of single blinding (Chen 1991; Nakashima 2004). Nine trials used adequate allocation concealment (Gyamlani 2000; ISIS-4 1995; MAGIC 2000; Raghu 1999; Santoro 2000; Shechter 1995; Singh 1990; Smith 1986; Woods 1992). Seven trials mentioned intention-to-treat analysis (Feldstedt 1991; ISIS-4 1995; MAGIC 2000; Santoro 2000; Singh 1990; Thogersen 1995; Woods 1992).

RESULTS

When there was no heterogeneity for the outcome, a fixed effect model was used to pool the data. Whenever heterogeneity was observed for the primary outcome (even after stratification) and secondary outcomes, both fixed and random effects models were used to pool the data.

Considering sources of clinical heterogeneity between the trials, it was clear that the different selection criteria of participants (suspected or confirmed acute myocardial infarction), characteristics of participants especially the length of time between the onset of symptoms and admission, dose of magnesium, the duration of intervention and follow up, and criteria for outcome measurement might explain heterogeneity among trials. To attempt to explore some of these sources of heterogeneity, we examined the effect of intravenous magnesium versus control on early mortality stratified by time since onset of symptoms (< 6 hours, 6+ hours), use of thrombolysis (used, not used), dose of magnesium used (< 75 mmol, 75+ mmol).

Effect of intravenous magnesium versus control on early mortality

There was significant heterogeneity among trials (X^2= 57.77, P < 0.0001) for the primary outcome of early mortality. Fixed-effect meta-analysis showed no difference in early mortality between the two groups (OR 0.99, 95%CI 0.94 to 1.04), while random-effects meta-analysis showed a significant reduction comparing magnesium with placebo (OR 0.66, 95% CI 0.53 to 0.82).

Stratified by time since onset of symptoms (< 6 hours, 6+ hours)

Eight trials (Abraham 1987; Gyamlani 2000; ISIS-4 1995; MAGIC 2000; Morton 1984; Raghu 1999; Santoro 2000; Woods 1992) provided information on early mortality, 16,320 participants on magnesium (1503 died) and 16,286 participants in placebo (1502 died) groups were admitted to hospitals less than 6 hours after the onset of symptoms. Heterogeneity was observed among trials (X^2=16.41, P = 0.02) and no difference was observed between the magnesium and placebo groups via both fixed effect model (OR = 1.00, 95% CI 0.93 to 1.08) and random effects model (OR = 0.88, 95% CI 0.72 to 1.08).

Two trials (ISIS-4 1995; Singh 1990) provided information on early mortality, 17,414 participants on magnesium (1294 died) and 17,471 participants on placebo (1234 died) groups were admitted to the hospital after 6 hours of onset of symptoms. There was no heterogeneity and no difference was observed between the two groups (OR = 1.06, 95% CI 0.97 to 1.15).

Stratified by use of thrombolysis (used, not used)

Four trials (ISIS-4 1995; MAGIC 2000; Raghu 1999; Zhu 2002) reported the use of thrombolysis in 21,873 (1618 died) participants on magnesium and 21,573 (1502 died) on placebo. There was heterogeneity among trials (X^2=11.36, P = 0.01). Meta-analysis with both fixed-effect model (OR = 1.07, 95% CI 0.99 to 1.15) and random effects model (OR = 0.91, 95% CI 0.69 to 1.20) showed that there was no difference on early mortality between the two groups.

Twelve trials (Abraham 1987; Feldstedt 1991; ISIS-4 1995; MAGIC 2000; Morton 1984; Rasmussen 1986; Shechter 1990; Shechter 1991; Shechter 1995; Singh 1990; Smith 1986; Zhu 2002) with 12,230 (1176 died) participants in magnesium and 12,362 (1269 died) in placebo groups did not use thrombolysis. There was heterogeneity among trials (X^2= 25.69, P = 0.007). Meta-analysis with a fixed-effect model showed no difference on early mortality in the magnesium group compared with placebo (OR=0.93, 95% CI 0.86-1.01), while a random-effects model showed a decrease in early mortality (OR = 0.73, 95% CI 0.56 to 0.94).

Stratified by dose of magnesium used (< 75 mmol, 75+ mmol)

Seventeen trials (Abraham 1987; Bhargava 1995; Ceremuzynski 1989; Gyamlani 2000; Nakashima 2004; Rasmussen 1986; Santoro 2000; Shechter 1990; Shechter 1991; Shechter 1995; Singh 1990; Smith 1986; Thogersen 1995; Urek 1996; Woods 1992; Wu 1992; Zhu 2002) with 33,850 (228 died) participants in magnesium and 3639 (355 died) in placebo groups infused magnesium less than 75 mmol within the first 24 hours. There was no heterogeneity among trials (X^2= 16.97, P = 0.39) and meta-analysis showed a decrease in early mortality compared with placebo (OR = 0.59, 95% CI 0.49 to 0.70).

Five trials (Feldstedt 1991; ISIS-4 1995; MAGIC 2000; Morton 1984; Raghu 1999) with 32,483 (2708 died) participants magnesium and 32,504 (2603 died) in placebo groups infused magensium 75 mmol or more within the first 24 hours. There was no heterogeneity (X^2= 6.72, P = 0.15) among trials and meta-analysis showed that there was no difference on early mortality between the two groups (OR = 1.04, 95% CI 0.99 to 1.11).

Effect of intravenous magnesium versus control on early morbidity

Ventricular fibrillation

Eleven trials (Abraham 1987; Bhargava 1995; Ceremuzynski 1989; Chen 1991; Feldstedt 1991; Gyamlani 2000; ISIS-4 1995; Morton 1984; Nakashima 2004; Wu 1992; Zhu 2002) provided information on ventricular fibrillation, 31,301 (1040 with ventricular fibrillation) participants in magnesium and 31,091 (1168 with ventricular fibrillation) in placebo groups. There was no heterogeneity among trials (X^2= 15.00, P = 0.13) and meta-analy-

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sis showed that magnesium could decrease ventricular fibrillation compared with placebo (OR = 0.88, 95% CI 0.81 to 0.96).

Ventricular tachycardia

Nine trials (Abraham 1987; Bhargava 1995; Ceremuzynski 1989; Chen 1991; Feldstedt 1991; Gyamlani 2000; Rasmussen 1986; Santoro 2000; Wu 1992) provided information on ventricular tachycardia, 601 (57 with ventricular tachycardia) participants in magnesium and 586 (101 with ventricular tachycardia) in placebo groups. There was heterogeneity among trials (X^2= 23.94, P = 0.002). Meta-analysis with both a fixed-effect model (OR = 0.45, 95% CI 0.31 to 0.66) and random-effects model (OR = 0.40, 95% CI 0.19 to 0.84) showed that magnesium could decrease ventricular tachycardia compared with placebo.

II-III heart block

Nine trials (Feldstedt 1991; ISIS-4 1995; MAGIC 2000; Parikka 1999; Shechter 1990; Shechter 1991; Shechter 1995; Urek 1996; Woods 1992) provided information on II-III heart block, 33,662 (1231 with II-III heart block) participants in magnesium and 33,676 (1177 with II-III heart block) in placebo groups. There was no heterogeneity among trials (X^2= 8.89, P = 0.35) and meta-analysis showed that no difference of effect on II-III heart block between magnesium and placebo groups (OR = 1.05, 95% CI 0.97 to 1.14)

Heart failure

Fourteen trials (Feldstedt 1991; Gyamlani 2000; ISIS-4 1995; MAGIC 2000; Morton 1984; Nakashima 2004; Parikka 1999; Rasmussen 1986; Santoro 2000; Shechter 1990; Shechter 1991; Shechter 1995; Woods 1992; Wu 1992) provided information on heart failure, 34,066 (5920 with heart failure) participants in magnesium and 34,074 (5602 with heart failure) in placebo groups. There was heterogeneity among trials (X^2=24.56, P=0.03). Meta-analysis with a fixed-effect model showed that magnesium could increase heart failure compared with placebo (OR=1.07, 95% CI 1.03 to 1.11), while a random-effects model showed that there is no difference of effect (OR=0.95, 95% CI 0.81 to 1.10).

Considering the main sources of heterogeneity, we stratified heart failure by time since onset of symptoms (< 6 hours, 6+ hours), use of thrombolysis (used, not used), dose of magnesium used (< 75 mmol, 75+ mmol). Data were available for patients admitted within 6 hours, not given thrombolysis and use of both low and high dose magnesium. Homogenous effects were achieved except for heart failure admitted within 6 hours. (1) Five trials (Gyamlani 2000; MAGIC 2000; Morton 1984; Santoro 2000; Woods 1992) provided information on heart failure, 4437 (762 with heart failure) participants in magnesium and 4418 (769 with heart failure) in placebo groups admitted patients within 6 hours. Heterogeneity was observed among trials (X^2= 16.23, P = 0.003). Meta-analysis by both fixed-effect (OR = 0.92, 95% CI 0.63 to 1.36) and random-effects models (OR = 0.98, 95% CI 0.88 to 1.10) showed that there was no difference in heart failure between magnesium and placebo groups. (2) Six trials (Feldstedt 1991; Morton 1984; Rasmussen 1986; Shechter 1990; Shechter 1991; Shechter 1995) which did not use thrombolysis provided information on heart failure, 413 (59 with heart failure) participants in magnesium and 434 (56 with heart failure) in placebo groups. There was no heterogeneity among trials and no difference on effect of heart failure between magnesium and placebo groups (OR = 1.11, 95% CI 0.74 to 1.68). (3) Ten trials (Gyamlani 2000; Nakashima 2004; Parikka 1999; Rasmussen 1986; Santoro 2000; Shechter 1990; Shechter 1991; Shechter 1995; Woods 1992; Wu 1992) that infused less than 75 mmol magnesium within the first 24 hours provided information on heart failure, 1752 (233 with heart failure) participants in magnesium and 1751 (300 with heart failure) in placebo groups. There was no heterogeneity among trials. Meta-analysis showed that magnesium could decrease heart failure compared with placebo (OR = 0.73, 95% CI 0.60 to 0.88). Four trials (Feldstedt 1991; ISIS-4 1995; MAGIC 2000; Morton 1984) that infused 75 mmol or more magnesium within the first 24 hours provided information on heart failure, 32,314 (5687 with heart failure) participants in magnesium and 32,323 (5302 with heart failure) in placebo groups. There was no heterogeneity among trials and meta-analysis showed that magnesium could increase heart failure compared with placebo groups (OR = 1.09, 95% CI 1.04 to 1.13).

Profound hypotension

Five trials (Abraham 1987; ISIS-4 1995; Morton 1984; Singh 1990; Woods 1992) provided information on profound hypotension, 30,324 (4854 with profound hypotension) participants in magnesium and 30,344 (4367 with profound hypotension) in placebo groups. There was no heterogeneity among trials and meta-analysis showed that magnesium could increase profound hypotension compared with placebo groups (OR = 1.13, 95% CI 1.09 to 1.19).

Cardiogenic shock

Twelve trials (Abraham 1987; Bhargava 1995; Ceremuzynski 1989; Gyamlani 2000; ISIS-4 1995; Nakashima 2004; Rasmussen 1986; Shechter 1990; Shechter 1991; Shechter 1995; Singh 1990; Zhu 2002) provided information on cardiogenic shock, 31,243 (1360 with cardiogenic shock) participants in magnesium and 31,091 (1268 with cardiogenic shock) in placebo groups. There was heterogeneity among trials (X^2= 21.80, P = 0.03). Meta-analysis with both fixed-effect (OR = 1.07, 95% CI 0.99 to 1.16) and random-effects models (OR = 0.65, 95% CI 0.41 to 1.02) showed that there was no difference on the effect of cardiogenic shock between the two groups.

Severe arrhythmia needing treatment or Lown 2-5

Ten trials (Chen 1991; MAGIC 2000; Rasmussen 1986; Shechter 1990; Shechter 1991; Shechter 1995; Singh 1990; Smith 1986; Urek 1996; Wu 1992) provided information on severe arrhythmia needing treatment or Lown 2-5, 3682 (258 with severe arrhythmia needing treatment or Lown 2-5) participants in magnesium and 3671 (341 with severe arrhythmia needing treatment

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or Lown 2-5) in placebo groups. There was heterogeneity among trials (X^2= 23.94, P = 0.002). Meta-analysis with both fixed-effect (OR = 0.72, 95% CI 0.60 to 0.85) and random-effects models (OR = 0.51, 95% CI 0.33 to 0.79) showed that magnesium could decrease severe arrhythmia needing treatment or Lown 2-5 compared with placebo.

Effect of intravenous magnesium versus control on adverse effects

Bradycardia

Four trials (Bhargava 1995; ISIS-4 1995; Rasmussen 1986; Woods 1992) with 30,266 (340 with bradycardia) participants in magnesium and 30,308 (233 with bradycardia) in placebo groups reported information on bradycardia. There was no heterogenity and meta-analysis showed that magnesium infusion caused more bradycardia compared with placebo treatment (OR = 1.49, 95% CI 1.26 to 1.77).

Flushing

Five trials (Abraham 1987; Gyamlani 2000; ISIS-4 1995; Raghu 1999; Santoro 2000) with 29,353 (269 with flushing) participants in magnesium and 29,391 (12 with flushing) in placebo groups reported information on flushing. There was heterogeneity among trials (x^2= 23.81, P < 0.0001). Meta-analysis with both fixed-effect (OR = 20.78, 95% CI 12.90 to 33.46) and random-effects models showed that magnesium infusion caused more flushing compared with placebo treatment (OR = 42.00, 95% CI 3.82 to 461.35).

A visual inspection of the funnel plot for early mortality showed evidence of absence of small negative trials (Figure 01).

DISCUSSION

Although the benefit and harm of magnesium have been debated over two decades and 73,363 patients have been studied in a series of 26 randomized controlled trials of magnesium over the past 26 years, there is still uncertainty about its effects. Focusing on the effect on early mortality, the most important outcome and least likely to be affected by difficulties with blinding or diagnostic criteria, it is clear that the findings from the smaller trials are not consistent with those of the very large ISIS-4 trial (which provided 71.65% of the overall weight of the meta-analysis), with substantial heterogeneity apparent (I^2 = 63.6%). In these circumstances, a fixed-effect model gives a null effect (OR = 0.99, 95%CI 0.94 to 1.04), and a random-effects model, which gives much less weight to ISIS-4, appears to demonstrate a benefit of magnesium (OR = 0.66, 95%CI 0.53 to 0.82). It has been argued that neither analysis is appropriate and that a Bayesian perspective can help reconcile the discordant ISIS-4 findings from the other trials. In this work, a sceptical prior together with a random-effects model resulted in a consistent, non-significant, effect on mortality whether ISIS-4 was included or excluded from consideration (Higgins 2002). However, it is essential to consider the possibility of publication bias as an explanation for the difference between ISIS-4 (and MAGIC, also large and null) and the other smaller trials. Egger's original exploration demonstrated evidence of an absence of small negative trials (Egger 1997) and this more detailed and updated search has failed to find any further small negative trials.

A question to be considered is whether ISIS-4 produced the 'wrong' answer by treating patients too late, using too high a dose of magnesium, or treating too many people on concomitant thrombolytic therapy. To examine this question, we examined the results stratified by these trial characteristics to determine whether heterogeneity within strata was reduced and whether the treatment effects differed between strata. In view of the hazards of generating spurious findings from sub-group analyses, we have limited our interpretation to the primary outcome of interest, early mortality.

- Time is critical in management of acute myocardial infarction. If thrombolytic treatment is not given, spontaneous reperfusion occurs in at least a third of patients during the first 12 to 24 hours after acute myocardial infarction (Woods 1995). The benefits from supplemental magnesium administration may be lost when there is a delay of more than 15 to 45 minutes after the onset of reperfusion (Antman 1995b). Although most included trials reported the time of acute myocardial infarction patients' admission or randomization after the onset of symptoms, the exact time of magnesium infusion after the onset of symptoms and in relation to reperfusion were not stated. Therefore we stratified the patients according to their admission time after onset of symptoms (< 6 hours, 6+ hours) and this reduced heterogeneity of effect quite markedly with X^2 falling from 55.77 (21 df) to 16.41 (7 df) and 1.88 (1 df) in the two strata. No statistical difference in early mortality was found by time of treatment, but the remaining largely very small trials that did not provide this information demonstrated a beneficial effect. These findings indicate that timing of treatment is not a plausible explanation for differences between ISIS-4 findings and those of other trials.
- Turning to the use of concomitant treatments, particularly thrombolytic therapy, there is no strong evidence that magnesium is better or worse than placebo in its effects on early mortality. Despite stratification, heterogeneity within strata remains suggesting that use of additional therapy is not a good explanation for heterogeneity of effect. The confidence intervals of early mortality include 1 for those patients treated with thrombolytics, but do not include 1 for those treated without thrombolytics via random effect model and in those trials where it was not clear whether thrombolytics were or were not used. Use of concomitant treatment such as thrombolysis might overlap or replace the cardioprotective effects of magnesium, but this result should be taken cautiously because of the persist heterogeneity after stratification.
- The dose of magnesium may be important. As ISIS-4 used only one dose, no internal comparison can be made within this trial

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which limits the value of the stratified analyses. Early mortality was substantially reduced in the trials using less than 75 mmol magnesium and homogeneity was achieved between trials in both high and low dose magnesium strata. The evidence on the appropriate dose of magnesium (Horner 1992; Woods 1992) was derived from a partial review of the randomized trials and is consequently not independent of the trial findings themselves. The issue of estimating the effects of different doses would require a new trial set up to test this specific hypothesis. If the post hoc evidence is taken at face value, the evidence suggests that rather than the effective dose of magnesium being the same for everyone, the treatment is effective on average at low doses, and ineffective at higher doses which seems implausible. However, the major problem in judging the findings of ISIS-4 revolve around the dose used.

For the secondary outcomes, homogeneous effects were seen for ventricular fibrillation, II-III degree heart block, profound hypotension and bradycardia and heterogeneity effects were seen for heart failure, cardiogenic shock, severe arrhythmia needing treatment or Lown 2-5 and flushing. Meta-analysis showed reductions in the odds of ventricular fibrillation, ventricular tachycardia, severe arrhythmia needing treatment or Lown 2-5, but increases in the odds of profound hypotension, bradycardia and flushing, and no difference in the odds of heart block, cardiogenic shock comparing magnesium with placebo. Inconsistent results were seen for heart failure. Fixed-effect analysis showed increases in the odds of heart failure, but random-effects analysis showed no difference comparing magnesium with placebo.

Careful laboratory studies, conducted since the ISIS-4 findings, have continued to explore the role of magnesium in reducing myocardial damage around the time of reperfusion, and have demonstrated its critical nature, with any benefit lost if treatment is delayed (Christensen 1995; Herzog 1995; Ravn 1999). Further examination of timing, dose and concomitant treatments in clinical patients might be rewarding.

Methodological quality

The quality of included trials was generally moderate or high, but some studies provided limited information on the procedure of study design, randomization, allocation concealment and blinding. We performed a sensitivity analysis for early mortality based on whether adequate allocation concealment was used or not. Meta-analysis showed that heterogeneity (X^2= 32.04, P < 0.0001) was observed for the nine trials (Gyamlani 2000; ISIS-4 1995; MAGIC 2000; Raghu 1999; Santoro 2000; Shechter 1990; Shechter 1995; Smith 1986; Woods 1992) with adequate allocation concealment. A fixed-effect model showed that there was no difference on early mortality between the two treatment groups (OR = 1.02, 95% CI 0.96 to 1.07), while a random-effects model showed magnesium could reduce the odds of early mortality (OR = 0.74, 95% CI 0.57 to 0.96) compared with placebo. No heterogeneity was observed for the 13 trials that did not provide information on allocation concealment and there was a decrease in early mortality in magnesium group compared with placebo (OR 0.61, 95% CI 0.49 to 0.76). It appeared that this aspect of methodological quality did not explain heterogeneity between trials. However, if our inability to classify trials on grounds of timing of treatment and use of concomitant thrombolytic therapy are considered as quality criteria, then there is evidence that quality of trials has had some influence on the effects seen, with those of lower quality tending to produce significant treatment effects.

Publication bias

Although we conducted extensive searching, we only included trials that were published in English and Chinese, or published in other languages but with an English abstract and information of interest. Most of the included trials have small sample size except four trials (ISIS-4 1995; MAGIC 2000; Woods 1992; Zhu 2002). The funnel plot for all included trials is not symmetrical and potential publication bias could not be avoided. We did not search for potentially relevant trials that had not been published.

Outcomes measurement

While we do not think it is likely that biased ascertainment of early deaths arose, the definition of clinical events such as heart failure, cardiogenic shock, bradycardia and hypotension varied in different trials and we recorded them based on the investigators' judgement in trials. It is possible that some bias in ascertainment could have arisen, particularly in smaller trials where allocation may not have been concealed and where outcome assessors were not blinded to treatment received.

AUTHORS' CONCLUSIONS

Implications for practice

In some parts of the world, magnesium is still viewed as an inexpensive, easy-to-use supplemental treatment for acute myocardial infarction. On the basis of evidence presented here we consider that it is unlikely that magnesium is beneficial in reducing mortality both in patients treated early and in patients treated late, and in patients already receiving thrombolytic therapy. It is unlikely that magnesium will reduce mortality when used at high dose of magnesium (> 75 mmol). Magnesium treatment may reduce the incidence of ventricular fibrillation, ventricular tachycardia, severe arrhythmia needing treatment or Lown 2-5, but it may increase the incidence of profound hypotension, bradycardia and flushing. The areas of uncertainty regarding the effect of magnesium on mortality remain the effect of low dose treatment (< 75 mmol) and in patients not treated with thrombolysis.

Given the availability of a range of effective treatments for acute myocardial infarction it would be preferable to ensure that these are used than to continue using magnesium for which there is inadequate evidence of efficacy.

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Implications for research

It seems unlikely that any further large-scale trials of magnesium in acute myocardial infarction will be conducted in the future. However the question of whether the dose of magnesium is important in determining efficacy when given early after symptom onset in people not eligible for thrombolysis remains uncertain and further trials may be needed.

POTENTIAL CONFLICT OF INTEREST

There are no potential conflicts of interest.

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* *Indicates the major publication for the study*

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TABLES

Characteristics of included studies

Study	**Abraham 1987**
Methods	Randomization: computer-generated random number, similar solutions being prepared for each patients. Blinding: double-blind (patients and physicians), placebo-controlled. Follow-up: complete.
Participants	94 patients with AMI were immediately transferred to the CCU and entered into the study; placebo group: 46, mean age 61.1y, magnesium group: 48, mean age 64.2 y.
Interventions	Treatment group: 2.4g of magnesium sulfate in 50 ml of 5% glucose solution. Control group: 50 ml of 5% glucose solution alone. Treatment duration: intravenously over a 20 minutes period for 3 days and monitor 72-h period.
Outcomes	Appearance of ventricular triplets, R-on-T phenomenon, or ventricular tachycardia or fibrillation and side effects, measurement of lymphocyte K and Mg.
Notes	
Allocation concealment	B – Unclear

Study	**Bhargava 1995**
Methods	Randomization: stratified randomization. Blinding: not stated, placebo controlled. Follow-up: complete.
Participants	78 consecutive proven patients with chest pain of 1-6h were randomized. 40 in treatment and 38 in control groups.
Interventions	Treatment group: 8 mmol magnesium sulphate over 5 min followed by 65 mmol over 24-h infusion. Control group: isotonic saline infusion. Duration of symptoms before randomization into Mg and placebo groups was the same(Mg: 5.3+/-3.3h vs placebo: 5.6+/-3.2h)
Outcomes	Arrhythmia: ventricular premature beats, ventricular tachycardia, ventricular fibrillation, supraventricular tachyarrhythmias, bradycardia and asystole. All cardiac events: reinfarction, mortality and coronary bypass surgery during hospital stay and at the end of 28 days
Notes	
Allocation concealment	B – Unclear

Study	**Ceremuzynski 1989**
Methods	Randomization: no detail. Blinding: not stated. Follow-up: complete.
Participants	48 patients with AMI within 12 h from onset of symptoms were randomly assigned to either control group (n = 23, age 43-81y), or magnesium group (n = 25, age 44-77y).
Interventions	Treatment group: 8 g MgSO4 in 500 mL 15% glucose for 24 h intravenously plus conventional treatment. Control group: conventional treatment.
Outcomes	Threatening arrhythmia (VT: >=3 consecutive VPC with a rate of > 120/min) and inhospital mortality.
Notes	

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Characteristics of included studies (*Continued*)

Allocation concealment	B – Unclear

Study	**Chen 1991**
Methods	Randomization: no detail. Blinding: outcome assessor was blinded to the allocation. Follow-up: complete.
Participants	62 patients with AMI was randomly allocated to Mg (n+32, mean age: 54.5 y) or placebo (n = 30, mean age: 51.1 y) groups. All patients was admitted within 24 h from onset of symptoms.
Interventions	Treatment group: MgSO4 2g/day for 3 days. Placebo group: 5% glucose.
Outcomes	Arrhythmia for 72 h.
Notes	
Allocation concealment	B – Unclear

Study	**Feldstedt 1991**
Methods	Randomization: block randomization. Blinding: double-blinded, placebo-controlled trial. Follow-up: 13 in Mg and 7 in placebo groups were withdraw without stated the reasons, intention-to-treat for in-hospital mortality.
Participants	298 patients, aged 75 y or less, with suspected AMI less than 8 h were randomized to either magnesium (n = 150, mean age = 59, range 28-75, confirmed AMI = 83) or placebo (n = 148, mean age = 61 y, range 41-75, confirmed AMI = 78) group.
Interventions	Treatment group: continuous infusion of 80 mmol magnesium chloride in 1000 mL dextrose Control group: matching placebo.
Outcomes	In-hospital death on the principle of intention to treat.
Notes	
Allocation concealment	B – Unclear

Study	**Gyamlani 2000**
Methods	Randomization: random patients numbers generated with the FoxPro database application, randomization codes were held by the pharmacy department and independent statistician only. Blinding: double-blind, placebo-controlled, identical treatment packs for trial and placebo treatments were manufactured in the production unit of the pharmacy service. Follow-up: complete
Participants	100 patients with proven AMI were randomly allocated to Mg group (n = 50, mean age: 56.1+/-12.28) or placebo group (n = 50, mean age: 57+/-11). All patients were admitted with symptoms less than 6 h. No lost to follow-up.
Interventions	Treatment group: 12g (50 mmol) in the first 24h, 3g (12 mmol) in the second 24h. Placebo group: equal volume of isotonic glucose. Mg was used within 2h after admission and within 30 minutes of thrombolytic therapy.
Outcomes	Serum magnesium, CK, all arrhythmia and conduction abnormalities, death within 4 weeks.
Notes	
Allocation concealment	A – Adequate

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Characteristics of included studies (*Continued*)

Study	**ISIS-4 1995**
Methods	Randomization: Entry to the study was by telephone to central 24 h randomisation services. Baseline details about the patients were to be recorded, either directly onto computer or onto computer-generated randomisation lists, before a specific numbered trial treatment pack was to be allocated. Blinding: open control, no placebo was given Follow-up: 1.7% was missing for both groups, analysis was based on intention-to-treat.
Participants	58,050 patients entering 1086 hospitals up to 24 h (median 8 h) after the onset of suspected acute myocardial infarction with no clear contraindications to the study treatments were randomised in a "2x2x2 factorial" study. 29011(confirmed AMI 26,264) in magnesium and 29,030 (confirmed AMI 26,261) in control group.
Interventions	Treatment group: 24 h of intravenous magnesium sulphate (8 mmol initial bonus injection over about 15 minutes followed by 72 mmol in about 50 mLinfused over 24 h) Control group: with no placebo infusion being given.
Outcomes	Mortality in first 5 weeks and other clinical events in hospital, e.g. ventricular fibrillation, II-III degree heart block, heart failure, cardiogenic shock, hypotension, bradycardia, flushing.
Notes	
Allocation concealment	A – Adequate

Study	**Ising 1990**
Methods	Randomization: no detail. Blinding: not stated. Follow-up: complete.
Participants	42 patients with AMI. Magnesium group: 22 (mean age = 56); control group: 20 (mean age = 56).
Interventions	Treatment group: 81 mval/day magnesium sulphate infusion 13+/-9h after the onset of severe pain for 3 days Control group: 80 mval/day NaCl infusion for 3 days.
Outcomes	Serious arrhythmia, i.e. number of patients with couplets and ventricular tachycardia.
Notes	
Allocation concealment	B – Unclear

Study	**MAGIC 2000**
Methods	Randomization: permuted block randomisation design, stratified by clinical center and stratum (stratum 1 with reperfusion therapy, stratum 2 without reperfusion therapy) and with a central interactive telephone voice response system. Blinding: double-blind, matched sterile water as placebo Follow-up: 3 in Mg and 2 in placebo groups were lost. Data analysis was based on intention-to-treat.
Participants	1924 in stratum 1 and 4289 in stratum 2 were randomised. 3113 in Mg and 3100 in placebo groups [median age: 70 (63-76) vs 70 (63-75)]. All patients received the blinded study drug within 6 h of onset of symptoms.
Interventions	Treatment group: 2 g intravenous bolus of MgSO4 over 15 minutes, followed by a 17 g infusion of MgSO4 over 24 h. Placebo group: blinded, matched intravenous bolus and 24 h infusion of sterile water.
Outcomes	Primary endpoint: all-cause mortality within 30 days. Secondary endpoints: treatment for heart failure, defibrillation of ventricular fibrillation or sustained ventricular tachycardia and treatment with a temporary pacemaker.
Notes	
Allocation concealment	A – Adequate

Study	**Morton 1984**
Methods	Randomization: random number table.

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Characteristics of included studies (*Continued*)

	Blinding: double-blind. Neither patients nor medical or nursing staff knew as to the allocation to the therapy. Follow-up: five were excluded from analysis.
Participants	76 patients with AMI within 8 h of onset were included. Treatment group: 40, age 54+/-1.6; Control group: 57+/-1.4. Duration of symptoms prior to entry (hrs) is 5.3+/-0.2 and 4.7+/-0.3 respectively.
Interventions	Treatment group: 36 h intravenous infusion of magnesium sulphate (0.75 mEq/kg/body weight/12 h). Control group: saline solution infusion.
Outcomes	Mortality within 2 days, dysrhythmias, blood pressure, heart rate and signs of heart failure.
Notes	This paper was also published in Magnesium 1984;3:346-352 by Morton et al. Data were collected from both papers
Allocation concealment	B – Unclear

Study	**Nakashima 2004**
Methods	Randomization: no detail. Blinding: single-blind. Follow-up: complete.
Participants	180 patients with successful PCI were randomly assigned. 89 in Mg and 91 in control groups with similar characteristics of age (67+/-11 vs 69+/-11), sex and time to admission (3.0+/-2.2 vs 3.1+/-2.4) after onset.
Interventions	Treatment group: bolus injection of 8 mmol of magnesium followed by an infusion of 24 mmol over 24 h. Control group: equivalent amount of normal saline. Other treatment: all patients underwent PCI, aspirin, heparin, nicorandil (4 mg/h for 3 days) use.
Outcomes	In-hospital mortality and clinical complications including death, heart failure, cardiogenic shock and ventribular fibrillation, left ventribular function
Notes	
Allocation concealment	B – Unclear

Study	**Nameki 2004**
Methods	Randomization: no detail. Blinding: not clear. Follow-up: 6 patients did not underwent LVG, left 34 patients duing 3 months follow-up.
Participants	40 patients with successful PCI were randomly assinged to nicorandil (13), Mg (13) and control groups (14) with similar baseline characteristics of age, sex.
Interventions	Treatment group: - nicorandil: 4 mg iv and 4 mg intracoronarily before reperfusion, followed by iv infusion at 4 mg/h for the subsequent 24 h. - magnesium: 10 mmol iv before reperfusion, followed by iv infusion at 0.4 mmol/h for the subsequent 24 h. Control: neither nicorandil nor magnesium was given. Other treatment: similar.
Outcomes	Left ventriculography was performed to measure EDVI, ESVI, EF, RWM. Reperfusion phenomena: chest pain, blood pressure decrease, ST elevation and reperfusion arrythmia
Notes	
Allocation concealment	B – Unclear

Study	**Parikka 1999**
Methods	Randomization: no detail. Blinding: double-blind placebo controlled.

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Characteristics of included studies (*Continued*)

	Follow-up: 5 in first 24 h and 15 at discharge were lost, no detail.
Participants	59 consecutive patients with < 12 h from onset of chest pain AMI was randomized to magnesium (n = 31, age 30-73, mean 60). or placebo (n = 26, age 36-74, mean=59) group.
Interventions	Treatment group: 8mmol MgSO4 in 10 min, 62 mmol in 24h. Placebo group: NaCl. Other treatment, e.g. beta-blocker, aspirin, ACE inhibitors, diuretics determined by attending clinician, thrombolytic treatment if appropriate start preceded the study infusion.
Outcomes	Number of supraventricular and ventricular premature beats, tachycardia, heart rate variability and conduction disturbance recorded by 24 h Holter prior to infusion and on 7th to 14th day in hospital. Heart failure diagnosed by radiology.
Notes	
Allocation concealment	B – Unclear

Study	**Raghu 1999**
Methods	Randomization: computerized randomization program. Blinding: double-blind, placebo controlled. Follow-up: complete.
Participants	350 confirmed AMI < 6 h from the onset of symptoms were randomized either to treatment (n = 181, mean age 53.1+/-10.8) or to control (n = 169, mean age 52.9+/-11.0).
Interventions	Treatment group: 18 g (75.6 mmol) of Mg sulphate over 24 h Control group: equivalent amount of saline. Mg were started immediately after completion of thrombolytic therapy.
Outcomes	30 day of mortality, tachycardia arrhythmia, reinfarction, post-infarct angina and flushing.
Notes	
Allocation concealment	A – Adequate

Study	**Rasmussen 1986**
Methods	Randomization: no detail. Blinding: double-blind, placebo-controlled. Follow-up: complete.
Participants	273 patients with suspected AMI were randomised to either Mg or placebo group. Of 130 patients with proven AMI, 56 (mean age 64.6, range 39-89) received Mg and 74(mean age 67.6, range 40-91) received placebo.
Interventions	Treatment group: 50 mmol MgCl2 during the first 24 h, 12 mmol during the second 24 h. Control group: isotonic glucose.
Outcomes	Mortality during first 4 weeks, proportion of arrhythmia needing treatment.
Notes	Another report based on the same group of patients, but mainly focused on the incidence of arrhythmia was published by clin. Cariol. 1987;10:351-356. Data were collected from both reports.
Allocation concealment	B – Unclear

Study	**Santoro 2000**
Methods	Randomization: random allocation was generated by computer and codes remained concealed until data collection and analysis were finished. Blinding: outcome assessor were blinded, placebo-controlled trial. Follow-up: analysis was made on an intention-to-treat basis.

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Characteristics of included studies (*Continued*)

Participants	150 patients were randomized to intravenous MgSO4 group (n = 75, age: 60+/-11) or placebo (n = 75, age: 60+/-12). All patients were admitted to CCU within 6h of symptom onset.
Interventions	Treatment group: 7 g (28 mmol) with 5 h. Placebo group: matching saline solution. Treatment was started immediately after randomization before all patients receiving angioplasty.
Outcomes	Primary endpoints: infarct zone wall motion score index at 30 days (infarct size). Secondary endpoints: CK peak values, VF or VT (> 6 consecutive beats > 120/min), death, heart failure during 30 days follow-up
Notes	
Allocation concealment	A – Adequate

Study	**Shechter 1990**
Methods	Randomization: no detail. Blinding: double-blind, placebo-controlled. Follow-up: complete.
Participants	115 consecutive patients with admission diagnosis of AMI were randomized. Of them, 103 with proven AMI were analyzed. 50 in magnesium and 53 in control groups. (mean age: 64 y vs 63 y; time from pain to treatment: 5.3+/-3.3 vs 5.3+/-3.0 respectively).
Interventions	Treatment group: 22 g (91.6 mmol) within 48 h (67 mmol within first 24 h). Control group: isotonic glucose. No prophylactic antiarrhythmic therapy, thrombolytic therapy was not routinely available.
Outcomes	In-hospital mortality and morbidity, e.g. arrhythmia, conduction disturbance, heart failure.
Notes	
Allocation concealment	B – Unclear

Study	**Shechter 1991**
Methods	Randomization: no detail. Blinding: double-blind, placebo-controlled. Follow-up: complete.
Participants	159 patients with documented AMI were randomized. Among 46 were older than 70 y (range:72-89, mean: 76+/-4) and analyzed. 21 in magnesium and 25 in control groups.
Interventions	Treatment group: 22 g (91.6 mmol) within 48 h (67 mmol within first 24 h). Control group: isotonic glucose. No prophylactic antiarrhythmic therapy, thrombolytic therapy was not routinely available.
Outcomes	Arrhythmia, conduction disturbance, heart failure and mortality.
Notes	
Allocation concealment	B – Unclear

Study	**Shechter 1995**
Methods	Randomization: computerized randomization program (EPISTAT). Blinding: double-blind, placebo-controlled trial. Follow-up: complete. Analysis only on documented 159 patients.
Participants	215 patients suspected with AMI and considered unsuitable candidates for thrombolysis were randomized. 194 patients with confirmed AMI were analyzed. 96 in magnesium and 98 in placebo groups (age: 66+/-12 vs 66+/-13; time from pain to treatment: 7.0+/-4.3, 7.1+/-2.2).

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Characteristics of included studies (*Continued*)

Interventions	Treatment group: 22 g (91.6 mmol) within 48 h (67 mmol within first 24 h). Control group: isotonic glucose. No prophylactic antiarrhythmic therapy and no thrombolytic therapy.
Outcomes	Arrhythmia, conduction disturbance, congestive heat failure, and hospital mortality.
Notes	
Allocation concealment	A – Adequate

Study	**Singh 1990**
Methods	Randomization: randomized by the nurse and residents to receive solution marked in identical bottles. Blinding: double-blind, placebo-controlled trial. Follow-up: 3 in Mg and 2 in placebo groups were lost and analysis was based on intention to treat.
Participants	326 patients suspected with AMI (264 confirmed and analyzed), admitted to the hospital within 8-12h of the onset of MI, were randomly assigned to one of the 4 groups.
Interventions	Treatment group: 5 g (8.12 mmol) of MgSO4 daily for 4 days. Placebo group: 2% dextrose solution for 3 days.
Outcomes	4 weeks complications (hypotension, pump failure with shock, arrhythmias requiring treatment) and mortality
Notes	The combination of short- and long-term effects were also published in International Journal of Clinical Pharmacology and Therapeutics. 1996;34(5):219-225. Data of mortality from Singh 1996, data of complications from singh1990.
Allocation concealment	A – Adequate

Study	**Smith 1986**
Methods	Randomization: the solutions were prepared in identical vials by the hospital pharmacy. Blinding: double-blind Follow-up: 6 in Mg and 9 in placebo groups were withdrawn, only documented patients were included in the analysis.
Participants	400 patients with suspected AMI were admitted. Among 200 were confirmed and included in the analysis. 92 in magnesium and 93 in placebo groups (mean age: 59.7+/-0.9 vs 58.4+/-2.2).
Interventions	Treatment group: 65 mmol MgSO4 given over 24 h. Placebo group: Saline.
Outcomes	Episodes of ventricular tachyarrhythmia and mortality within 24h.
Notes	
Allocation concealment	A – Adequate

Study	**Thogersen 1995**
Methods	Randomization: stratified randomization by fibrinolytic therapy or not. Blinding: double-blind. Follow-up: 12 in Mg and 11 in placebo groups were withdrawn and analysis was intention to treat.
Participants	252 patients with suspected AMI were included. 130 in Mg and 122 in placebo groups (mean age: 67+/-11 vs 67+/-11; admission time: 9.8+/-21.8 vs 8.1+/-9.1; confirmed AMI: 57 vs 60; thrombolytic treatment: 39 vs 38).
Interventions	Treatment group: 50 mmol within 24 h. Placebo group: isotonic NaCl.
Outcomes	All clinically important arrhythmias after the first 24 h and all serious cardiac events (AMI, coronary bypass surgery, death). Unfortunately, most of the data were combination of short and follow-up effect. Analysis was based on intention to treatment.

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Characteristics of included studies (*Continued*)

Notes	Another report based on the same group of patients was published in International Journal of Cardiology 1993;39:13-22. Data were collected from both reports.
Allocation concealment	B – Unclear

Study	**Urek 1996**
Methods	Randomization: no detail. Blinding: double blind placebo controlled study. Follow-up: complete.
Participants	61 patients with documented AMI. 31 in Mg and 30 in placebo groups (mean age: 60.5 vs 63.2; time from onset of pain to treatment: < 12 h).
Interventions	Treatment group: 17 g MgSO4 with first 24 h. Placebo group: saline.
Outcomes	Severe arrhythmias, hospital mortality and conduction disturbances.
Notes	Because of language difficulty, detail information need help from interpreter.
Allocation concealment	B – Unclear

Study	**Woods 1992**
Methods	Randomization: computer-generated blocked randomization schedule and codes were held by the pharmacy department and the independent statistician only. Blinding: double blind, placebo controlled study by using identical treatment packs. Follow-up: 9 in Mg and 7 in placebo groups were lost with reasons, but excluded the 28-day mortality analysis. Intention-to-treat analysis was stated.
Participants	2316 patients with suspected AMI in the preceding 24h were included. 1159 in Mg and 1157 in placebo groups (mean age: 61.4+/-11.4 vs 62.2+/-11.5; confirmed AMI: 754 vs 754; number of patients treated with thrombolysis: 419 vs 402).
Interventions	Treatment group: 8 mmol over 5 min, 65 mmol over 24h. Placebo group: physiological saline.
Outcomes	28-day mortality, morbidity e.g. LVF, hypotension, heart block bradycardia, tachyarrhythmias.
Notes	Another report based on same group of patient was published on Br Heart J 1994;71:141-145.
Allocation concealment	A – Adequate

Study	**Wu 1992**
Methods	Randomization: no detail was given. Blinding: not stated. Follow-up: not stated.
Participants	248 suspected AMI were randomized and 227 were confirmed and included in the study. 125 in treatment and 102 in placebo groups.
Interventions	Treatment group: 2.5 g MgSO4 once or twice a day for 7-14 days. Placebo group: conventional treatment. Conventional study was equal in two groups.
Outcomes	Arrhythmia and mortality within 4 weeks.
Notes	
Allocation concealment	B – Unclear

Study	**Zhu 2002**
Methods	Randomization: stratified randomization, multi-center.

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	Blinding: open trial. Follow-up: complete.
Participants	3179 eligible AMI patients in proceeding 24 h were randomized to either treatment (n = 1691, admission time = 9.04 h, age = 62.4+/-11.0) or control (n = 1488, admission time = 9.01, age = 63.2+/-11.0) group. 809 in treatment group and 668 in control group received thrombolysis.
Interventions	Treatment group: 100 mL (4 g) potassium-magnesium aspartate IV. for the first day, 50 ml for rest 4 days plus routine AMI treatment. Control group: same routine AMI treatment as treatment group.
Outcomes	Mortality rate within 28 days, arrhythmia.
Notes	
Allocation concealment	B – Unclear

AMI: acute myocardial infarction
CCU: coronary care unit
h: hours
K: potassium
Mg: magnesium
MgCl2: magnesium chloride
MgSO4: magnesium sulfate
NaCl: sodium chloride
PCi: percutaneous coronary intervention
y: years

Characteristics of excluded studies

Study	Reason for exclusion
Abraham 1994	Compare magnesium with propranolol.
Balkin 1994	Compare magnesium with propranolol.
Flather 1994	Pilot study of ISIS-4.
Leone 1991	Not indicated as RCT by the authors.
Petri 1985	Only abstract.
Rasmussen 1988	Long term effect study.
Shechter 2003	Long term effect study.
Smith 1985	Only abstract.
Su 1997	Published as abstract without available data.
Sun 1990	Claimed to be an RCT, but a retrospective study.
Woods 1994	Long term effect.
Xu 1990	Published as abstract without available data.

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ANALYSES

Comparison 01. Magnesium vs placebo on mortality

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 mortality by time of admission	23	72472	Odds Ratio (Fixed) 95% CI	0.99 [0.94, 1.04]
02 mortality by use of thrombolytic therapy	25	71434	Odds Ratio (Fixed) 95% CI	0.99 [0.93, 1.04]
03 mortality by dose of magnesium	22	72476	Odds Ratio (Fixed) 95% CI	0.99 [0.94, 1.04]

Comparison 02. Magnesium vs placebo on morbidity

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Ventricular fibrillation	11	62392	Odds Ratio (Fixed) 95% CI	0.88 [0.81, 0.96]
02 Ventricular tachycardia	9	1187	Odds Ratio (Fixed) 95% CI	0.45 [0.31, 0.66]
03 II-III heart block	9	67338	Odds Ratio (Fixed) 95% CI	1.05 [0.97, 1.14]
04 Heart failure	14	68140	Odds Ratio (Fixed) 95% CI	1.07 [1.03, 1.11]
05 Profound hypotension	5	60668	Odds Ratio (Fixed) 95% CI	1.13 [1.09, 1.19]
06 Cardiogenic shock	12	62334	Odds Ratio (Fixed) 95% CI	1.07 [0.99, 1.16]
07 severe arrhythmia needing treatment	10	7353	Odds Ratio (Fixed) 95% CI	0.72 [0.60, 0.85]

Comparison 03. Magnesium vs placebo on side effect

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Bradycardia	4	60574	Odds Ratio (Fixed) 95% CI	1.49 [1.26, 1.77]
02 Flushing	5	58744	Odds Ratio (Fixed) 95% CI	20.78 [12.90, 33.46]

COVER SHEET

Title Intravenous magnesium for acute myocardial infarction

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Contribution of author(s)

Jing Li:
contributed to the development of the protocol, studies selection, assessement of methodological quality, data extraction, data analysis and production of the complete review
Qing Zhang:
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Mingming Zhang:
contributed to part of the development of the protocol, studies selection, assessement of methodological quality, data extraction, production of the complete review and as a language advisor
Matthias Egger:
contributed to part of the development of the protocol, production of the complete review and as a methodological advisor

Issue protocol first published 2000/4

Review first published 2007/2

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Date of most recent SUBSTANTIVE amendment	09 February 2007
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Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	01 June 2006
Date authors' conclusions section amended	14 November 2006
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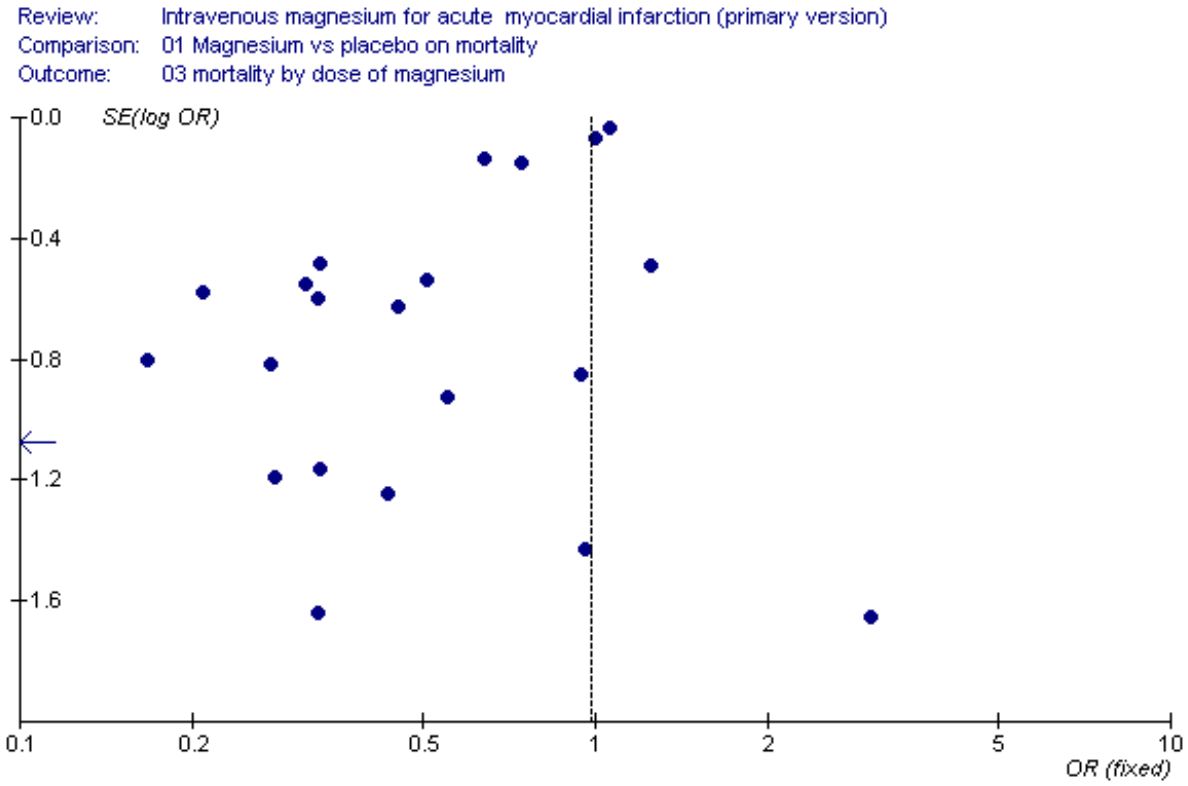
GRAPHS AND OTHER TABLES

Figure 01.



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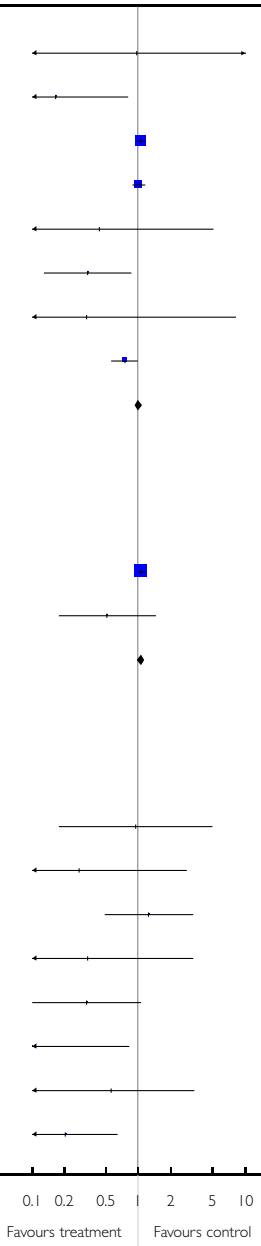
Analysis 01.01. Comparison 01 Magnesium vs placebo on mortality, Outcome 01 mortality by time of admission

Review: Intravenous magnesium for acute myocardial infarction

Comparison: 01 Magnesium vs placebo on mortality

Outcome: 01 mortality by time of admission

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 admission time <6 hrs					
Abraham 1987	1/48	1/46		0.0	0.96 [0.06, 15.77]
Gyamlani 2000	2/50	10/50		0.4	0.17 [0.03, 0.81]
ISIS-4 1995	928/11675	880/11648		29.9	1.06 [0.96, 1.16]
MAGIC 2000	475/3113	472/3100		14.8	1.00 [0.87, 1.15]
Morton 1984	1/40	2/36		0.1	0.44 [0.04, 5.02]
Raghu 1999	6/169	18/181		0.6	0.33 [0.13, 0.86]
Santoro 2000	0/75	1/75		0.1	0.33 [0.01, 8.20]
Woods 1992	90/1150	118/1150		4.0	0.74 [0.56, 0.99]
Subtotal (95% CI)	16320	16286		49.9	1.00 [0.93, 1.08]
Total events: 1503 (Treatment), 1502 (Control)					
Test for heterogeneity chi-square=16.41 df=7 p=0.02 I^2 =57.4%					
Test for overall effect z=0.05 p=1					
02 admission time >= 6 hrs					
ISIS-4 1995	1288/17333	1223/17390		41.7	1.06 [0.98, 1.15]
Singh 1990	6/81	11/81		0.4	0.51 [0.18, 1.45]
Subtotal (95% CI)	17414	17471		42.1	1.06 [0.97, 1.15]
Total events: 1294 (Treatment), 1234 (Control)					
Test for heterogeneity chi-square=1.88 df=1 p=0.17 I^2 =46.8%					
Test for overall effect z=1.32 p=0.2					
03 admission time not specified or mixture					
Bhargava 1995	3/40	3/38		0.1	0.95 [0.18, 5.00]
Ceremuzynski 1989	1/25	3/23		0.1	0.28 [0.03, 2.88]
Feldstedt 1991	10/150	8/148		0.3	1.25 [0.48, 3.26]
Nakashima 2004	1/89	3/91		0.1	0.33 [0.03, 3.27]
Rasmussen 1986	4/56	14/74		0.4	0.33 [0.10, 1.06]
Shechter 1990	1/50	9/53		0.3	0.10 [0.01, 0.82]
Shechter 1991	2/21	4/25		0.1	0.55 [0.09, 3.37]
Shechter 1995	4/96	17/98		0.6	0.21 [0.07, 0.64]



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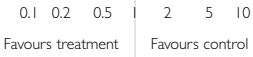
Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Smith 1986	2/92	7/93		0.3	0.27 [0.06, 1.35]
Thogersen 1995	4/130	8/122		0.3	0.45 [0.13, 1.54]
Urek 1996	1/31	0/30		0.0	3.00 [0.12, 76.58]
Wu 1992	5/125	12/102		0.5	0.31 [0.11, 0.92]
Zhu 2002	101/1691	134/1488		4.9	0.64 [0.49, 0.84]
Subtotal (95% CI)	2596	2385		8.0	0.55 [0.44, 0.69]
Total events: 139 (Treatment), 222 (Control)					
Test for heterogeneity chi-square=14.04 df=12 p=0.30 I^2 =14.5%					
Test for overall effect z=5.26 p<0.00001					
Total (95% CI)	36330	36142		100.0	0.99 [0.94, 1.04]
Total events: 2936 (Treatment), 2958 (Control)					
Test for heterogeneity chi-square=57.77 df=22 p=<0.0001 I^2 =61.9%					
Test for overall effect z=0.48 p=0.6					



Analysis 01.02. Comparison 01 Magnesium vs placebo on mortality, Outcome 02 mortality by use of thrombolytic therapy

Review: Intravenous magnesium for acute myocardial infarction

Comparison: 01 Magnesium vs placebo on mortality

Outcome: 02 mortality by use of thrombolytic therapy

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 with thrombolytic therapy					
ISIS-4 1995	1387/19937	1264/19763		44.2	1.09 [1.01, 1.18]
MAGIC 2000	175/958	161/961		4.9	1.11 [0.88, 1.41]
Raghu 1999	6/169	18/181		0.6	0.33 [0.13, 0.86]
Zhu 2002	50/809	59/668		2.3	0.68 [0.46, 1.01]
Subtotal (95% CI)	21873	21573		52.0	1.07 [0.99, 1.15]
Total events: 1618 (Treatment), 1502 (Control)					
Test for heterogeneity chi-square=11.36 df=3 p=0.010 I^2 =73.6%					
Test for overall effect z=1.78 p=0.08					
02 Without thrombolytic therapy					
Abraham 1987	1/48	1/46		0.0	0.96 [0.06, 15.77]

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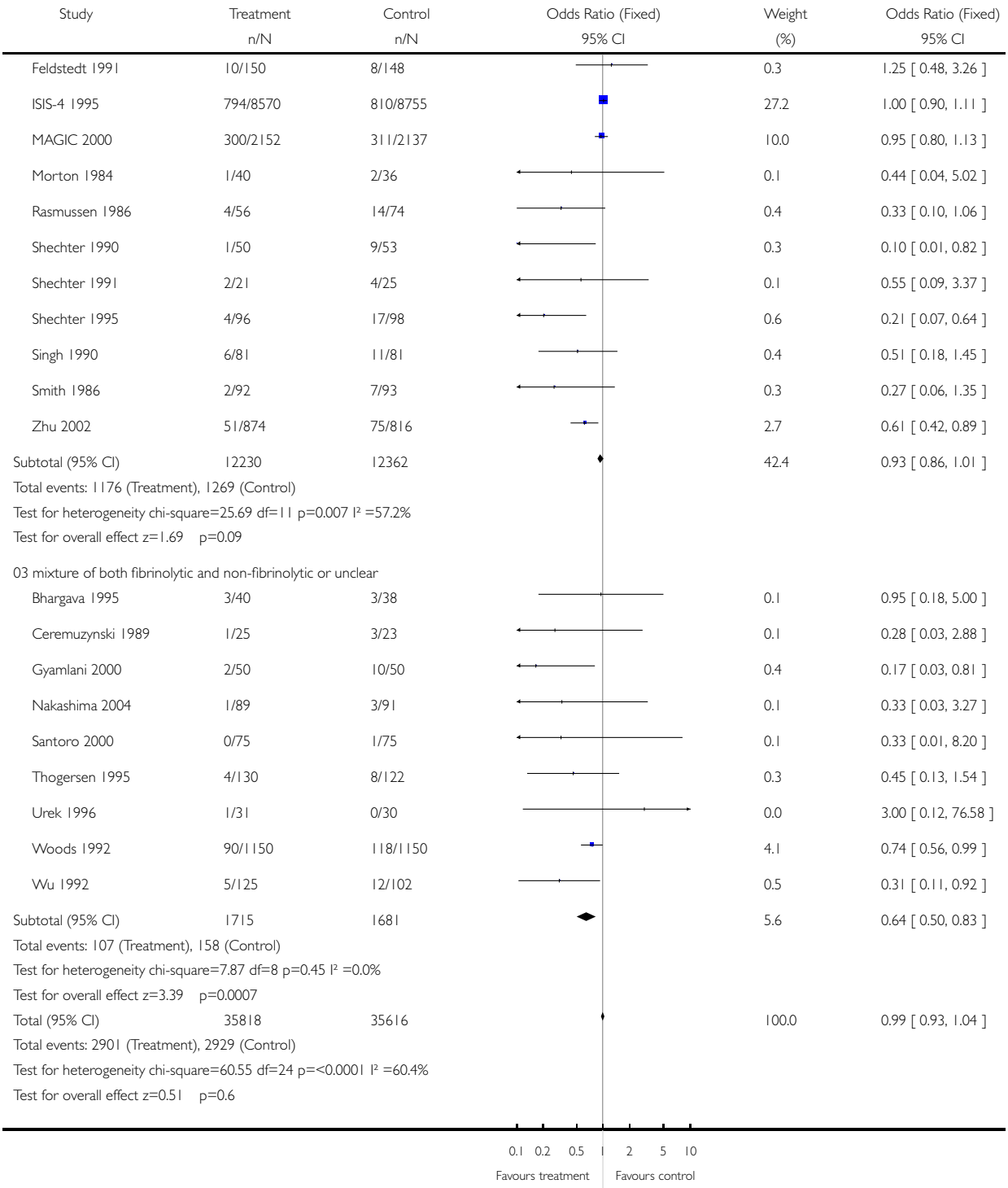

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Feldstedt 1991	10/150	8/148		0.3	1.25 [0.48, 3.26]
ISIS-4 1995	794/8570	810/8755		27.2	1.00 [0.90, 1.11]
MAGIC 2000	300/2152	311/2137		10.0	0.95 [0.80, 1.13]
Morton 1984	1/40	2/36		0.1	0.44 [0.04, 5.02]
Rasmussen 1986	4/56	14/74		0.4	0.33 [0.10, 1.06]
Shechter 1990	1/50	9/53		0.3	0.10 [0.01, 0.82]
Shechter 1991	2/21	4/25		0.1	0.55 [0.09, 3.37]
Shechter 1995	4/96	17/98		0.6	0.21 [0.07, 0.64]
Singh 1990	6/81	11/81		0.4	0.51 [0.18, 1.45]
Smith 1986	2/92	7/93		0.3	0.27 [0.06, 1.35]
Zhu 2002	51/874	75/816		2.7	0.61 [0.42, 0.89]
Subtotal (95% CI)	12230	12362		42.4	0.93 [0.86, 1.01]
Total events: 1176 (Treatment), 1269 (Control)					
Test for heterogeneity chi-square=25.69 df=11 p=0.007 I^2 =57.2%					
Test for overall effect z=1.69 p=0.09					
03 mixture of both fibrinolytic and non-fibrinolytic or unclear					
Bhargava 1995	3/40	3/38		0.1	0.95 [0.18, 5.00]
Ceremuzynski 1989	1/25	3/23		0.1	0.28 [0.03, 2.88]
Gyamlani 2000	2/50	10/50		0.4	0.17 [0.03, 0.81]
Nakashima 2004	1/89	3/91		0.1	0.33 [0.03, 3.27]
Santoro 2000	0/75	1/75		0.1	0.33 [0.01, 8.20]
Thogersen 1995	4/130	8/122		0.3	0.45 [0.13, 1.54]
Urek 1996	1/31	0/30		0.0	3.00 [0.12, 76.58]
Woods 1992	90/1150	118/1150		4.1	0.74 [0.56, 0.99]
Wu 1992	5/125	12/102		0.5	0.31 [0.11, 0.92]
Subtotal (95% CI)	1715	1681		5.6	0.64 [0.50, 0.83]
Total events: 107 (Treatment), 158 (Control)					
Test for heterogeneity chi-square=7.87 df=8 p=0.45 I^2 =0.0%					
Test for overall effect z=3.39 p=0.0007					
Total (95% CI)	35818	35616		100.0	0.99 [0.93, 1.04]
Total events: 2901 (Treatment), 2929 (Control)					
Test for heterogeneity chi-square=60.55 df=24 p=<0.0001 I^2 =60.4%					
Test for overall effect z=0.51 p=0.6					

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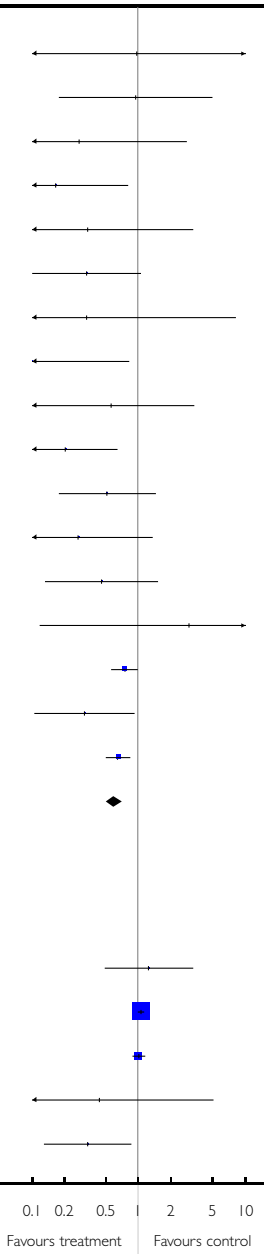
Analysis 01.03. Comparison 01 Magnesium vs placebo on mortality, Outcome 03 mortality by dose of magnesium

Review: Intravenous magnesium for acute myocardial infarction

Comparison: 01 Magnesium vs placebo on mortality

Outcome: 03 mortality by dose of magnesium

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 Mg dose <75 mmol					
Abraham 1987	1/48	1/46		0.0	0.96 [0.06, 15.77]
Bhargava 1995	3/40	3/38		0.1	0.95 [0.18, 5.00]
Ceremuzynski 1989	1/25	3/23		0.1	0.28 [0.03, 2.88]
Gyamlani 2000	2/50	10/50		0.4	0.17 [0.03, 0.81]
Nakashima 2004	1/89	3/91		0.1	0.33 [0.03, 3.27]
Rasmussen 1986	4/56	14/74		0.4	0.33 [0.10, 1.06]
Santoro 2000	0/75	1/75		0.1	0.33 [0.01, 8.20]
Shechter 1990	1/50	9/53		0.3	0.10 [0.01, 0.82]
Shechter 1991	2/21	4/25		0.1	0.55 [0.09, 3.37]
Shechter 1995	4/96	17/98		0.6	0.21 [0.07, 0.64]
Singh 1990	6/81	11/81		0.4	0.51 [0.18, 1.45]
Smith 1986	2/92	7/93		0.3	0.27 [0.06, 1.35]
Thogersen 1995	4/130	8/122		0.3	0.45 [0.13, 1.54]
Urek 1996	1/31	0/30		0.0	3.00 [0.12, 76.58]
Woods 1992	90/1150	118/1150		4.0	0.74 [0.56, 0.99]
Wu 1992	5/125	12/102		0.5	0.31 [0.11, 0.92]
Zhu 2002	101/1691	134/1488		4.9	0.64 [0.49, 0.84]
Subtotal (95% CI)	3850	3639		12.6	0.59 [0.49, 0.70]
Total events: 228 (Treatment), 355 (Control)					
Test for heterogeneity chi-square=16.97 df=16 p=0.39 I^2 =5.7%					
Test for overall effect z=6.03 p<0.00001					
02 Mg dose >= 75 mmol					
Feldstedt 1991	10/150	8/148		0.3	1.25 [0.48, 3.26]
ISIS-4 1995	2216/29011	2103/29039		71.6	1.06 [1.00, 1.13]
MAGIC 2000	475/3113	472/3100		14.8	1.00 [0.87, 1.15]
Morton 1984	1/40	2/36		0.1	0.44 [0.04, 5.02]
Raghu 1999	6/169	18/181		0.6	0.33 [0.13, 0.86]



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Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Subtotal (95% CI)	32483	32504		87.4	1.04 [0.99, 1.11]
Total events: 2708 (Treatment), 2603 (Control)					
Test for heterogeneity chi-square=6.72 df=4 p=0.15 I^2 =40.5%					
Test for overall effect z=1.52 p=0.1					
Total (95% CI)	36333	36143		100.0	0.99 [0.94, 1.04]
Total events: 2936 (Treatment), 2958 (Control)					
Test for heterogeneity chi-square=57.77 df=21 p=<0.0001 I^2 =63.6%					
Test for overall effect z=0.48 p=0.6					

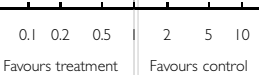
Analysis 02.01. Comparison 02 Magnesium vs placebo on morbidity, Outcome 01 Ventricular fibrillation

Review: Intravenous magnesium for acute myocardial infarction

Comparison: 02 Magnesium vs placebo on morbidity

Outcome: 01 Ventricular fibrillation

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Abraham 1987	0/48	2/46		0.2	0.18 [0.01, 3.93]
Bhargava 1995	2/40	3/38		0.3	0.61 [0.10, 3.89]
Ceremuzynski 1989	0/25	1/23		0.1	0.29 [0.01, 7.59]
Chen 1991	0/32	1/30		0.1	0.30 [0.01, 7.72]
Feldstedt 1991	2/150	3/148		0.3	0.65 [0.11, 3.97]
Gyamlani 2000	0/50	2/50		0.2	0.19 [0.01, 4.10]
ISIS-4 1995	992/29011	1087/29039		92.5	0.91 [0.83, 0.99]
Morton 1984	2/40	1/36		0.1	1.84 [0.16, 21.22]
Nakashima 2004	7/89	4/91		0.3	1.86 [0.52, 6.58]
Wu 1992	1/125	7/102		0.7	0.11 [0.01, 0.90]
Zhu 2002	34/1691	57/1488		5.2	0.52 [0.33, 0.79]
Total (95% CI)	31301	31091		100.0	0.88 [0.81, 0.96]
Total events: 1040 (Treatment), 1168 (Control)					
Test for heterogeneity chi-square=15.00 df=10 p=0.13 I^2 =33.3%					
Test for overall effect z=2.90 p=0.004					



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Analysis 02.02. Comparison 02 Magnesium vs placebo on morbidity, Outcome 02 Ventricular tachycardia

Review: Intravenous magnesium for acute myocardial infarction

Comparison: 02 Magnesium vs placebo on morbidity

Outcome: 02 Ventricular tachycardia

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Abraham 1987	3/48	7/46		7.9	0.37 [0.09, 1.53]
Bhargava 1995	13/40	26/38		21.3	0.22 [0.09, 0.58]
Ceremuzynski 1989	7/25	18/23		16.0	0.11 [0.03, 0.40]
Chen 1991	0/32	4/30		5.4	0.09 [0.00, 1.76]
Feldstedt 1991	1/150	0/148		0.6	2.98 [0.12, 73.74]
Gyamlani 2000	3/50	11/50		12.3	0.23 [0.06, 0.87]
Rasmussen 1986	7/56	10/74		8.9	0.91 [0.32, 2.57]
Santoro 2000	18/75	11/75		9.9	1.84 [0.80, 4.22]
Wu 1992	5/125	14/102		17.6	0.26 [0.09, 0.75]
Total (95% CI)	601	586		100.0	0.45 [0.31, 0.66]

Total events: 57 (Treatment), 101 (Control)

Test for heterogeneity chi-square=23.94 df=8 p=0.002 I^2 =66.6%

Test for overall effect z=4.14 p=0.00003

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Analysis 02.03. Comparison 02 Magnesium vs placebo on morbidity, Outcome 03 II-III heart block

Review: Intravenous magnesium for acute myocardial infarction

Comparison: 02 Magnesium vs placebo on morbidity

Outcome: 03 II-III heart block

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Feldstedt 1991	8/150	0/148		0.0	17.72 [1.01, 309.78]
ISIS-4 1995	1115/29011	1068/29039		90.8	1.05 [0.96, 1.14]
MAGIC 2000	63/3113	56/3100		4.9	1.12 [0.78, 1.61]
Parikka 1999	0/31	1/26		0.1	0.27 [0.01, 6.91]
Shechter 1990	7/50	12/53		0.9	0.56 [0.20, 1.55]
Shechter 1991	2/21	5/25		0.4	0.42 [0.07, 2.44]
Shechter 1995	10/96	15/98		1.2	0.64 [0.27, 1.51]
Urek 1996	1/31	1/30		0.1	0.97 [0.06, 16.19]
Woods 1992	25/1159	19/1157		1.6	1.32 [0.72, 2.41]
Total (95% CI)	33662	33676		100.0	1.05 [0.97, 1.14]

Total events: 1231 (Treatment), 1177 (Control)

Test for heterogeneity chi-square=8.89 df=8 p=0.35 I^2 =10.0%

Test for overall effect z=1.16 p=0.2

Analysis 02.04. Comparison 02 Magnesium vs placebo on morbidity, Outcome 04 Heart failure

Review: Intravenous magnesium for acute myocardial infarction

Comparison: 02 Magnesium vs placebo on morbidity

Outcome: 04 Heart failure

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Feldstedt 1991	7/150	5/148		0.1	1.40 [0.43, 4.51]
Gyamlani 2000	15/50	25/50		0.4	0.43 [0.19, 0.97]
ISIS-4 1995	5069/29011	4730/29039		84.5	1.09 [1.04, 1.14]
MAGIC 2000	597/3113	562/3100		9.9	1.07 [0.94, 1.22]
Morton 1984	14/40	5/36		0.1	3.34 [1.06, 10.51]
Nakashima 2004	18/89	28/91		0.5	0.57 [0.29, 1.13]
Parikka 1999	7/31	6/26		0.1	0.97 [0.28, 3.36]

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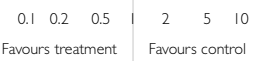
Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Rasmussen 1986	1/56	1/74		0.0	1.33 [0.08, 21.69]
Santoro 2000	6/75	5/75		0.1	1.22 [0.35, 4.18]
Shechter 1990	13/50	13/53		0.2	1.08 [0.44, 2.63]
Shechter 1991	6/21	10/25		0.1	0.60 [0.17, 2.07]
Shechter 1995	18/96	22/98		0.4	0.80 [0.40, 1.60]
Woods 1992	130/1159	172/1157		3.3	0.72 [0.57, 0.92]
Wu 1992	19/125	18/102		0.4	0.84 [0.41, 1.69]
Total (95% CI)	34066	34074		100.0	1.07 [1.03, 1.11]
Total events: 5920 (Treatment), 5602 (Control)					
Test for heterogeneity chi-square=24.56 df=13 p=0.03 I^2 =47.1%					
Test for overall effect z=3.25 p=0.001					



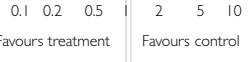
Analysis 02.05. Comparison 02 Magnesium vs placebo on morbidity, Outcome 05 Profound hypotension

Review: Intravenous magnesium for acute myocardial infarction

Comparison: 02 Magnesium vs placebo on morbidity

Outcome: 05 Profound hypotension

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Abraham 1987	1/48	2/46		0.1	0.47 [0.04, 5.35]
ISIS-4 1995	4781/29011	4300/29039		98.3	1.14 [1.09, 1.19]
Morton 1984	1/40	0/36		0.0	2.77 [0.11, 70.23]
Singh 1990	15/66	9/66		0.2	1.86 [0.75, 4.62]
Woods 1992	56/1159	56/1157		1.5	1.00 [0.68, 1.46]
Total (95% CI)	30324	30344		100.0	1.13 [1.09, 1.19]
Total events: 4854 (Treatment), 4367 (Control)					
Test for heterogeneity chi-square=2.38 df=4 p=0.67 I^2 =0.0%					
Test for overall effect z=5.56 p<0.00001					



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Analysis 02.06. Comparison 02 Magnesium vs placebo on morbidity, Outcome 06 Cardiogenic shock

Review: Intravenous magnesium for acute myocardial infarction

Comparison: 02 Magnesium vs placebo on morbidity

Outcome: 06 Cardiogenic shock

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Abraham 1987	1/48	1/46		0.1	0.96 [0.06, 15.77]
Bhargava 1995	0/40	1/38		0.1	0.31 [0.01, 7.81]
Ceremuzynski 1989	1/25	0/23		0.0	2.88 [0.11, 74.23]
Gyamlani 2000	2/50	5/50		0.4	0.38 [0.07, 2.03]
ISIS-4 1995	1306/29011	1173/29039		92.2	1.12 [1.03, 1.21]
Nakashima 2004	10/89	12/91		0.9	0.83 [0.34, 2.04]
Rasmussen 1986	0/56	7/74		0.5	0.08 [0.00, 1.43]
Shechter 1990	1/50	6/53		0.5	0.16 [0.02, 1.38]
Shechter 1991	1/21	4/25		0.3	0.26 [0.03, 2.55]
Shechter 1995	1/96	11/98		0.9	0.08 [0.01, 0.66]
Singh 1990	4/66	4/66		0.3	1.00 [0.24, 4.18]
Zhu 2002	33/1691	44/1488		3.8	0.65 [0.41, 1.03]
Total (95% CI)	31243	31091		100.0	1.07 [0.99, 1.16]

Total events: 1360 (Treatment), 1268 (Control)

Test for heterogeneity chi-square=21.80 df=11 p=0.03 I^2 =49.5%

Test for overall effect z=1.80 p=0.07

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Analysis 02.07. Comparison 02 Magnesium vs placebo on morbidity, Outcome 07 severe arrhythmia needing treatment

Review: Intravenous magnesium for acute myocardial infarction

Comparison: 02 Magnesium vs placebo on morbidity

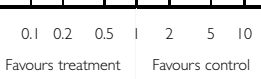
Outcome: 07 severe arrhythmia needing treatment

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Chen 1991	7/32	19/30		5.3	0.16 [0.05, 0.50]
MAGIC 2000	149/3113	147/3100		48.1	1.01 [0.80, 1.28]
Rasmussen 1986	12/56	14/74		3.3	1.17 [0.49, 2.77]
Shechter 1990	16/50	24/53		5.4	0.57 [0.25, 1.27]
Shechter 1991	8/21	14/25		2.7	0.48 [0.15, 1.58]
Shechter 1995	26/96	39/98		9.7	0.56 [0.31, 1.03]
Singh 1990	11/66	30/66		8.6	0.24 [0.11, 0.54]
Smith 1986	5/92	7/93		2.3	0.71 [0.22, 2.31]
Urek 1996	7/31	11/30		3.0	0.50 [0.16, 1.55]
Wu 1992	17/125	36/102		11.8	0.29 [0.15, 0.55]
Total (95% CI)	3682	3671		100.0	0.72 [0.60, 0.85]

Total events: 258 (Treatment), 341 (Control)

Test for heterogeneity chi-square=32.52 df=9 p=0.0002 I^2 =72.3%

Test for overall effect z=3.70 p=0.0002



Analysis 03.01. Comparison 03 Magnesium vs placebo on side effect, Outcome 01 Bradycardia

Review: Intravenous magnesium for acute myocardial infarction

Comparison: 03 Magnesium vs placebo on side effect

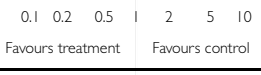
Outcome: 01 Bradycardia

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Bhargava 1995	2/40	1/38		0.4	1.95 [0.17, 22.40]
ISIS-4 1995	211/29011	133/29039		59.7	1.59 [1.28, 1.98]
Rasmussen 1986	2/56	6/74		2.3	0.42 [0.08, 2.16]
Woods 1992	125/1159	93/1157		37.6	1.38 [1.04, 1.83]
Total (95% CI)	30266	30308		100.0	1.49 [1.26, 1.77]

Total events: 340 (Treatment), 233 (Control)

Test for heterogeneity chi-square=2.97 df=3 p=0.40 I^2 =0.0%

Test for overall effect z=4.58 p<0.00001



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Analysis 03.02. Comparison 03 Magnesium vs placebo on side effect, Outcome 02 Flushing

Review: Intravenous magnesium for acute myocardial infarction

Comparison: 03 Magnesium vs placebo on side effect

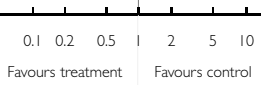
Outcome: 02 Flushing

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Abraham 1987	16/48	0/46		2.6	47.22 [2.73, 815.40]
Gyamlani 2000	5/50	0/50		3.4	12.21 [0.66, 226.97]
ISIS-4 1995	89/29011	12/29039		90.3	7.44 [4.07, 13.60]
Raghu 1999	152/169	0/181		0.4	3163.29 [188.67, 53035.96]
Santoro 2000	7/75	0/75		3.4	16.53 [0.93, 294.91]
Total (95% CI)	29353	29391		100.0	20.78 [12.90, 33.46]

Total events: 269 (Treatment), 12 (Control)

Test for heterogeneity chi-square=23.81 df=4 p=<0.0001 I^2 =83.2%

Test for overall effect z=12.48 p<0.00001



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