Effects of intravenous magnesium in suspected acute myocardial infarction: overview of randomised trials

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Abstract

Objective—**To investigate the effect of intravenous magnesium on mortality in suspected acute myocardial infarction.**

Design—**Systematic overview of all available randomised trials in which patients were allocated to receive either intravenous magnesium or otherwise similar treatment without magnesium.**

Setting—**Coronary care units of several hospitals.**

Patients—**1301 patients in seven randomised trials.**

Main outcome measure—**Short term mortality.**

Results—**Considering the seven trials collectively there were 25 (3·8%) deaths among 657 patients allocated to receive magnesium and 53 (8·2%) deaths among 644 patients allocated control, generally during hospital follow up. This represents a 55% reduction in the odds of death (p<0·001) with 95% confidence intervals ranging from about one third to about two thirds. 70 of 648 patients allocated magnesium compared with 109 of 641 controls had serious ventricular arrhythmias, suggesting that magnesium reduces the incidence, though the definition varied among trials. Other adverse effects were rare in the limited number of patients for whom this data were available.**

Conclusion—**Despite the limited number of patients randomised this overview suggests that intravenous magnesium therapy may reduce mortality in patients with acute myocardial infarction. Further large scale trials to confirm (or refute) these findings are desirable.**

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Introduction

The relevance of magnesium to both the incidence and the management of ischaemic heart disease is not well understood. Geographical comparisons of entire regions indicate that death rates from ischaemic heart disease tend to be higher where magnesium concentrations in soil and water are low,[1] and case-control studies indicate that magnesium concentrations tend to be lower, and calcium concentrations higher, in those who die of ischaemic heart disease than in those who die of other causes.[2]

Several actions of the magnesium ion could contribute towards some cardioprotective effects.[3] Low concentrations of magnesium in laboratory animals seem to potentiate catecholamine induced myocardial necrosis.[4] This may be partly due to the increased coronary artery tone and the increased response to vascoconstrictors (such as angiotensin, serotonin, noradrenaline, and potassium) that is associated with reduced extracellular magnesium concentrations.[5] Early after the onset of myocardial ischaemia, infusion of magnesium might limit the progression of ischaemic to infarcted myocardium and reduce the risk of arrhythmias being induced by raised local concentrations of catecholamines. Increasing serum magnesium concentrations might also limit damage by inhibiting calcium influx into myocardial cells[6,7] or by reducing peripheral resistance, or both.[8] The antiplatelet effects of magnesium[9] may also have a role in preventing propagation of coronary artery thrombus and reocclusion of the infarct related coronary artery after spontaneous or fibrinolytic induced recanalisation. It is not clear, however, that platelet function would be further inhibited by magnesium in the presence of aspirin, which is now routinely used in acute myocardial infarction.[10]

Magnesium has been shown to limit infarct size in dogs,[11] and infusions of magnesium have also been shown in animal studies to increase the threshold for electrical excitation of myocardial cells,[12] thereby reducing the likelihood that an injury current will create an abnormal focus of excitation near the ischaemic or infarcted tissue. Patients with low magnesium concentrations who have acute myocardial infarction or congestive heart failure more commonly have ventricular arrhythmias,[13,14] and magnesium seems to be effective in the treatment of torsades de pointes[15,16] and of some arrhythmias that are refractory to conventional antiarrhythmic treatment.[17] Magnesium infusions in acute myocardial infarction have therefore been suggested to prevent serious arrhythmias during the day or two after infarction, when serum magnesium concentrations tend to fall[18] and patients are at a particular risk of ventricular fibrillation.

The need for properly randomised evidence on whether arrhythmias and related mortality can be reduced by magnesium has been reinforced by recent doubts about the safety of some other antiarrhythmic drugs. In some countries (including the United States[19] but not Britain[10]) prophylactic lignocaine was commonly used in acute myocardial infarction to prevent ventricular arrhythmias. Recently, however, two independent overviews of the randomised trials involving over 9000 patients have indicated that prophylactic lignocaine may be associated with an increase in total mortality.[20,21] These concerns have been reinforced by the results of the cardiac arrhythmia suppression trial,[22] indicating increased mortality with the use of encainide and flecainide in patients with previous myocardial infarction. In addition, an overview of the trials of other class I antiarrhythmic agents shows no benefit when used routinely after myocardial infarction.[23] Future trials of antiarrhythmic drugs must determine clearly whether there are reductions not just in arrhythmias but in mortality.

The known contraindications to magnesium infusions are few and the treatment regimens are simple and apparently safe. Several randomised controlled trials of intravenous magnesium in suspected acute myocardial infarction have now been conducted.[24-34] We conducted an overview of their results. These trials have each included only a few dozen or a few hundred patients and their results are therefore subject to substantial chance fluctuations. However, when taken together more reliable conclusions (that are less subject to biases or to random errors) can be drawn.[35,36]

Methods

SELECTION OF TRIALS AND ACQUISITION OF DATA

We conducted a search to obtain data on mortality for all randomised patients in all completed, published or unpublished, unconfounded trials of intravenous magnesium in suspected acute myocardial infarction. We scanned the literature by formal computer aided searches, by examining the reference lists of relevant papers, and by asking other investigators about other published or unpublished trials. We excluded controlled trials in which investigators could determine the treatment allocation before deciding whether to enter the patients (for example, trials with allocation that was alternate or based on odds or even dates, or trials with retrospectively determined "historical" controls) even if they were described as randomised, as such methods may introduce bias into allocating treatment and so obscure or exaggerate treatment effects. When the data collected did not include mortality for some randomised patients (for example, patients excluded from analysis because of the failure to confirm the diagnosis of acute myocardial infarction), this information was sought by correspondence[34] with the investigators so that intention to treat analysis could be conducted.[26,29,31-34]

STATISTICAL METHODS

The statistical methods used to analyse the results from these trials have been described previously[37,38] and a detailed description of the relation between medical common sense and the principles and practice of trial overviews may be found in the recent report of the Early Breast Cancer Trialists' Collaborative Group.[39] The fundamental principle is that patients allocated to active treatment in one trial should be compared directly only with those allocated to control in the same trial and not with patients in any other trial. For each trial the number of events observed (O) in the treated group is contrasted with the number that would have been expected (E) if treatment had no effect. If treatment was beneficial the observed minus expected value would tend to be negative (and approximately equal to half the number of deaths prevented by treatment[38]). Although in any one trial this favourable tendency might be obscured by chance, it should stand out more clearly when the grand total of all the values from the individual trials is examined.

Formal statistical tests of whether treatment is without effect require calculation of z, the number of standard deviations by which the grand total of the observed minus expected values differs from zero and comparison of z with tables of the normal distribution (for example, $z=-1{\cdot}96$ suggests a two sided p value of about 0·05 in favour of treatment).

Assessment of treatment effects from the combined data assumes that information is available from all, or from an unbiased sample of all, randomised trials, without important bias due to the unavailability of data from unpromising trials or from patients withdrawn after randomisation. It does not, however, assume that the real effects of treatments are the same size in different trials, but merely that any real effects will tend to be in the same direction. An estimate of the "typical" ratio of the odds of dying among patients allocated magnesium with that among controls is given by the formula $e^{((O-E)/V)}$ with an approximate 95% confidence interval estimated by the formula $e^{((O-E)/V \pm 1{\cdot}96/SD)}$, where V is the variance and SD the square root of V.[38] Odds ratios less than 1·0 indicate protection.

Tests for heterogeneity of treatment effects between trials can be performed, but in practice such heterogeneity tests are of limited value, partly because they are so insensitive to any real differences that may exist but chiefly because some heterogeneity will almost

TABLE I—*Design of trials evaluating intravenous magnesium in suspected acute myocardial infarction*

Trial	Time treatment started	No of randomised patients: With follow up	No of randomised patients: Without follow up	Exclusion criteria
Morton *et al*[24-26]	<8 h after pain	76	5	>70 years; Killip class III-IV; 2nd-3rd degree atrioventricular block
Rasmussen *et al*[27,28]	<3 h after admission	270	3	Creatinine >300 μmol/l; 2nd-3rd degree atrioventricular block; insulin dependent diabetes
Smith *et al*[29]	<1 h after admission	400	0	Creatinine >300 μmol/l; 3rd degree atrioventricular block
Abraham *et al*[30]	Soon after admission	94	?Few without confirmed myocardial infarction	Systolic blood pressure ≤90 mm Hg; cardiac shock; advanced atrioventricular block
Feldstedt *et al*[31,32]	<8 h after pain	298	?2	Sinoatrial block, 2nd-3rd degree atrioventricular block; systolic blood pressure ≤80 mm Hg; creatinine >300 mmol/l; insulin dependent diabetes
Shechter *et al*[33]	Soon after admission	115	0	Cardiogenic shock; bundle branch block; advanced atrioventricular block
Ceremuzynski *et al*[34]	<12 h after pain	48	0	Pulmonary oedema; cardiogenic shock; systolic blood pressure ≤100 mm Hg; advanced atrioventricular block

All trials were double blind except that of Ceremuzynski *et al*, which was single blind.

TABLE II—*Trial treatments and serum magnesium concentrations*

					Mean (SE) serum magnesium (mmol)/l)			
					Before treatment		After treatment	
Trial	Magnesium salt	Total magnesium administered	Infusion rate	Duration of treatment (h)	Magnesium group	Control group	Magnesium group	Control group
Morton *et al*[24-26]	$MgSO_4$	1·125 mmol/kg (90 mmol/80 kg)	0·03125 mmol/kg/h (2·5 mmol/h/80 kg)	36	0·9†	0·8†	1·4‡	0·8†
Rasmussen *et al*[27,28]	$MgCl_2$	62 mmol	5·0 mmol/h for 6 hrs 1·1 mmol/h for 18 hrs 0·5 mmol/h for 24 hrs	48	0·75‡	0·77‡	1·23‡**	0·72‡
Smith *et al*[29]	$MgSO_4$	65 mmol	2·71 mmol/h	24	0·80 (0·01)§	0·80 (0·01)§	1·51 (0·03)§*	0·80 (0·01)§
Abraham *et al*[30]	$MgSO_4$	30 mmol	10 mmol over 20 min repeated on 3 days	48	0·92 (0·02)	0·91 (0·01)	1·07 (0·02)‖	0·90 (0·01)‖
Feldstedt *et al*[31,32]	$MgCl_2$	80 mmol	40 mmol for 8 h 40 mmol for 16 h	24		0·83¶	1·52-1·62††	0·81-0·84‡‡
Shechter *et al*[33]	$MgSO_4$	88 mmol	8·0 mmol/h for 3 h 1·9 mmol/h for 21 h 1·0 mmol/h for 24 h	48	NA	NA	NA	NA
Ceremuzynski *et al*[34]	$MgSO_4$	32 mmol	1·33 mmol/h	24	0·76 (0·03)	0·77 (0·03)	1·00 (0·03)	0·76 (0·04)

†Concentrations estimated from figures in published reports.
‡Concentrations reported only for the 130 with confirmed infarction. Ranges (mmol/l): before treatment 0·51-0·98; after 24 hours, magnesium group=0·77-2·27, control group=0·45-1·03.
§Concentrations reported only for the 185 with confirmed infarction.
‖Concentrations measured 2 h after giving the first 20 min magnesium or placebo injection.
¶Median concentrations for both groups.
††Median concentrations between 8 to 24 h after starting infusion.
‡‡Median concentrations during first three days.
*p<0·05; **p<0·001 for the comparison of before and after treatment serum magnesium concentrations.
NA=not available.

TABLE III—*Mortality in randomised trials of intravenous magnesium in suspected acute myocardial infarction*

Trial	Follow up duration	Basic data (No dead/No followed up) Magnesium group	Control group	Statistical calculations for magnesium group only: Observed minus expected deaths (O−E)	Variance of (O−E)	Significance
Morton *et al*[24-26]	Hospital	1/40	2/36	−0·6	0·7	NS
Rasmussen *et al*[27,28]	30 days	9/135	23/135	−7·0	7·1	<0·01
Smith *et al*[29]	24 h	2/200	7/200	−2·5	2·2	NS
Abraham *et al*[30]	Hospital	1/48	1/46	−0·0	0·5	NS
Feldstedt *et al*[31,32]	Hospital	10/150	8/148	+0·9	4·2	NS
Shechter *et al*[33]	Hospital	1/59	9/56	−4·1	2·3	<0·01
Ceremuzynski *et al*[34]	Hospital	1/25	3/23	−1·1	0·9	NS
Crude total		25/657 (3·8%)	53/644 (8·2%)	−14·4	18·0	<0·001

Typical odds ratio (95% confidence interval) 0·45 (0·28 to 0·71)

certainly exist no matter what a formal test for heterogeneity may indicate.[39]

Results

DESCRIPTION OF TRIALS

Seven randomised trials of the effects of intravenous magnesium in suspected acute myocardial infarction were identified, involving 1301 patients (table I). Six trials used double blind methods of randomisation,[24-33] one trial used a single blind method.[34] Detailed examination of baseline characteristics found no significant imbalance suggestive of biases in treatment allocation in any trial. No trial that claimed to be randomised was rejected.

Treatment was started soon after admission to hospital, generally within 12 hours of the onset of chest pain. Some studies included in their principal analyses only those patients in whom infarction was confirmed by electrocardiography or enzyme changes occurring after randomisation, but we obtained follow up data, at least on mortality, for 99·4% of all randomised patients (irrespective of whether or not infarction was confirmed) so that reasonably unbiased intention to treat analyses were possible. All studies excluded patients with advanced atrioventricular block. Additionally, in some studies, patients with elevated serum creatinine concentrations, hypotension (systolic blood pressure $\leq$80, $\leq$90, or $\leq$100 mm Hg), severe cardiac failure, cardiogenic shock, or age >70 years were excluded. In other studies, however, such exclusions were not considered necessary.

Magnesium sulphate was infused in five studies and magnesium chloride in the remaining two studies (table II). The total dose infused varied between 30 mmol and about 90 mmol of magnesium dissolved in as little as 100 ml and as much as 2000 ml of isotonic saline or 5% glucose, with dosage dependent on body weight in one study[24-26] and fixed in the other six. The duration of the infusions also varied, ranging from 24 to 48 hours, with 20 minute bolus injections given on three successive days instead of an infusion in one study.[30] All of the studies were placebo controlled.

Six of the seven trials provided some information on serum magnesium concentrations (table II). The mean pretreatment concentrations were 0·8-0·9 mmol/l and were similar among patients allocated magnesium and those allocated placebo. After randomisation the mean serum concentrations differed by about 0·5 (range 0·2 to 0·7) mmol/l between treatment and control groups. This difference was largely or wholly due to an increase in serum magnesium in the treatment group, as there was little change among the controls.

OVERALL EFFECT ON MORTALITY

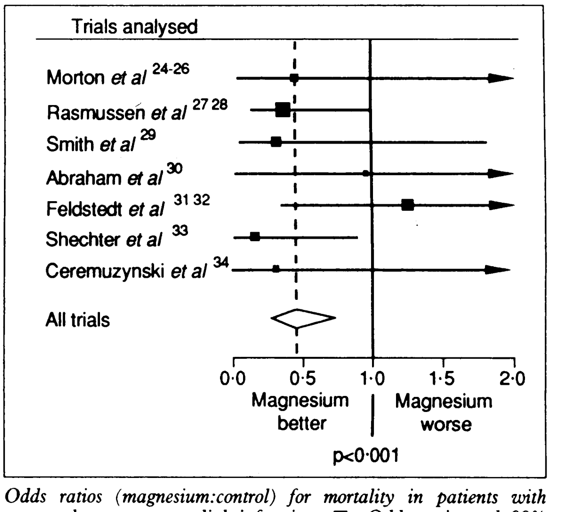
In general, data on mortality were available for almost all randomised patients until they were discharged from hospital. In one study,[29] however, only those deaths occurring during the first 24 hours after randomisation were available despite correspondence with the investigators, while in another study "short-term" follow up included all deaths in the first month.[27,28] In six of the seven studies mortality was lower in the magnesium treated group than in the control group, and these differences were significant ($p<0·01$) in two of these studies (table III).[27,28,33] Overall, the difference in mortality between the 657 patients allocated magnesium and the 644 controls was highly significant: 25 deaths (3·8%) versus 53 deaths (8·2%), $p<0·001$. Typically in these trials the odds of death was reduced by about one half, with 95% confidence intervals for this difference running from about one third to about two thirds (figure). A test for heterogeneity between the various trial results was not significant ($\chi^2=7·6$, df=6, $p>0·1$). The study by Rasmussen *et al*[27,28] contributes substantially to the effect on mortality, but the apparent reductions in mortality in this trial (63% (SD 24); $p<0·01$) and in all other trials combined (49% (22); $p=0·03$) are both significantly different from zero and are not significantly different from each other.

After correspondence with the investigators early mortality data were unavailable for eight patients from two trials, who were not followed up because infarction was not confirmed. Such patients generally have a low mortality so their exclusion is not likely to have biased our results. Furthermore, consideration of those trials in which all patients were followed up produces similar results (49% (23) reduction in odds; $p<0·03$) to those seen overall. Separate analysis of the six trials that were double blind also indicates a reduction in mortality similar to the overall results (64% (17) reduction in odds, $z=3·2$, $p<0·001$).

Data on longer term mortality are available from only two studies. One year mortality in the study by Rasmussen *et al* was 20% in the magnesium group compared with 32% in the placebo group ($p<0·02$).[27,28] In that study the difference in mortality developed during the first month (7% *v* 17%, $p<0·01$), with little further divergence during the remainder of the first year (15% *v* 18%; NS). In the other study that provides data on deaths after discharge no difference in mortality was observed either early or late, with 22 deaths among patients allocated magnesium and 24 among the controls after a median follow up of about 8 months.[31,32]

SERIOUS MORBIDITY AND POSSIBLE ADVERSE EFFECTS

Information on the development of serious ventricu-



Odds ratios (magnesium:control) for mortality in patients with suspected acute myocardial infarction. ■=*Odds ratio and 99% confidence interval (areas of the squares are proportional to amount of information contributed by trial),* ◇=*95% confidence interval for the overview. Vertical solid line denotes no difference in mortality between treatment and control, while the vertical broken line denotes a 55% reduction in the odds of death* lar arrhythmias was available for all trials (table IV). Ventricular arrhythmias were less common in the magnesium group than in the control group in six of the seven studies, and the difference was significant in two. When all the available information on serious arrhythmias was considered together, there was a significantly lower incidence ($p<0\cdot001$) among patients allocated magnesium. The definitions of serious arrhythmias differed among the trials, so some potential for bias exists in the assessment of the effects of magnesium as the type of arrhythmia chosen for emphasis in the trial might have been influenced by the observed results. Limitation of infarct size was studied systematically in only one study,[24-26] where infarct size (as estimated by concentrations of the MB isomer of creatine kinase) was smaller, though not significantly so, in the magnesium group. Another study found that fewer patients allocated magnesium had infarction confirmed,[27 28] but this difference was only marginally significant ($p=0\cdot04$) and was not supported by the available data from other trials.

Possible serious adverse effects of magnesium, such as conduction disturbances or heart failure, were not always systematically looked for. Data on the development of heart failure were available from five of the seven trials (table V). However, the definitions used in the trials varied and the numbers of events were small. Although there were no apparent increases (or decreases) among patients allocated magnesium compared with controls, the data are too limited and too incomplete to do more than suggest that magnesium is not associated with any large excesses. Intravenous magnesium produced flushing in some patients,[30] and hypotension was reported,[30] but these effects rarely (if ever) required discontinuation of the magnesium infusion.

Discussion

This overview of seven randomised controlled trials of intravenous magnesium in 1301 patients with suspected acute myocardial infarction indicates that, in patients at relatively high risk, treatment reduces mortality during the first few weeks by between one third and two thirds. If real, this is a substantial benefit as intravenous magnesium is likely to be suitable for almost all patients with suspected myocardial infarction, the drug costs are small, there are few contraindications, and serious side effects are rare. Magnesium could be used widely not only in developed countries but in countries with limited medical resources. Even if magnesium infusions could reduce mortality by only one quarter (that is, somewhat less than is suggested even by the lower limit of the 95% confidence interval for this overview) this would be of considerable public health importance worldwide, avoiding tens of thousands of deaths annually.

The general judgment that underlies this approach to the trials of intravenous magnesium is that, although different infusion regimens or different recognisable categories of patient in these trials may have different sized risk reductions, it is less likely that the direction of any effects will be different. This means that an overview of their findings makes good medical sense. (It also makes good statistical sense as biases due to selective emphasis on particular studies need to be avoided.) Even collectively, the total number of deaths available for inclusion in the overview was small (25 in the magnesium group *v* 53 in the control group) so withdrawal of some randomised patients or unavailability of trials with less favourable results could, in principle, change the results. For short term mortality such biases are likely to be only small as the net effect is large (over three standard deviations); mortality by allocated treatment is available for almost all randomised patients (although it is not clear whether the reported durations of follow up in the trials were prospectively determined or were influenced by the results); and few, if any, completed trials of substantial size are likely to have been overlooked.

For the effects of treatment of serious ventricular arrhythmias, although some data are available on almost all patients and the apparent risk reduction is large, the decision about what type of arrhythmias to

TABLE IV—*Arrhythmias in randomised trials of intravenous magnesium in suspected acute myocardial infarction*

Trial	Type of arrhythmia	Follow up duration	Basic data (No dead/No followed up): Magnesium group	Control group	Statistical calculations for magnesium group only: Observed minus expected deaths (O−E)	Variance of (O−E)	Significance
Morton *et al*[24-26]	Ventricular fibrillation	Hospital	2/40	1/36	0·4	0·7	NS
Rasmussen *et al*[27 28]	Arrhythmias requiring treatment	7 days	22/135	36/135	−7·0	11·4	<0·05
Smith *et al*[29]	Ventricular arrhythmias requiring treatment	24 h	5/200	9/200	−2·0	3·4	NS
Abraham *et al*[30]	Serious arrhythmias	Hospital	7/48	16/46	−4·7	4·4	NS
Feldstedt *et al*[31 32]	Fatal arrhythmias	Hospital	2/150	3/148	−0·5	1·2	NS
Shechter *et al*[33]	Major arrhythmias	Hospital	16/50	24/53	−3·4	6·2	NS
Ceremuzynski *et al*[34]	Ventricular arrhythmias	Hospital	16/25	20/23	−2·8	2·3	NS
Crude total			70/648 (10·8%)	109/641 (17·0%)	−20·0	29·6	<0·001
Typical odds ratio (95% confidence interval) 0·51 (0·36 to 0·73)							

TABLE V—*Cardiac failure in randomised trials of intravenous magnesium in suspected acute myocardial infarction*

Trial	Definition of cardiac failure	Follow up duration	Basic data (No dead/No followed up): Magnesium group	Control group	Statistical calculations for magnesium group only: Observed minus expected deaths (O−E)	Variance of (O−E)	Significance
Morton *et al*[24-26]	Killip class III (pulmonary oedema)	48 h	1/40	2/36	−0·6	0·7	NS
Rasmussen *et al*[27 28]	Fatal cardiac failure	4 weeks	1/56	8/74	−2·9	2·1	<0·05
Smith *et al*[29]	NA	24 h	NA	NA	NA	NA	
Abraham *et al*[30]	Cardiogenic shock	Hospital	1/48	2/46	−0·5	0·7	NS
Feldstedt *et al*[31 32]	Fatal cardiac failure	Hospital	7/150	5/148	+1·0	2·9	NS
Shechter *et al*[33]	Clinical cardiac failure	Hospital	13/50	15/53	−0·6	5·1	NS
Ceremuzynski *et al*[34]	NA	Hospital	NA	NA	NA	NA	
Crude total			23/344 (6·7%)	32/357 (9·0%)	−3·6	11·5	>0·05
Typical odds ratio (95% confidence interval) 0·73 (0·41 to 1·30)							

NA=Not available.

emphasise in the trials might have been influenced by the observed pattern of results. Substantial biases in our arrhythmia analyses cannot, therefore, be ruled out. Bias is more likely for other measures of serious morbidity as such events were not prospectively defined and were not generally available either from the published reports or even, by correspondence, from the investigators.

IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

Our study provides strong evidence that intravenous magnesium may have a beneficial effect on mortality. The mortality results of most of the seven small trials, included in the overview are not separately persuasive although the results on arrythmias are more conclusive.[27-34] In the absence of data from large trials of intravenous magnesium, however, it may be most prudent to be guided by our overall results rather than by undue emphasis on any of the small studies. Larger trials are being conducted (the second Leicester intravenous magnesium intervention trial: LIMIT-2[40]) and planned (ISIS-4), and these should help to determine the safety and efficacy of adding intravenous magnesium to current regimens including other effective treatments such as intravenous β blockers,[41] intravenous fibrinolytic treatment,[42] and oral antiplatelet treatment.[42] Some smaller studies are also needed to investigate the mechanisms by which magnesium may exert any beneficial effects and to help devise simple but effective magnesium regimens that could have widespread applicability.

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