

# Does Magnesium Have a Role in the Treatment of Patients with Coronary Artery Disease?

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## Abstract

Hypomagnesemia is common in hospitalized patients, especially in elderly patients with coronary artery disease (CAD) and/or those with chronic heart failure. Hypomagnesemia is associated with increased all cause mortality and mortality from CAD. Magnesium supplementation improves myocardial metabolism, inhibits calcium accumulation and myocardial cell death; it improves vascular tone, peripheral vascular resistance, afterload and cardiac output, reduces cardiac arrhythmias and improves lipid metabolism. Magnesium also reduces vulnerability to oxygen-derived free radicals, improves endothelial function and inhibits platelet function, including platelet aggregation and adhesion, which potentially confers upon magnesium physiologic and natural effects similar to adenosine-diphosphate inhibitors such as clopidogrel. However, data regarding the use of magnesium in patients with acute myocardial infarction (AMI) are conflicting. Although some previous relatively small randomized clinical trials demonstrated a remarkable reduction in mortality when intravenous magnesium was administered to relatively high risk AMI patients, two recently published large-scale randomized clinical trials (the Fourth International Study of Infarct Survival [ISIS 4] and Magnesium in Coronaries [MAGIC]) were unable to demonstrate any advantage of intravenous magnesium over placebo. Nevertheless, the theoretical benefits of magnesium supplementation as a cardio-protective agent in CAD patients, promising results from animal and human studies, its relatively low-cost and ease of handling requiring no special expertise, together with its excellent tolerability, gives magnesium a place in treating CAD patients, especially in those at high risk, such as CAD patients with heart failure, the elderly and hospitalized patients with hypomagnesemia. Furthermore, magnesium therapy is indicated in life-threatening ventricular arrhythmias such as torsades de pointes and intractable ventricular tachycardia.

The prevalence of hypomagnesemia in hospitalized patients ranges from 8–30%.<sup>[1]</sup> Elderly patients, particularly those with coronary artery disease (CAD) and/or chronic heart failure (CHF), can have low body magnesium levels, the mechanisms of which are likely to be multi-factorial. Evidence suggests that the occidental ‘American-type diet’ is relatively deficient in magnesium,<sup>[2,3]</sup> while the ‘oriental diet’, characterized by a greater intake of fruits and vegetables, is richer in magnesium.<sup>[4]</sup> It has also been observed that patients with CAD absorb more magnesium during magnesium loading tests than those without CAD, suggesting that CAD is associated with excessive magnesium loss and a relative magnesium-deficient state.<sup>[5]</sup>

Epidemiologic evidence linking magnesium deficiency to CAD has been investigated for more than 3 decades.<sup>[6-10]</sup> In the Atherosclerosis Risk in Communities (ARIC) Study,<sup>[11]</sup> the relationship

between serum and dietary magnesium and CAD incidence over 4–7 years of follow-up was examined in a sample of 13 922 middle-aged adults free of CAD at baseline from four US communities. After adjustment for traditional risk factors, the relative risk of CAD across quartiles of serum magnesium levels was 1.00, 0.92, 0.48, and 0.44 ( $p$  for trend = 0.009), suggesting that low serum magnesium levels may be involved in the pathogenesis of CAD.<sup>[11]</sup> The National Health and Nutrition Examination Survey Epidemiologic Follow-up Study also demonstrated that serum magnesium levels were inversely associated with mortality from ischemic heart disease and all-cause mortality.<sup>[12]</sup>

Since the advent of thrombolytic therapy the in-hospital mortality of patients with acute myocardial infarction (AMI) has been reduced from 14–16% to 6–8%.<sup>[13]</sup> Nevertheless, it is estimated that only 15–22% of patients with AMI in the US and 35% in

Israel receive thrombolytic therapy.<sup>[14]</sup> Approximately two-thirds of patients with AMI still not being treated with thrombolytic agents for a variety of reasons, have a high in-hospital mortality rate (14–20%), which is particularly prevalent in the elderly.<sup>[15]</sup>

In the Second Prevention Reinfarction Israeli Nifedipine Trial (SPRINT-2), performed before the thrombolytic era, 11% of the patients (653 of 5839) were >75 years of age and their in-hospital mortality rate was 36%.<sup>[16]</sup> In the early 1990s Behar et al.<sup>[15]</sup> found that in Israel, only 18% of patients with AMI aged >75 years received thrombolysis and in-hospital mortality in this subset was 9% compared with 33% in elderly patients who did not receive thrombolysis. Age has been increasingly recognized as a critical determinant of outcome in patients with AMI. The relationship is relatively flat until 60 years of age, when the risk of death increases dramatically.<sup>[17]</sup> Morbidity and mortality from thrombolytic therapy, particularly resulting from intracranial hemorrhage is higher in this subset of elderly patients.<sup>[18]</sup> Montague et al.<sup>[19]</sup> found that 4% of patients with AMI aged  $\geq 70$  years received thrombolysis, and the in-hospital mortality among them was 27%. Maggioni et al.<sup>[20]</sup> recently demonstrated that in-hospital mortality in patients who presented with a first AMI, and were eligible for thrombolytic therapy, was much higher in those aged >70 years compared with younger patients (19% vs 2.8%). Elderly patients with AMI are also at higher risk for mechanical revascularization (percutaneous transluminal coronary angioplasty and coronary artery bypass surgery), and therefore constitute a sub-group of high risk patients.<sup>[21]</sup> The number of elderly patients who experience AMI is growing, and the in-hospital mortality in this group remains high, despite the fact that age *per-se* is no longer a contraindication to thrombolysis.<sup>[22,23]</sup>

Magnesium intake in the elderly tends to be low, and their susceptibility to magnesium deficiency is intensified by diminished intestinal absorption and increased urinary output of magnesium.<sup>[5,24,25]</sup> In addition, they may be taking magnesium-wasting medications such as diuretics, digoxin, laxatives etc., which are likely to exacerbate their vulnerability to magnesium deficiency.<sup>[5]</sup>

The purpose of this review is to summarize the physiologic and pharmacologic effects of magnesium supplementation and discuss the rationale for treating all patients with AMI, including high-risk populations, such as the elderly and those who are ineligible for thrombolysis.

## 1. The Rationale for Magnesium in AMI

Magnesium is the second most abundant intracellular cation in the human body, second only to potassium, and is involved in more than 300 different enzymatic reactions, including glucose activity, the synthesis of fat, protein and nucleic acids; the meta-

bolism of adenosine triphosphate (ATP); muscle contraction; and some membrane transport systems.

Available data suggest that a combination of mechanisms may act additively or even synergistically to protect myocytes during AMI.<sup>[1,26]</sup> Exogenous administration of magnesium prevents intracellular depletion of magnesium, potassium and high-energy phosphates, improves myocardial metabolism and prevents intramitochondrial calcium accumulation and reduces vulnerability to oxygen-derived free radicals.<sup>[27]</sup> The various physiological mechanisms by which magnesium can influence cardiovascular function are presented in table I. Furthermore, the effect of magnesium on infarct size has also been investigated.<sup>[26,28–38]</sup> Most importantly, the effect of magnesium has also been evaluated in patients with AMI.<sup>[39–58]</sup>

### 1.1 Impact of Magnesium on Vascular Tone

Magnesium is considered to be nature's physiologic calcium channel antagonist.<sup>[59–61]</sup> It reduces the release of calcium from and into the sarcoplasmic reticulum and protects the cell against calcium overload under conditions of ischemia. Magnesium reduces systemic and pulmonary vascular resistance, with concomitant decrease in blood pressure and a slight increase in cardiac index.<sup>[28,62,63]</sup> Elevation of extracellular magnesium levels reduces arteriolar tone and tension in a wide variety of arteries<sup>[29,64,65]</sup> and potentiates the dilatory action of some endogenous (adenosine, potassium and some prostaglandins) and exogenous (isoproterenol and nitroprusside) vasodilators.<sup>[29,64,66,67]</sup> As a result, magnesium has a mild inhibitory effect on systolic blood pressure,<sup>[68,69]</sup> may reduce afterload and thus unload the ischemic ventricle. Kugiyama et al.<sup>[70]</sup> demonstrated that exercise-induced angina pectoris is suppressed by intravenous magnesium in patients with variant angina, most probably as a result of improvement of regional myocardial blood flow by suppression of coronary artery spasm. Altura and Altura<sup>[71]</sup> found in an experimental vascular smooth muscle model that magnesium deficiency, through potentiation of increased cellular calcium activity, might be responsible for the arterial hypertension that accompanies toxemia of pregnancy. The

**Table I.** Magnesium can influence cardiovascular function by acting on the following physiological mechanisms

Mechanism	Reference
Vascular tone	28,29,59-72
Cardiac rhythm	73-82
Lipid metabolism	30,83-87
Coagulation system and platelet function	31-35,88-97
Endothelial function	98-100
Cardiac functional capacity	101,102

proven effectiveness of parenteral magnesium therapy in toxemia of pregnancy<sup>[29]</sup> is most likely the result of its calcium antagonist action.

### 1.2 Impact of Magnesium on Cardiac Rhythm

Magnesium deficiency is associated with intracellular hypokalemia, hypernatremia and augmentation of cell excitability.<sup>[73]</sup> Magnesium has modest electrophysiologic effects: it prolongs the actual and corrected sinus node recovery time, prolongs the atrioventricular nodal function, relative and effective refractory periods, slightly increases the QRS duration during ventricular pacing at cycle lengths of 250 and 500 milliseconds, and increases the atrial-His interval and atrial paced-cycle length causing atrioventricular nodal Wenckebach conduction.<sup>[74]</sup> Zwilinger<sup>[75]</sup> in 1935 was the first to recognize that magnesium has an antiarrhythmic effect when used to convert paroxysmal tachycardia to sinus rhythm. Later on it was successfully used in patients with resistant ventricular tachycardias,<sup>[76]</sup> ventricular arrhythmias induced by digitalis toxicity<sup>[77,78]</sup> and in those with episodes of torsade de pointes, a life threatening ventricular arrhythmia.<sup>[79]</sup>

Magnesium was also found to be effective in the termination of episodes of supraventricular arrhythmia, such as multifocal atrial tachycardia<sup>[80]</sup> and increased the susceptibility of atrial tachycardia to pharmacological conversion with digoxin.<sup>[81]</sup>

The American Heart Association has recently recommended magnesium as the third drug of choice (after amiodarone and lidocaine) in the resuscitation of patients with pulseless ventricular tachycardias or ventricular fibrillation.<sup>[82]</sup>

### 1.3 Impact of Magnesium on Lipid Metabolism

The role magnesium plays in lipid regulation is interesting, although not yet fully understood. Magnesium is an important cofactor of two enzymes that are essential in lipid metabolism: lecithin-cholesterol acyltransferase (LCAT) and lipoprotein lipase. In a rabbit model animals were fed a regular diet, or a high cholesterol diet supplemented with varying amounts of magnesium, and it was that the addition of supplemental magnesium achieved a dose-dependent reduction in both the area of the aortic lesions and the cholesterol content of the aorta.<sup>[83]</sup> Rats, on the other hand, placed on diets severely deficient in magnesium developed adverse lipid changes.<sup>[84]</sup> In another rat model, magnesium deficient diets led to the increased plasma levels of total cholesterol, low density lipoprotein-cholesterol and triglycerides, with a proportionate reduction in plasma levels of high density lipoprotein-cholesterol (HDL-C).<sup>[85]</sup>

In a clinical study, Rassmussen et al.<sup>[30]</sup> gave magnesium 15 mmol/day for 3 months and found a 27% reduction in plasma

levels of triglycerides and very low-density lipoprotein-cholesterol (VLDL-C), and reduction in plasma levels of apoprotein B and elevation of plasma HDL-C levels. Davis et al.<sup>[86]</sup> demonstrated a significant improvement in the ratio of HDL-C to LDL-C plus VLDL-C, by administering magnesium 18 mmol/day in a 4-month clinical trial.

Niemela et al.<sup>[87]</sup> showed that in men, but not in women, platelet intracellular magnesium levels significantly inversely correlated with serum levels of total cholesterol ( $r = -0.52$ ,  $p < 0.02$ ), LDL-C ( $r = -0.54$ ,  $p < 0.009$ ) and apolipoprotein B ( $r = -0.42$ ,  $p < 0.04$ ). These investigators also speculated that decreased platelet intracellular magnesium level is a possible marker for platelet membrane alterations that may affect platelet involvement in thrombosis and atherogenesis.<sup>[87]</sup>

### 1.4 Anticoagulant/Antiplatelet Properties of Magnesium

In 1943 Greville and Lehmann<sup>[88]</sup> found that a small amount of magnesium added to fresh, unclotted human plasma prolonged the clotting time. During and shortly after the 2nd World War magnesium sulfate was widely used in Germany as a muscle relaxant, and it was observed that after such treatment the blood of patients examined postmortem was unclotted.<sup>[89]</sup> In 1959 Anstall et al.<sup>[90]</sup> demonstrated that magnesium inhibits human blood coagulation.

Adams and Mitchel found that magnesium, both topically and parenterally, suppressed thrombus formation and increased the concentration of ADP which was required to initiate thrombus production at human minor injury sites.<sup>[91]</sup> Some experimental studies have demonstrated the antiplatelet effects of magnesium, which may prevent the propagation of coronary artery thrombi or reocclusion of the infarct-related coronary artery after spontaneous or fibrinolysis-induced recanalization.<sup>[31,91-93]</sup> Recently some studies have demonstrated that magnesium reduces platelet aggregation in healthy volunteers.<sup>[92]</sup> High plasma magnesium levels inhibit blood coagulation<sup>[90]</sup> and thrombus formation *in vivo*,<sup>[91]</sup> diminish platelet aggregation,<sup>[31,32,93]</sup> reduce synthesis of platelet agonist thromboxane A<sub>2</sub>,<sup>[84]</sup> and inhibit thrombin-stimulated calcium influx.<sup>[31]</sup>

Platelet activation is a key element in acute vascular thrombosis, which is important in the pathogenesis of AMI and complications of coronary balloon angioplasty and stenting. Studies have demonstrated that magnesium can suppress platelet activation by either inhibiting platelet-stimulating factors, such as thromboxane A<sub>2</sub>, or by stimulating synthesis of platelet-inhibitory factors, such as prostacyclin (PGI<sub>2</sub>).<sup>[32,33,92]</sup> Intravenous administration of magnesium to healthy volunteers, inhibited both ADP-induced platelet aggregation by 40% and the binding of fibrinogen or surface expression of glycoprotein IIb-IIIa complex GMP-140 by 30%.<sup>[32]</sup>

Thus, pharmacological concentrations of magnesium effectively inhibit platelet function *in vitro* and *ex vivo*.

Gawaz et al. demonstrated that spontaneous (and ADP-induced) P-selectin surface expression on platelets and platelet-leukocyte adhesion was increased in symptomatic patients with CAD compared with healthy controls.<sup>[94]</sup> However, intravenous magnesium administration significantly reduced both platelet surface expression of P-selectin and platelet-leukocyte adhesion *ex vivo*. In both whole blood and isolated neutrophil suspension, magnesium dose-dependently inhibited platelet adhesion to neutrophils.<sup>[94]</sup>

Using an *ex-vivo* perfusion (Badimon) chamber,<sup>[95]</sup> we recently demonstrated that platelet-dependent thrombosis was significantly increased in stable CAD patients with low mononuclear intracellular levels of magnesium, despite antiplatelet treatment with aspirin.<sup>[34]</sup>

Furthermore, we wanted to determine whether oral magnesium treatment inhibits platelet-dependent thrombosis in patients with CAD and therefore conducted a randomized, prospective, double-blind, crossover, placebo-controlled trial.<sup>[35]</sup> Forty-two patients with stable CAD were randomized to receive either magnesium oxide tablets (800–1200 mg/day, MAG-OX<sup>®</sup> 400, Blaine Pharmaceuticals, Inc., Kentucky, USA) or placebo for 3 months (phase 1), followed by a 4-week washout period, and the alternative treatment for 3 months (phase 2).<sup>[35]</sup>

After 3 months' treatment with oral magnesium, the median platelet-dependent thrombosis was significantly reduced by 35%; however, there was no significant change in patients who received placebo. The antithrombotic effect of magnesium treatment was observed despite the 100% utilization of aspirin therapy. There was no significant effect of magnesium treatment on serum lipid levels, platelet aggregation, P-selectin expression, and monocyte-derived tissue factor procoagulant activity.<sup>[35]</sup>

In an *in-vitro* model of platelet-dependent thrombosis in rats, Ravn and coworkers<sup>[96]</sup> found that early administration of intravenous magnesium inhibited arterial thrombus formation, which was associated with suppression of platelet aggregation only at higher doses. Other investigators also demonstrated that intravenous magnesium sulfate reduces platelet aggregation in healthy volunteers.<sup>[92]</sup> On the molecular level these effects are probably modulated via reduction of intracellular calcium mobilization.<sup>[33]</sup>

Platelet adhesion is likely to be much more sensitive to suppression with lower plasma magnesium concentrations (as achieved via oral magnesium) than aggregation. Thus, the antiplatelet adhesion effects of magnesium may account for the significant effects it has on platelet-dependent thrombosis formation with minimal

effects on *in vitro* platelet aggregation and  $\alpha$ -granule release reaction (P-selectin expression).<sup>[35]</sup>

Gawaz et al.<sup>[32]</sup> demonstrated that platelet aggregation, fibrinogen binding, and expression of P-selectin on the platelet surface, are all effectively inhibited by intravenous magnesium supplementation. Since glycoprotein IIb-IIIa is the only glycoprotein on the platelet surface that binds fibrinogen, Gawaz et al. speculated that magnesium supplementation directly impairs fibrinogen interaction with the glycoprotein IIb-IIIa complex.<sup>[32]</sup> Since fibrinogen binding to the platelet membrane and surface expression of P-selectin requires previous cellular activation,<sup>[97]</sup> the inhibitory effect of magnesium might be a consequence of direct interference of the cation with the agonist-receptor interaction or with the intracellular signal transduction event. Fibrinogen-glycoprotein IIb-IIIa interaction is regulated by divalent cations, and at pharmacological concentrations magnesium may inhibit the binding of fibrinogen to glycoprotein IIb-IIIa by altering receptor conformation. This might be caused by competition between magnesium and calcium ions for calcium-binding sites in the glycoprotein IIb subunit.<sup>[97]</sup>

### 1.5 Impact of Magnesium on Endothelial Function

In a randomized, double-blind, placebo-controlled trial, we recently randomized 50 patients with stable CAD (41 men, mean age  $67 \pm 11$  years) to receive either oral magnesium 30 mmol/day (total magnesium 730 mg/day, Magnosolv<sup>®</sup>-Granulate, Asta Medica Arzneimittel Ges.m.b.H., Vienna, Austria) or placebo for 6 months.<sup>[98]</sup>

Endothelium-dependent brachial artery flow-mediated vasodilation and endothelium-independent nitroglycerin (glyceryl trinitrate)-mediated vasodilation, were assessed before and after the 6-month trial period, using high-resolution ultrasound. Intracellular magnesium levels were assessed from sublingual cells by X-ray dispersion.<sup>[99]</sup>

Compared with placebo, oral magnesium therapy significantly increased post-intervention intracellular magnesium levels ( $36.2 \pm 5.0$  vs  $32.7 \pm 2.7$  mEq/L,  $p < 0.02$ ). There was a significant correlation in the total population between baseline intracellular magnesium levels and baseline flow-mediated vasodilation ( $r = 0.48$ ,  $p < 0.01$ ).<sup>[98]</sup> We demonstrated for the first time that magnesium intervention resulted in a significant improvement in post-intervention flow-mediated endothelium-dependent vasodilation, a finding which was not evident with placebo ( $15.5 \pm 12.0$  vs  $4.4 \pm 2.5\%$ ,  $p = 0.02$ ).<sup>[98]</sup>

In a canine model Pearson et al.<sup>[100]</sup> demonstrated that hypomagnesemia selectively impaired the release of NO from coro-

1 Use of the trade name is for product identification only and does not imply an endorsement

nary endothelium. Because NO is a potent endogenous nitrovasodilator and inhibitor of platelet aggregation and adhesion, it has been hypothesized that hypomagnesemia may promote vasoconstriction and coronary thrombosis.

### 1.6 Impact of Magnesium on Infarct Size

Hypomagnesemia may increase coronary and systemic vasoconstriction and afterload.<sup>[28,64]</sup> Administered soon after the onset of myocardial ischemia, magnesium infusion may limit the progression of ischemia, which in turn could reduce the risk of arrhythmias resulting from raised local catecholamine levels.<sup>[36]</sup> Although not yet fully understood, magnesium plays an interesting role in lipid regulation. Some laboratory and clinical trials have demonstrated that magnesium reduces serum levels of total cholesterol and LDL-C, while it increases serum levels of HDL-C.<sup>[30]</sup> Low concentrations of magnesium in laboratory animals seem to potentiate catecholamine-induced myocardial necrosis.<sup>[36]</sup> Magnesium deficiency may adversely influence the healing and re-endothelialization of vascular injuries, the healing of myocardial infarction, and may also result in delayed or inadequate angiogenesis.<sup>[34]</sup> Such effects could potentially lead to inadequate development of collaterals and infarct expansion. Magnesium reduces vulnerability to oxygen-derived free radicals,<sup>[27]</sup> reperfusion injury<sup>[35]</sup> and stunning of the myocardium.<sup>[37,38]</sup> Experimental work has shown hypercoagulability and increased platelet aggregation during hypomagnesemia, which could contribute to thrombus formation.<sup>[32]</sup> High magnesium supplementation is inversely related to platelet aggregation and ATP release.<sup>[31]</sup> It can dose-dependently inhibit platelet aggregation in response to a variety of agonists and stimulate PGI<sub>2</sub> synthesis.<sup>[33]</sup>

### 1.7 Clinical Trials of Magnesium in Patients with AMI

#### 1.7.1 Therapeutic Efficacy

In the last decade, eight prospective, randomized, double-blind controlled trials have been reported, comparing intravenous magnesium to placebo in patients with AMI, mainly without thrombolytic therapy.<sup>[39-47,103]</sup> Morton et al.,<sup>[103]</sup> who published their study in 1984, were the pioneers who were the first to show that magnesium reduced in-hospital mortality in patients with AMI patients, and also suggest that magnesium could reduce the infarct size by 20% in patients in Killip class I.

Each of the first seven trials comprised small numbers of patients and was performed in the pre-thrombolytic era. In the eighth trial, second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2), 70% of the 2316 patients did not receive thrombolytic therapy.<sup>[47]</sup> Despite the difference in study protocols and in patient selection criteria, the results were similar. The mortality

odds ratio of the trials without thrombolysis, demonstrated that magnesium reduced in-hospital mortality by almost 19%, mainly by reducing the incidence of serious arrhythmias and left ventricular heart failure by one-quarter.<sup>[1,47,48]</sup>

The LIMIT-2 trial<sup>[47]</sup> randomized 2316 patients in a median of 3 hours from the onset of chest pain (74% were actually randomized in less than 6 hours). It was a protocol requirement that magnesium be infused coincident with thrombolysis, a treatment that was administered to 36% of patients. Thus, LIMIT-2 was likely to have achieved elevated intracellular magnesium levels at the time of reperfusion in patients undergoing thrombolysis; the relatively early enrollment of patients not receiving thrombolysis, combined with prompt administration of magnesium after enrollment, also means that intracellular magnesium levels were probably elevated when spontaneous reperfusion occurred in patients not undergoing pharmacologic reperfusion. At 28 days, all-cause mortality was reduced by 24% in magnesium recipients. That infarct size limitation led to the magnesium-induced reduction in mortality in LIMIT-2, is indirectly evidenced by the 25% lower rate of CHF observed during the hospital phase of treatment in magnesium-treated patients, and the >20% reduction in ischemic heart disease-related mortality over long-term follow-up, that now extends to a mean of 4.5 years.<sup>[49]</sup>

In a prospective, randomized, double-blind, placebo-controlled trial, 215 patients with AMI who were considered unsuitable for thrombolysis (late arrival, advanced age, and the commonly accepted contraindications to thrombolysis), received either magnesium (22g [92 mmol/L] of MgSO<sub>4</sub>) for 48 hours (n = 107) or equivalent volumes of isotonic glucose as placebo (n = 108).<sup>[50]</sup> The two groups had similar risk factors, received the same conventional therapy in the Coronary Care Unit (CCU), and had similar average time of 7 hours from onset of chest pain to initiation of treatment, which was an average of 5 hours earlier than the comparable subgroup in the fourth International Study of Infarct Survival (ISIS-4).<sup>[51]</sup>

The striking finding was the reduction of in-hospital mortality in patients who received magnesium compared with placebo (4% vs 17%; p < 0.01). Cardiogenic shock was the main cause of death in patients not receiving magnesium, and it accounted for only one death in those who received magnesium therapy. It should be mentioned that 77 patients (38%) were >70 years of age. Compared with placebo, intravenous magnesium also reduced in-hospital mortality in these high-risk patients (10 vs 3 deaths). Magnesium also reduced the incidence of arrhythmias and CHF in this subgroup of patients.

The situation became unexpectedly disappointing with the presentation of ISIS-4 results.<sup>[51]</sup> In this mega-trial conducted in approximately 58 000 patients with suspected or definite AMI,

almost 70% of patients received thrombolytic therapy. The mortality rate at 35 days was 7.6% in the magnesium group and 7.2% in the placebo group, suggesting no survival-benefit with magnesium administration, and even the possibility of slightly deleterious effects. Survival curves were identical even after 1 year of follow-up. Of the 17 000 patients who did not receive thrombolytic therapy, the mortality rate was 9.3% in both the magnesium and in the control placebo group. The magnesium dosage was almost identical to that used in the LIMIT-2 study, but with open control. However, the time from onset of symptoms to randomization was substantially longer (median of 8 vs 3 hours). The 30% of patients not given a thrombolytic agent were randomized at a median of 12 hours after onset of symptoms. The likelihood of reperfusion occurring (either induced or spontaneous) during magnesium treatment was therefore low. The low mortality rate in the ISIS-4 control group, the late enrollment of patients, particularly those who did not receive thrombolytic treatment, plus the fact that magnesium infusions were delayed by 1–2 hours after thrombolytic therapy, suggest that the possibility that the majority of patients in ISIS-4 were at low mortality risk and that an elevated magnesium blood level was not reached until well beyond the narrow time window for salvage of myocardium or prevention of reperfusion injury suggested by experimental data.<sup>[37,38,52-54]</sup>

The lack of therapeutic effects of magnesium when administered as in ISIS-4 are in full accord with the results of various experimental animal models, where the beneficial effects of magnesium have generally been greater when it was given before reperfusion.<sup>[52]</sup> In a swine model, the duration of myocardial stunning of brief coronary occlusion (8 minutes) and reperfusion was exacerbated by magnesium deficiency and ameliorated by pretreatment with intravenous magnesium.<sup>[37,38]</sup> Mortality reduction with magnesium is greater in patients with the a high baseline risk (as in Rasmussen's<sup>[39]</sup> and our<sup>[50]</sup> trials).<sup>[38,54,55]</sup> In ISIS-4 the late administration of magnesium might have resulted in infarct extension due to hypotension, which was more pronounced in ISIS-4 (in patients who received magnesium compared with placebo) compared with LIMIT-2.<sup>[54,55]</sup>

In a double-blind, placebo-controlled, parallel study, Galloe et al.<sup>[56]</sup> reported on 468 myocardial infarction survivors (aged 31–92 years) who received magnesium hydroxide 15 mmol/L or placebo daily for 1 year. Magnesium therapy increased the incidence of cardiac events, (no data were available on concomitant medications during the study), cardiac ejection fraction and invasive procedures in the two study groups.

In a prospective, double-blind, placebo-controlled trial, our group randomly assigned 194 patients with AMI, considered unsuitable for thrombolytic therapy at the time of enrollment, to receive intravenous magnesium (n = 96) or isotonic glucose as

placebo (n = 98).<sup>[50]</sup> All-cause mortality was significantly lower after a mean follow-up of 4.5 years in the magnesium-treated group compared with the placebo group (18 vs 33 patients,  $p < 0.01$ ).<sup>[57]</sup> Left ventricular ejection fraction at rest, measured in all patients who survived the last year of follow-up, was significantly higher in patients who received magnesium versus placebo ( $0.51 \pm 0.10$  vs  $0.44 \pm 0.14$ ,  $p < 0.05$ ). Thus, the favorable effects of intravenous magnesium therapy can last several years after short term treatment, probably due to preserved left ventricular ejection fraction.

The recently published Magnesium in Coronaries (MAGIC) trial<sup>[104]</sup> randomized 6213 patients  $\geq 65$  years, of whom an unexpected high percentage (45%) were female with acute ST elevation AMI  $< 6$  hours who were eligible for reperfusion therapy (median age 73 years) [stratum 1]; or patients of any age who were not eligible for reperfusion therapy (median age 67 years) [stratum 2], to a 2g intravenous bolus of magnesium sulphate, administered over 15 minutes, followed by a 17g infusion of magnesium sulphate over 24 hours (n = 3113) or matching placebo (n = 3100). Early administration of magnesium (median time from the onset of symptoms: 3.8 hours) in high-risk patients with acute ST elevation AMI  $< 6$  hours had no effect on 30-day mortality. At 30 days (the longest follow-up period), 475 (15.3%) patients in the magnesium therapy did not change the incidence of heart failure compared to placebo. Compared to the MAGIC trial, our study<sup>[50]</sup> with thrombolysis-ineligible AMI patients, of whom one third was  $> 75$  years, and therefore quite similar to the stratum 2 patients in MAGIC, received high doses of intravenous magnesium sulphate for longer periods of time compared to MAGIC (22g vs 19g and 48 hours compared with 24 hours, respectively). A significantly higher proportion of the MAGIC study population received aspirin,  $\beta$ -blockers and ACE inhibitors than in our study population<sup>[50]</sup>, and as a result the postulated cardioprotective actions of magnesium could have been superseded by the effects of these medical regimens.<sup>[104]</sup>

### 1.7.2 Adverse Effects

Magnesium supplementation is relatively well tolerated.<sup>[26]</sup> In all previous randomized controlled clinical trials only few adverse effects were reported. In the ISIS-4 trial<sup>[51]</sup> with 58 000 patients with suspected AMI, no overall increase in the incidence of second or third degree heart block was observed, although there was a slight, but not convincingly significant, excess during or just after the magnesium infusion. In ISIS-4 intravenous magnesium was associated with a small but significant increases in heart failure, cardiogenic shock and death attributed to cardiogenic shock. These magnesium-associated excesses were not confirmed in the LIMIT 2 trial<sup>[47]</sup> with 1500 and in the MAGIC trial<sup>[104]</sup> with 6200

AMI patients. Sinus bradycardia, however, was observed in some<sup>[47,48,51]</sup> but not all<sup>[26,104]</sup> randomized clinical trials but this was not clinically significant. As magnesium is a physiological calcium competitor, rapid intravenous (bolus) administration is prohibited as it can reduce blood pressure. Therefore, a slow intravenous bolus dose of 1gm over 5 minutes is recommended.<sup>[104]</sup> A patient with normal renal function secretes magnesium rapidly through the kidneys. Normally the kidneys filter approximately 2.5g of magnesium and reclaim 95%, excreting some 100 mg/dL into the urine to maintain homeostasis. Approximately 25–30% is reclaimed in the proximal tube through a passive transport system that depends on sodium reabsorption and tubular fluid flow. Usually, as serum magnesium concentration increases, there is a linear increase in urinary magnesium excretion, paralleling that of insulin. With normal kidney function, hypermagnesemia or magnesium intoxication does not develop, even during high intravenous magnesium infusion.<sup>[26,47,51,104]</sup>

### 1.8 Impact of Magnesium on Cardiac Functional Capacity

To determine whether increased intracellular levels of magnesium are associated with enhanced functional capacity, we performed symptom-limited exercise treadmill testing in 42 patients with stable CAD (37 men, mean age  $68 \pm 9$  years).<sup>[101]</sup> Intracellular level of magnesium was found to be an independent and significant predictor of exercise duration ( $R = 0.31$ ,  $p = 0.02$ ) in a multivariate stepwise regression model. Patients with above normal intracellular levels of magnesium had a significantly greater mean functional capacity, measured in higher achieved metabolic equivalents and exercise duration, compared with patients with intracellular levels of magnesium below normal, possibly via ventricular unloading.<sup>[101]</sup>

We recently randomized 187 stable CAD patients with prior myocardial infarction (151 men and 36 women, mean age  $63 \pm 10$  years [age range 42–83 years]) from Israel, Austria and the US to treatment with oral magnesium (Magnosolv<sup>®</sup>-Granulat, total magnesium 365mg solved as magnesium citrate, Asta Medica, Vienna, Austria) [ $n = 94$ ] or placebo ( $n = 93$ ) for 6 months. At 6 months magnesium treatment significantly increased exercise duration, decreased exercise-induced chest pain, and improved quality-of-life parameters compared with placebo, suggesting a potential mechanism whereby magnesium could beneficially alter outcomes in patients with CAD.<sup>[102]</sup>

## 2. Conclusions

Magnesium supplementation has been demonstrated both theoretically and experimentally to decrease ischemic myocardial

damage and reduce mortality in subsets of high-risk patients, including the elderly and/or patients not suitable for thrombolysis, if administered prior to reperfusion. It is a low cost therapy, easy to handle and relatively free of adverse effects. For maximum effectiveness, it appears to be important to administer magnesium as soon as possible in patients with AMI (anywhere along the route between the patient's home and the CCU), so that levels are elevated when spontaneous reperfusion occurs in patients who do not receive reperfusion therapy.<sup>[55]</sup>

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