Results from the Magnesium in Coronaries Trial

Presented at the European Society of Cardiology Congress
August 31–September 4, 2002, Berlin, Germany

[*Rev Cardiovasc Med.* 2003;4(4):250-254]

Key words: Myocardial infarction • Reperfusion • Magnesium • MAGIC Trial • LIMIT-2 Trial • ISIS-4 Trial

Between 1989 and 1996, 13 clinical trials involving approximately 6300 patients provided discordant results regarding the benefit of magnesium in patients with acute evolving myocardial infarction.[1–3] The smallest and earliest trials demonstrated an overall benefit, as did the Leicester Intravenous Magnesium Intervention (LIMIT-2) Trial of 2316 patients, results of which were published in 1992.2 Nonetheless, the largest trial to date, ISIS-4 (International Studies of Infarct Survival), involving 58,050 patients, was entirely negative. The Magnesium in Coronaries (MAGIC) Trial, under the auspices of the National Heart, Lung, and Blood Institute, was initiated in an attempt to resolve this controversy. Dr. Elliot Antman presented the results of the MAGIC trial at the 2002 Congress of the European Society of Cardiology in Berlin, and the results have been published.

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The MAGIC Trial

MAGIC was a double-blind, randomized, placebo-controlled trial of 6213 high-risk patients with ST-segment elevation acute myocardial infarction (STEMI). Patients were enrolled at 278 sites in 14 countries worldwide between April 1999 and March 2002. High-risk patients were defined as those older than 65 years who were eligible for reperfusion therapy (stratum 1), or patients who, despite STEMI, were considered ineligible for reperfusion therapy, irrespective of age (stratum 2). The primary endpoint was 30-day mortality. Therapy consisted of a 2 g, intravenous bolus of magnesium followed by 17 g, 24-hour infusion. Treatment was initiated a mean of 3.8 hours after symptom onset and continued for 24 hours in 91% of

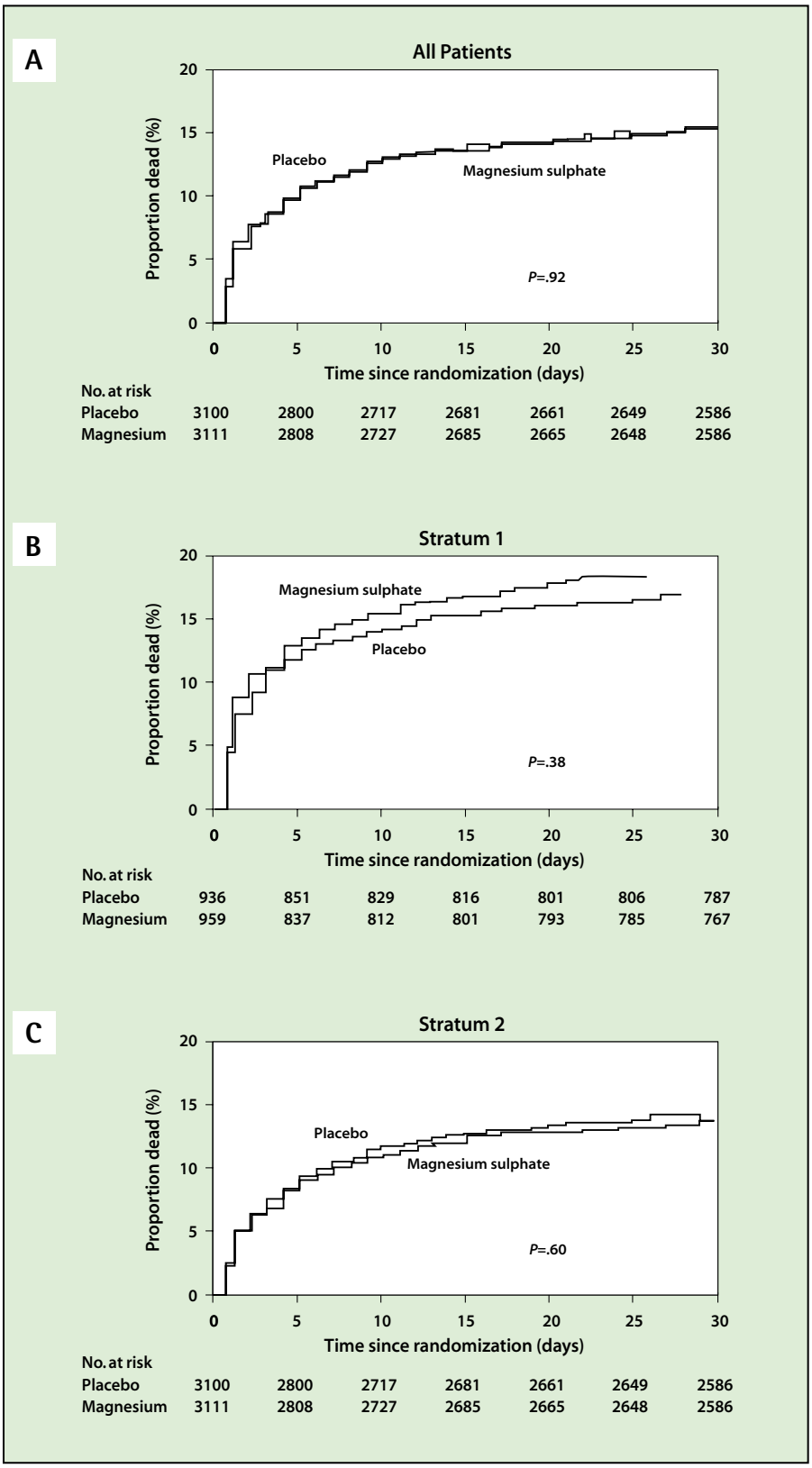

Figure 1. *Kaplan-Meier Curves for mortality in the MAGIC Trial. Survival is almost identical in the trial overall* **(A)** *and when patients were categorized by entry criteria (strata 1 and 2)* **(B, C).** *Other extensive subgroup analyses also did not demonstrate any significant differences. Reproduced with permission from Antman.*[4]

patients, and in 96% the study drug was administered either before or concomitant with the administration of a thrombolytic agent (this was an area of some controversy in the ISIS-4 Trial—see discussion section below. 3113 patients were randomized to the magnesium arm and 3100 to placebo.

Baseline variables were evenly distributed between magnesium and placebo patients. By design, this was a high-risk group of patients, with a median age of 70 years; 45% were female, 56% had anterior myocardial infarctions, and pulmonary congestion at presentation was noted in 12%. This distribution of higher-risk variables is not often seen in trials of thrombolytic therapy. The most widely used thrombolytic agent was streptokinase.

Results

The trial was conclusively negative, with an almost identical survival rate of 85% between groups on an intention-to-treat analysis (Figure 1). Within the two major subgroups (strata 1 and 2), there was again no difference between magnesium and placebo, and this also applied to prespecified subgroup analyses according to time to treatment (≥3 hours vs <3 hours), prior myocardial infarction, diabetes, region of the world, gender, and associated drug therapy. In regard to secondary endpoints, including therapy for congestive heart failure, defibrillation for ventricular fibrillation or sustained ventricular tachycardia, and the need for a temporary pacemaker, there were again no differences.

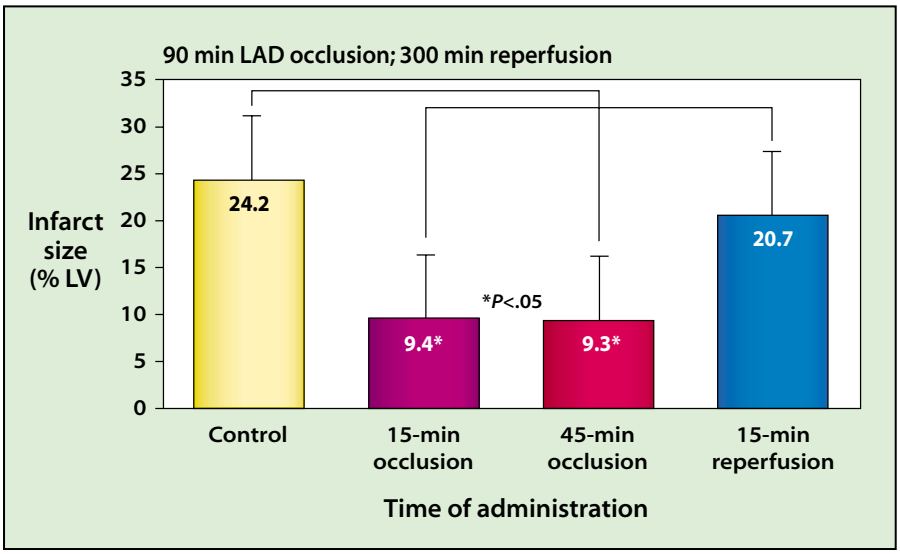

Figure 2. *The effect of the timing of magnesium administration in relationship to the onset of reperfusion in an experimental (canine) model of occlusion and reperfusion. In this model, magnesium was effective in reducing infarct size, but only when given prior to reperfusion. LAD, left anterior descending coronary artery; LV, left ventricle. Data from Christensen et al.*[13]

The conclusions were decisive, and led to the recommendation that there is no indication for the routine administration of this drug. Because there did not appear to be any harm from magnesium use, its administration for electrolyte depletion may be continued.

Discussion

In the case of MAGIC, a long-standing controversy has been resolved by a conclusively negative trial. The use of magnesium in myocardial infarction is certainly an issue that has deserved the extensive investigation it has received. First, the drug is very inexpensive (approximately U.S. $5.00 per dose), it is relatively nontoxic, easily administered, and widely available. These considerations aside, magnesium appeared to be an attractive adjunctive therapy in acute myocardial infarction, based on animal studies that implied a number of beneficial physiologic effects, in addition to prior evidence from some trials, which pointed in a hopeful direction.

Physiologic Actions of Magnesium

From a theoretical and experimental perspective, there are many plausible explanations for a potential benefit from magnesium therapy in patients with myocardial infarction.[5–7] Magnesium is an important component or cofactor in multiple intracellular enzymatic processes that are related to mitochondrial function, energy production, cell volume control, and ionic gradients across the sarcolemma. It has previously been shown that magnesium deficiency has adverse cardiovascular consequences.[7] The adverse effects of magnesium deficiency are: many involving the myocardium, increased atherogenesis, increased platelet aggregation, increased coronary and system vascular resistance, and repolarization abnormalities leading to an arrhythmogenic substrate.[5,6,8,9]

Magnesium has effects on myocardium, the vascular endothelium, and platelets. At a myocardial level, magnesium has been shown to inhibit the deleterious effects of calcium flux; it reduces vulnerability to free oxygen radicals, and may also reduce myocardial oxygen demand. It acts as a coronary and systemic vasodilator and may promote collateral formation. In vitro, magnesium inhibits platelet aggregations.

The proposed benefits of magnesium in the setting of reperfusion therapy are multifactorial, but one concept of "reperfusion injury" is that injured myocytes lose their ability to regulate cell volume, and this leads to a decrease in cytosolic magnesium levels and an increase in cytosolic calcium levels. The combination could lead to irreversible mitochondrial damage.[10]

In animal studies of the experimental model of occlusion and reperfusion, magnesium has been shown to reduce infarct size, but it would appear that the drug must be administered prior to or immediately at the onset of reperfusion for this to be effective (Figure 2).[10–13] This has been a contentious issue in regard to the interpretation of clinical trials (see below). In the isolated rat heart, the inhibitory effects of magnesium on calcium flux have been shown to attenuate subsequent postischemic myocardial stunning.[11] In addition, in magnesium-depleted dogs, infarct size was significantly increased.[14]

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Clinical Trials

A meta-analysis of seven randomized,

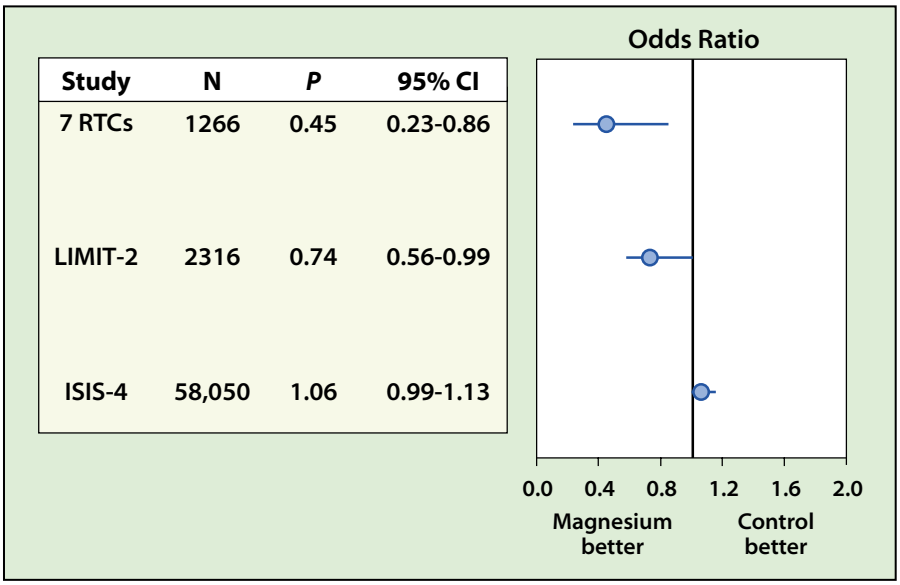


Figure 3. *Meta-analysis of the results of randomized, controlled trials (RCTs) of magnesium therapy and acute myocardial infarction prior to the results of the MAGIC Trial. LIMIT-2, Leicester Intravenous Magnesium Intervention; ISIS-4, International Studies of Infarct Survival; CI, confidence interval. Data from Teo and Yusuf[9] and Shechter et al.[18]*

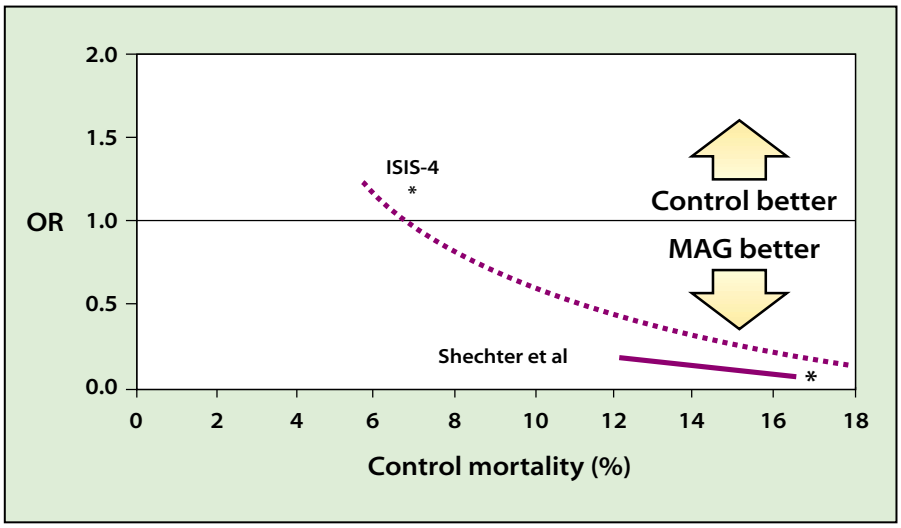
placebo-controlled trials performed between 1980 and 1990, comprising a total of 1266 patients, demonstrated a mortality reduction of approximately 45% in magnesium-treated patients (Figure 3). In 6 of the 7 trials, a trend toward a lower mortality was noted.[2,15,16] These trials took place before the widespread introduction of reperfusion therapy. The LIMIT-2 Trial of 2316 patients, published in 1992, in which 30% of patients were receiving thrombolytic therapy, demonstrated a 24% reduction in mortality, which was statistically significant but with wide confidence intervals.[2] The largest trial, ISIS-4 (58,050 patients), showed no benefit from magnesium, and a nonsignificant trend in the reverse direction was present (Figure 3).[3]

A subsequent meta-analysis by Antman suggested that the benefits of magnesium were confined to higher-risk patients, with a controlled (placebo) group mortality of 15.2%, and suggested that the lower risk of patients in ISIS-4 may have contributed to a lack of benefit in that trial (Figure 4).[17] In this respect, a small trial from Israel in high-risk patients demonstrated a very large mortality reduction with magnesium.[18]

Explanations for the lack of effect in ISIS-4 centered around the low mortality in the control group and uncertainty as to the timing of magnesium as related to the timing of administration of reperfusion therapy.[8] In ISIS-4, patients were randomized a median of 8 hours after the onset of chest pain, but the protocol specified that thrombolytics be administered prior to magnesium, and the time window for the infusion of magnesium was 24 hours. Moreover, the precise time from randomization to the administration of lytics and magnesium was not recorded. For these reasons it was thought that the issue of magnesium administration, particularly in patients receiving reperfusion therapy, had not been conclusively resolved.

Moreover, because the trials demonstrating the apparent benefits of magnesium therapy took place 10–20 years ago, there was also the strong possibility that the protective

Figure 4. *Illustration of the benefit, or lack thereof, from magnesium (MAG) according to the mortality in the placebo or control arm of the randomized trial. As the mortality in the control group exceeds approximately 8%, there appears to be a benefit from magnesium. The control-group mortality in ISIS-4 and the Israeli trial of Shechter et al[18] are superimposed on the figure. These data point to the fact that it might be very difficult to detect an additional mortality-reducing effect from magnesium when the mortality in the control population is low. Data from Antman.[17]*



effects of magnesium noted in earlier studies could be negated by the more powerful actions of current myocardial infarction therapy. In other words, benefits noted earlier may well have been real but may subsequently have been overpowered by overlapping benefits from current treatments used in acute myocardial infarction.[1]

So, the stage was set for a final, definitive trial of magnesium in high-risk patients. It was thought that we should not discard an inexpensive, potentially beneficial drug without unambiguous demonstration of its efficacy or lack thereof. MAGIC has brought this era to a decisive conclusion, and in conjunction with the ISIS-4 Trial it has determined that there is no indication for the routine administration of magnesium in acute myocardial infarction. Given the low cost of the drug, it is a pity that it does not work as we might have hoped, but this is another demonstration of the value of evidence-based medicine. If magnesium was going to be shown to be effective, it certainly would have been most likely in higher-risk populations, and MAGIC certainly put this to the test.

There is another inexpensive therapy that shows promise, namely, glucose, insulin, and potassium (GIK). This combination of agents was first used more than 40 years ago, and preliminary trials have been promising.[19] More definitive data again must await the evidence from large, ongoing, randomized, controlled trials. ■

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Main Points

- Previous trials of magnesium in patients with acute evolving myocardial infarction have provided inconsistent results: the LIMIT-2 Trial demonstrated an overall benefit, but the ISIS-4 Trial was entirely negative. The Magnesium in Coronaries (MAGIC) Trial was initiated in an attempt to resolve this controversy.
- MAGIC was a double-blind, randomized, placebo-controlled trial of 6213 high-risk patients with ST-segment elevation acute myocardial infarction. Therapy consisted of an intravenous bolus of magnesium followed by 24-hour infusion. The primary endpoint was 30-day mortality.
- The results from MAGIC were conclusively negative, with an almost identical survival rate of 85% between groups on an intention-to-treat analysis. This held true for all subgroup analyses and also in regard to secondary endpoints.
- In the case of MAGIC, a long-standing controversy has been resolved by a conclusively negative trial. Data from the trial led to the recommendation that there is no indication for the routine administration of magnesium in myocardial infarction.