ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction

*ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group**

Summary

58 050 patients entering 1086 hospitals up to 24 h (median 8 h) after the onset of suspected acute myocardial infarction (MI) with no clear contraindications to the study treatments (in particular, no cardiogenic shock or persistent severe hypotension) were randomised in a "2 × 2 × 2 factorial" study. The treatment comparisons were: (i) 1 month of oral captopril (6·25 mg initial dose titrated up to 50 mg twice daily) versus matching placebo; (ii) 1 month of oral controlled-release mononitrate (30 mg initial dose titrated up to 60 mg once daily) versus matching placebo; and (iii) 24 h of intravenous magnesium sulphate (8 mmol initial bolus followed by 72 mmol) versus open control. There were no significant "interactions" between the effects of these three treatments, and the results for each are based on the randomised comparison of about 29 000 active versus 29 000 control allocated patients.

Captopril There was a significant 7% (SD 3) proportional reduction in 5-week mortality (2088 [7·19%] captopril-allocated deaths *vs* 2231 [7·69%] placebo; 2p=0·02), which corresponds to an absolute difference of 4·9 SD 2·2 fewer deaths per 1000 patients treated for 1 month. The absolute benefits appeared to be larger (perhaps about 10 fewer deaths per 1000) in certain higher-risk groups, such as those presenting with a history of previous MI or with heart failure. The survival advantage appeared to be maintained in the longer term (5·4 [SD 2·8] fewer deaths per 1000 at 12 months). Captopril was associated with an increase of 52 (SD 2) patients per 1000 in hypotension considered severe enough to require termination of study treatment, of 5 (SD 2) per 1000 in reported cardiogenic shock, and of 5 (SD 1) per 1000 in some degree of renal dysfunction. It produced no excess of deaths on days 0–1, even among patients with low blood pressure at entry.

Mononitrate There was no significant reduction in 5-week mortality, either overall (2129 [7·34%] mononitrate-allocated deaths *vs* 2190 [7·54%] placebo) or in any subgroup examined (including those not receiving short-term non-study intravenous or oral nitrates at entry). Further follow-up did not indicate any later survival advantage. The only significant side-effect of the mononitrate regimen studied was an increase of 15 (SD 2) per 1000 in hypotension. Those allocated active treatment had somewhat fewer deaths on days 0–1, which is reassuring about the safety of using nitrates early in acute MI.

Magnesium There was no significant reduction in 5-week mortality, either overall (2216 [7·64%] magnesium-allocated deaths *vs* 2103 [7·24%] control) or in any subgroup examined (including those treated early or late after symptom onset or in the presence or absence of fibrinolytic or antiplatelet therapies, or those at high risk of death). Further follow-up did not indicate any later survival advantage. In contrast with some previous small trials, there was a significant excess with magnesium of 12 (SD 3) per 1000 in heart failure and of 5 (SD 2) per 1000 in reported cardiogenic shock during or just after the infusion period. Magnesium was also associated with an increase of 11 (SD 2) per 1000 in hypotension considered severe enough to require termination of study treatment, of 3 (SD 0·6) per 1000 in bradycardia, and of 3 (SD 0·4) per 1000 in a cutaneous flushing or burning sensation (but assessment of magnesium involved open control). There was no evidence of a net adverse effect on mortality on days 0–1.

Because of its size, ISIS-4 provides reliable evidence about the effects of adding each of these three treatments to established treatments for acute MI. Intravenous magnesium was ineffective, and although oral nitrate therapy appeared safe it did not produce a clear reduction in 1-month mortality. Other trials have shown that starting long-term converting enzyme inhibitor (CEI) therapy in the weeks or months after MI in patients with impaired ventricular function avoids about 2 deaths per 1000 patients per month of treatment. ISIS-4, GISSI-3, and smaller studies now collectively demonstrate that, for a wide range of patients without clear contraindications, CEI therapy started early in acute MI prevents about 5 deaths per 1000 in the first month (2p=0·006), with somewhat greater benefits in higher-risk patients. This benefit from 1 month of early CEI treatment seems to persist for at least the first year.

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Introduction

The purpose of ISIS-4 was the reliable assessment, by randomising several tens of thousands of patients, of the effects on mortality and major morbidity of the addition of each of three widely practicable treatments—1 month of oral converting enzyme inhibitor (CEI), 1 month of oral nitrate, and 24 h of intravenous magnesium—to the currently standard treatments for a wide range of patients, low-risk as well as high-risk, with definite or suspected acute myocardial infarction (MI).[1,2]

*Collaborators and participating centres are listed at the end of the report

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Converting enzyme inhibitors in acute MI

Following MI, ventricular remodelling and dilation can occur, leading to an increased risk of heart failure, cardiac rupture, arrhythmia, and death.[3-5] Ventricular dilation begins within days or weeks of the onset of acute MI,[6-9] and the renin-angiotensin system is activated within the first few hours or days.[10,11] Activation of the renin-angiotensin system may increase the heart rate and systemic vascular resistance and decrease coronary artery perfusion, which may result in infarct expansion.[12] The increase in systemic vascular resistance may also increase myocardial wall stress, predisposing to various complications, including progressive ventricular dilation, during the early recovery phase after infarction.[12,13] In addition, activation of the renin-angiotensin system may have adverse effects on endogenous fibrinolytic activity.[14] In animal experiments, early use of CEIs seemed to limit infarct expansion, increase collateral flow to the infarct zone, reduce the incidence of reperfusion arrhythmias, and limit the necrosis of cardiac myocytes.[12,15-18] If, therefore, CEI therapy could be started safely in the acute phase of MI, and continued for at least the first month, then it might be of value for a wide range of patients (in addition to any benefits of long-term CEI therapy in patients with clinical heart failure or other evidence of impaired ventricular function[19-21]). Despite concerns about hypotension,[7,22] several relatively small randomised clinical trials of CEI therapy started early in acute MI have suggested promising effects on neuroendocrine activation, arrhythmias, infarct expansion, and ventricular dilation and function[23-33] (with greater effects when treatment was started in the acute phase rather than a few days later[34]). But, for death and major morbidity, small studies cannot reliably assess either any small benefits or small hazards that might exist.

Nitrates in acute MI

Nitrate therapy may reduce myocardial workload during acute myocardial infarction by reducing peripheral vascular resistance and blood pressure. Both intravenous and oral nitrate therapy have been shown, not only in laboratory animals but also in clinical studies, to limit infarct size, to improve left ventricular function and to reduce remodelling.[35] Before the current trial, results had been reported from only a few thousand acute MI patients in randomised trials of intravenous or oral nitrates (generally of short duration—ie, just a few days).[24,25,33,36,37] Individually, the mortality results from these trials were inconclusive, but an overview suggested that short-term nitrates might reduce early mortality by as much as one-third (although there was a wide range of uncertainty about this estimate). Especially where indicated for the relief of symptoms, the use of intravenous or other short-term nitrates is already quite common, and longer-term use of nitrates is now being considered. Continuous exposure to nitrates can lead to a state of pharmacological tolerance that limits their clinical efficacy,[38,39] but this can be minimised by use of controlled-release formulations (as in the present study).[40]

Magnesium in acute MI

In experimental infarction, infusions of magnesium can limit myocardial damage, perhaps by inhibiting calcium influx into ischaemic myocardial cells and by reducing coronary artery tone,[41,42] and can increase the threshold for depolarisation of cardiac myocytes, thereby reducing the likelihood of cardiac arrhythmia caused by injury currents near ischaemic or infarcted tissue.[43] In human beings, magnesium infusion can reduce peripheral vascular resistance and increase cardiac output without any corresponding increase in cardiac work.[44] Thus, magnesium infusions started early after the onset of myocardial ischaemia might limit infarct size, prevent serious arrhythmias, and reduce mortality. Collectively, the results of eight small randomised trials of intravenous magnesium in a total of just over 1000 patients with suspected acute MI suggested a mortality reduction of about one-half[1,45,46] (which was, however, thought likely to be an exaggeration of any real benefit[45,47]). Lately, the larger Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) in over 2000 patients with suspected acute MI reported a smaller effect.[48,49] But, although the apparent reduction in 28-day mortality of about one-quarter in LIMIT-2 is conventionally significant ($2p=0{\cdot}04$), the statistical uncertainty about this estimate is great, with the confidence interval ranging from a halving in mortality to no material difference in survival. Moreover, the results of that study did not support its prespecified hypotheses that magnesium prevented progression of infarction or reduced the frequency of early arrhythmias (but, instead, retrospectively found a reduction in reported clinical heart failure).[48-50]

Need for randomised evidence in several tens of thousands of patients

Since antiplatelet and fibrinolytic therapy were likely to be used widely in ISIS-4, the 1-month mortality in this study was expected to be only about 8% (as among the patients in ISIS-2 who were allocated both of these treatments[51]). Systematic overviews of the previous trials of nitrates and of magnesium suggested mortality reductions of at least 10–20%.[1] But, because those overviews each involved only small numbers of deaths, even their highly significant mortality reductions did not reliably demonstrate that nitrates or magnesium provided any real benefit (see Discussion). No such mortality information was available for the use of CEIs in acute MI, but the effects seen in the small studies led to hopes that this too might reduce mortality by 10–20% (with, perhaps, greater effects emerging with long-term follow-up). The aim in ISIS-4, therefore, was to randomise at least 40 000 patients—and, preferably, substantially more—so as to minimise the risk of false-negative findings in ISIS-4, or in the aggregate of ISIS-4 and other relevant study results. Pilot studies in over 1000 patients had indicated that, even in combination, the study treatments were well tolerated in acute MI,[23,24] so an efficiently "factorial" design could be adopted. Appropriate statistical analysis of such a design allows each patient to contribute fully to assessment of the separate effects of each of the study treatments without any material loss of statistical power, whilst also providing some information about their combined effects.[1,52]

Patients and methods

Eligibility

Patients were eligible if they were thought to be within 24 h of the onset of symptoms of suspected acute MI with no clear indications for, or contraindications to, any one of the study treatments—CEI, nitrate, or magnesium. The only exception was that patients who were to be given intravenous or other non-

study nitrate for just a few days could still be entered. (Such use of non-study nitrates was recorded at randomisation to allow separate analysis of the effects of the 1-month study nitrate regimen among patients who were not, at the time of randomisation, being given non-study nitrates.) Contra-indications were specified not by the protocol but by the responsible physician, and so it was merely suggested that these might include *either* conditions associated with a high risk of adverse effects, such as cardiogenic shock, persistent severe hypotension (systolic blood pressure [SBP] persistently <90–100 mm Hg, especially with right ventricular infarction or poor peripheral perfusion) or evidence of severe fluid depletion (perhaps due to chronic diuretic use), *or* conditions associated with only a small likelihood of worthwhile benefit, such as negligibly low risk of cardiac death or high risk of death from some other life-threatening disease. Heart block was described as not being an absolute contraindication, even though an increase in plasma magnesium can slow atrio-ventricular conduction.[44]

Randomisation

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. The computer used a "minimisation" algorithm,[53] which limited chance differences between the treatment groups in these baseline features.

Treatment

Antiplatelet therapy was recommended (and was received by 94% of randomised patients), together with fibrinolytic therapy when considered indicated (used in 70%). Study treatment was generally to be started *immediately* after the early lytic phase (ie, the first hour or so) of any fibrinolytic regimen. Details of the type of fibrinolytic and of the timing of the treatments were sought from a 1000-patient random sample of all patients in the study. Nine-tenths of the fibrinolytic therapy was with streptokinase, which produces a coronary artery patency rate of about 50–60% by 90 min.[54] For patients receiving both fibrinolytic and magnesium infusions, the magnesium was begun within 2 h of the start of the fibrinolytic in about half of all randomised patients—and in about three-quarters of those randomised within 0–6 h of the onset of their symptoms. So, a large proportion of fibrinolytic-treated patients allocated magnesium would have had substantially raised blood magnesium during reperfusion.

Study treatments were conveniently packaged, with the tablets provided in calendar packs. (The contents were checked, and found to be correct, in random samples taken throughout the study.) Comparisons in the 2×2×2 factorial study design were as follows:

Captopril comparison Half of all patients were allocated randomly to receive 1 month of oral captopril (Capoten: 6·25 mg initial dose, 12·5 mg 2 h later, 25 mg 10–12 h later and then 50 mg twice daily for 28 days) and half to receive placebo.

Mononitrate comparison Half of all patients were allocated randomly to receive 1 month of oral controlled-release isosorbide mononitrate (Imdur: 30 mg initial dose, 30 mg 10–12 h later, and then 60 mg each morning for 28 days) and half to receive placebo.

Magnesium comparison Half of all patients were allocated randomly to receive 24 h of intravenous magnesium sulphate (8 mmol initial bolus injection over about 15 min followed by 72 mmol in about 50 ml infused over 24 h) and half to open control (with no placebo infusion being given, partly because flushing and other cutaneous signs and symptoms from the initial bolus were thought likely to "unblind" active treatment).

The study treatments were to be stopped only if interruption was judged to be clearly indicated by the responsible doctor. Doctors were free to use any additional therapy.

Discharge

After discharge, a simple single-sided discharge form was to be completed. This provided further identifiers to assist central follow-up of any deaths after discharge, and brief details of compliance with study treatment in hospital, of the use of non-study treatments, of possible side-effects of study treatment, of major events in hospital, and of the likely primary cause of death if the patient had died before discharge. When a small excess of renal complications was observed with captopril (see Results), further details were sought for central review by a renal physician blinded to treatment allocation. The severity of reported renal dysfunction was to be classified centrally as: mild (peak creatinine less than 300 μmol/l and managed without specific therapeutic intervention); moderate (peak creatinine ≥300 and <700 μmol/l and/or specific therapeutic interventions, other than dialysis); or severe (peak creatinine ≥700 μmol/l and/or the use of dialysis).

Follow-up

By November, 1994, discharge forms were available for 98% of all patients. There were no significant differences between the treatment groups in the percentages missing: 1·8% captopril *vs* 1·6% placebo; 1·7% mononitrate *vs* 1·8% placebo; 1·7% magnesium *vs* 1·7% open control. Surviving patients left hospital at a median of 9 days. Follow-up after discharge was only of mortality, and was conducted through government records wherever possible. The completeness of mortality follow-up is 97% to 5 weeks, 86% to 6 months, 68% to 1 year, and 81% to Oct 5, 1993 (see below), with no significant differences in follow-up between the treatment groups. About nine-tenths of all deaths in the first 5 weeks occur in hospital, and combination of the information from discharge forms with that from the other sources of mortality follow-up suggests that about 99% of the 5-week deaths among the 58 050 randomised patients are included in this report.

Statistical methods

Whether or not the study treatment was actually given, patients remained in their originally allocated treatment group for an "intention-to-treat" analysis.[55] The protocol specified three main comparisons: (i) oral captopril versus placebo; (ii) oral controlled-release mononitrate versus placebo; and (iii) intravenous magnesium versus open control. Originally these comparisons were to be of 5-week *vascular* mortality, but since only 0·8% of the deaths within the first 5 weeks in the ISIS-3 trial were classified as non-vascular (and this classification is somewhat arbitrary)[56] the steering committee, blind to the ISIS-4 results, decided to change this to *total* mortality. The most important subsidiary comparisons of 5-week mortality were to be: (i) study mononitrate versus placebo, subdivided by non-study nitrate treatment at randomisation; and (ii) assessment of whether the combination of captopril and controlled-release mononitrate produced an outcome that was clearly different from what might have been expected from their separate effects. The effects on longer-term mortality to at least 5 weeks after randomisation stopped (ie, to Oct 5, 1993), on particular modes of death, and on various non-fatal events in hospital were also to be reported. For major endpoints (such as death), the lack of a placebo infusion for those not allocated magnesium is not a problem, but it may be of some relevance for less objective measures (such as minor complications, or particular modes of death).

For events in hospital and deaths during the first 5 weeks, analyses involve simple comparisons of total numbers affected, whereas comparisons of survival to 12 months involve time-to-death analyses by logrank methods.[55] Absolute differences are given as benefits per 1000 patients treated, and proportional differences are given as odds ratios (or percentage reductions in the odds), along with their standard deviations (SD) or confidence intervals (CI). Two-sided p-values (2p) are cited throughout. For principal comparisons, 95% CIs are used (and 2p>0·05 is described as "not significant"), whereas for subgroups

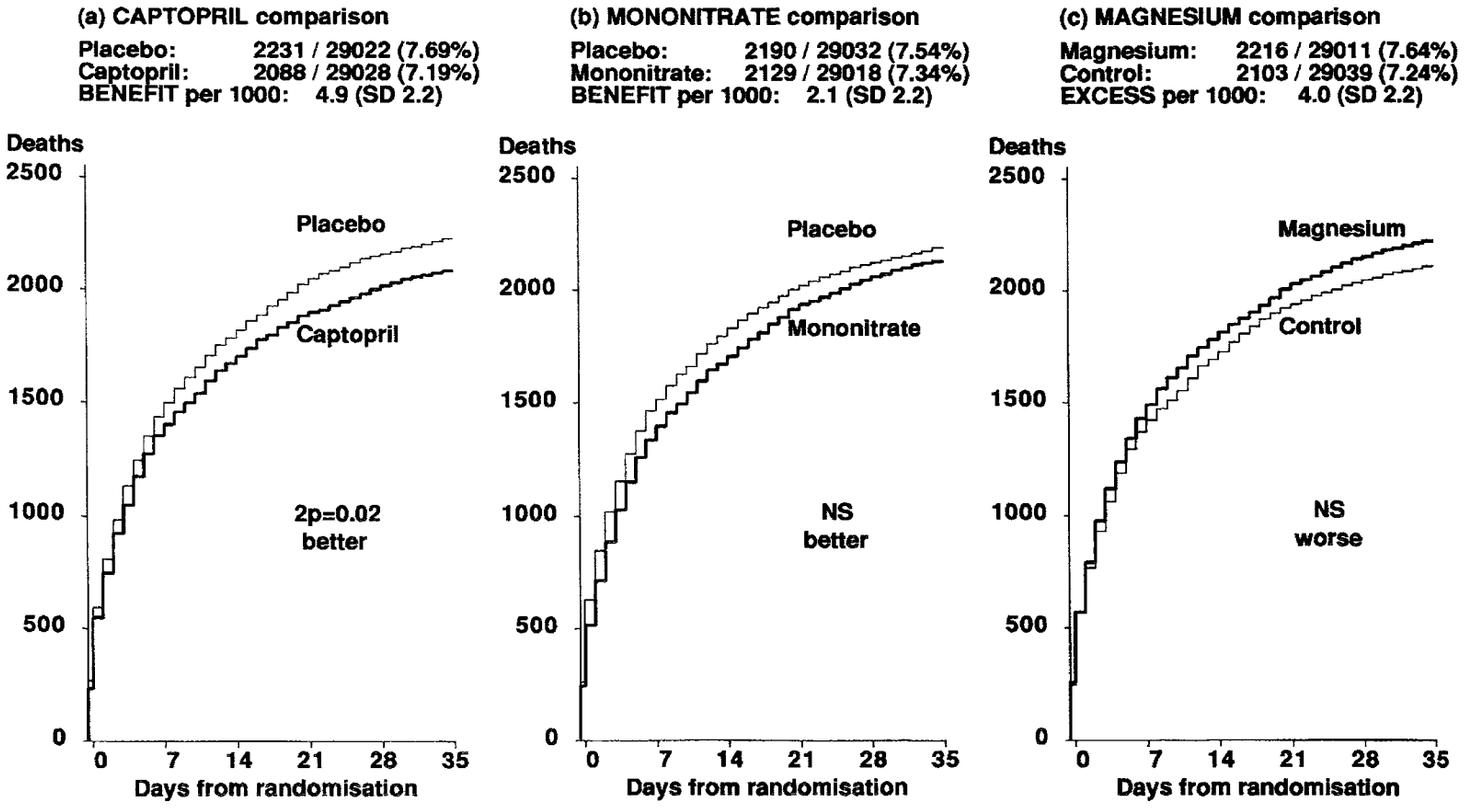

Figure 1: **Cumulative mortality reported in days 0-35**
(a) All patients allocated one month of oral captopril (thicker line) *vs* all allocated matching placebo; (b) All patients allocated one month of oral controlled-release mononitrate (thicker line) *vs* all allocated matching placebo; (c) All patients allocated 24 hours of intravenous magnesium sulphate (thicker line) *vs* all allocated open control.

or subsidiary outcomes, 99% CIs are used (and 2p>0·01 is described as "not significant").

The aim was to randomise at least 40 000 patients[1] and so, at the beginning of the study (in July 1991), sufficient treatment was made available for the randomisation of up to 60 000. During recruitment, the steering committee, pharmaceutical companies, collaborators, and administrative staff were to remain ignorant of the interim results, which were reviewed periodically by an independent data monitoring committee.[1] No clear differences emerged during this monitoring, and no information was provided to suggest that the study should stop. The steering committee decided, therefore, to continue randomisation until Aug 31, 1993, by which time almost all of the study drugs would have been used.

Patient characteristics and treatment

Between July, 1991 and August, 1993, 1086 hospitals in thirty-one countries randomised 58 050 patients within 24 h (median 8 h) of the onset of suspected acute MI. The large size (and the use of "minimisation"[53]) ensured good balance between the treatment groups for the main pre-randomisation prognostic features that were measured (see subgroup analyses below), and this is likely to be true of those that were not. Of the patients randomised, 79% had ST elevation on their presenting electrocardiogram, 40% were within 6 h of symptom onset, 28% were aged 70 years or over, 74% were male, 2% had SBP <100 mm Hg, 17% had a history of previous MI, and 14% had clinical heart failure. At entry to the study, non-study intravenous nitrates were being used in 47% of patients and other short-term non-study nitrates (excluding occasional sublingual use) in another 8%. Chronic diuretic use was recorded in 12%.

98% of randomised patients started their study tablets. Among patients allocated active-captopril, 83% continued study tablets until discharge (or death in hospital) compared with 87% of those allocated placebo-captopril. Of those discharged alive, 81% of those allocated active-captopril were discharged on the study tablets compared with 85% of those allocated placebo-captopril. Among patients allocated active-mononitrate, 85% continued study tablets until discharge (or death in hospital) and 83% were discharged on the study tablets, compared with 87% and 85%, respectively, of those allocated placebo-mononitrate. Among those allocated intravenous magnesium, 93% received some (study or non-study) magnesium, and the study infusion was started in 92% and completed in 88%, while among those allocated open control only 5% received some intravenous magnesium.

After randomisation, the use of non-study treatments in hospital was evenly balanced between the study treatment groups (94% of patients receiving antiplatelet therapy, 70% fibrinolytic therapy, 54% intravenous nitrate, 6% some other non-study nitrate, 9% intravenous beta-blocker, 21% antiarrhythmics, and 5% non-study CEI), except that non-study CEIs were used slightly less commonly among patients allocated active-captopril than among those allocated placebo-captopril (4·7% *vs* 6·0%; 2p<0·0001). There was substantial variation in the use of intravenous nitrates in participating countries (about three-quarters of patients from the USA, Norway, Argentina, Germany, and Poland compared with about one-quarter or less of those from the UK, Sweden, Brazil, and New Zealand).

Infarction was confirmed in 92% of all randomised patients, 4% were recorded as having suffered a subsequent reinfarction during their hospital stay, and, despite the large proportion of elderly patients, the incidence of stroke was only 1·0%. Patients with

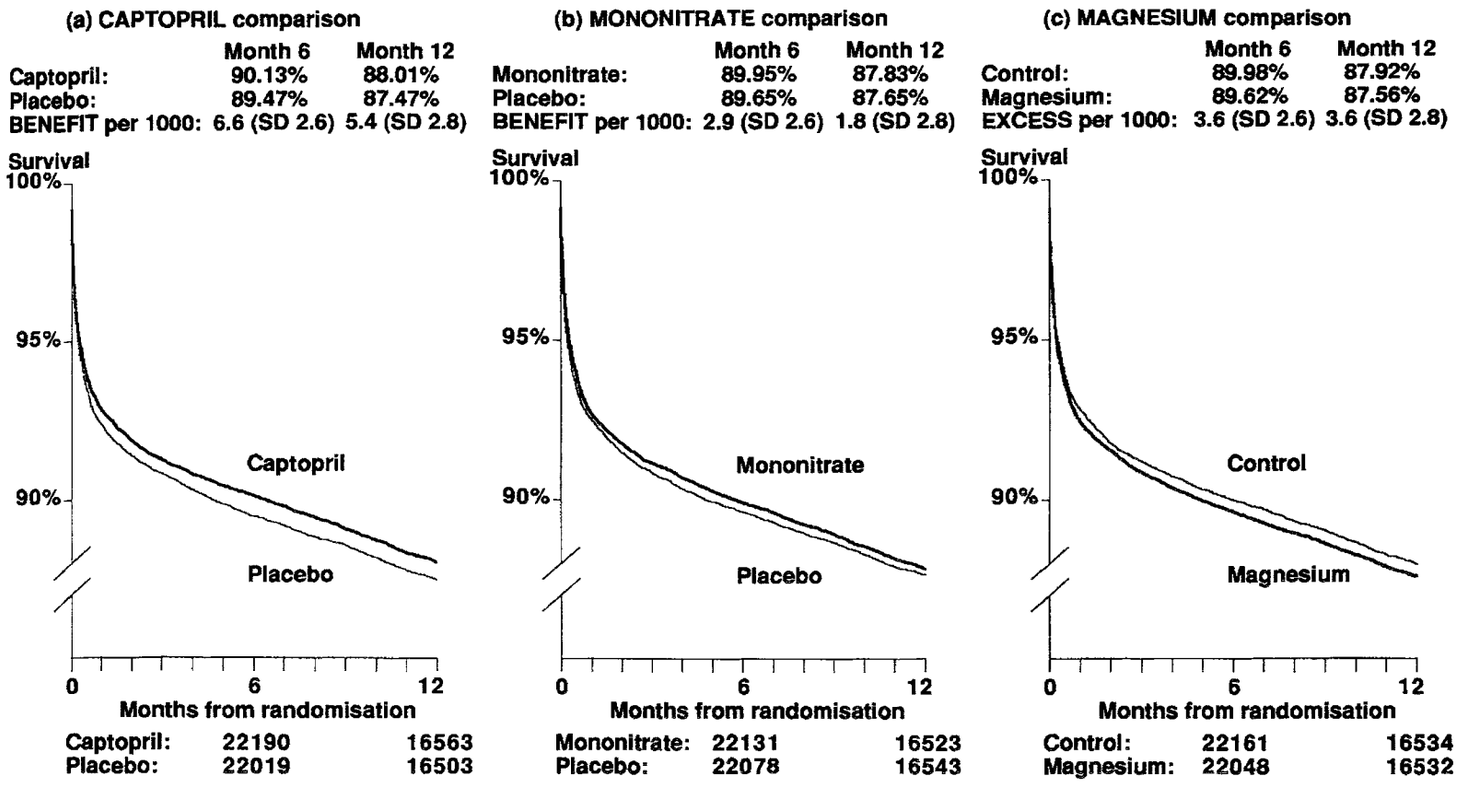

Figure 2: **Life-table estimates of 12-month survival**
Comparisons (a), (b), and (c) as in figure 1. Median follow-up is 15 months, and follow-up by life-table methods is 86% complete to 6 months and 68% complete to 12 months[55]. Log-rank observed minus expected numbers of deaths (with negative values indicating fewer treatment group deaths than expected), and their variances, during days 36-365 and days 366+, respectively: (a) −13·55 and 533·4, −6·71 and 125·2; (b) −8·44 and 533·4, −6·84 and 125·2; (c) −3·67 and 533·4, +1·94 and 125·2. These indicate that for none of the comparisons was there any adverse mortality trend after day 35.

cardiogenic shock or persistent severe hypotension were generally excluded from the study, so the reported incidence of subsequent cardiogenic shock was low (4%, compared with 7% in ISIS-3[56]), whereas heart failure was reported quite commonly (17% in ISIS-4 and in ISIS-3).

Results: oral captopril versus placebo

Effects on mortality in first 5 weeks and later

During the first 5 weeks there were 2088 (7·19%) deaths recorded among 29 028 captopril-allocated patients compared with 2231 (7·69%) among 29 022 patients allocated matching placebo (figure 1a). This 7% (SD 3) proportional reduction in the odds of death during days 0–35 is statistically significant (95% CI of 13% to 1% reduction; 2p=0·02) and corresponds to an absolute difference of 4·9 (SD 2·2) fewer deaths per 1000 patients treated with captopril for 1 month. Reassuringly, there appeared to be somewhat fewer deaths in the first day or two of treatment (deaths on days 0–1: 549 [1·89%] captopril *vs* 593 [2·04%] placebo). The benefits of early captopril treatment seemed to persist for at least one year (figure 2a: 5·4 [SD 2·8] fewer deaths per 1000 at 12 months), with a small non-significant benefit after the first month.

Since the 1-month mortality difference is only moderately significant, the chief need is to consider these results together with the randomised evidence from other similar trials (see Discussion), rather than to consider various subdivisions of the ISIS-4 results, which are of limited reliability for statistical reasons. The proportional reductions in 5-week mortality with captopril appeared to be fairly similar in the presence and in the absence of the other study treatments (ie, mononitrate or magnesium: figure 3a), suggesting there were no strong interactions between the effects of the different study treatments. Nor were the effects of captopril in any of the other patient subgroups examined clearly different from the 7% proportional reduction observed overall (figure 4a). So, although the absolute benefits appeared to be particularly large in some high-risk patient groups—such as those with a previous history of MI (18 fewer deaths per 1000) or those with clinically evident heart failure at entry (14 fewer deaths per 1000)—these differences may have been inflated by the play of chance, and the actual benefits in such patients may be smaller (perhaps about 10 fewer deaths per 1000). Similarly, although data-dependent subgroup analyses suggest little effect on 5-week mortality in some other patient groups—such as the elderly—these do not provide statistically reliable evidence that the real effects in these subgroups are different from those observed overall. So, the overall result provides indirect evidence of benefit in older patients, which is in accord with the GISSI-3 results with lisinopril among older patients.[57]

Concerns had been expressed about the effects of the early use of CEIs on mortality among patients presenting with low systolic blood pressures.[58] But, although there were slightly more deaths in days 0–35 with captopril among those with entry SBP <100 mm Hg (96 [14·2%] captopril *vs* 83 [12·4%] placebo; NS), this apparent adverse effect was not statistically significantly different from the overall benefit and was not supported by the opposite pattern among those with SBP of 100–104 mm Hg (112 [7·5%] *vs* 136 [9·4%]; NS). More importantly,

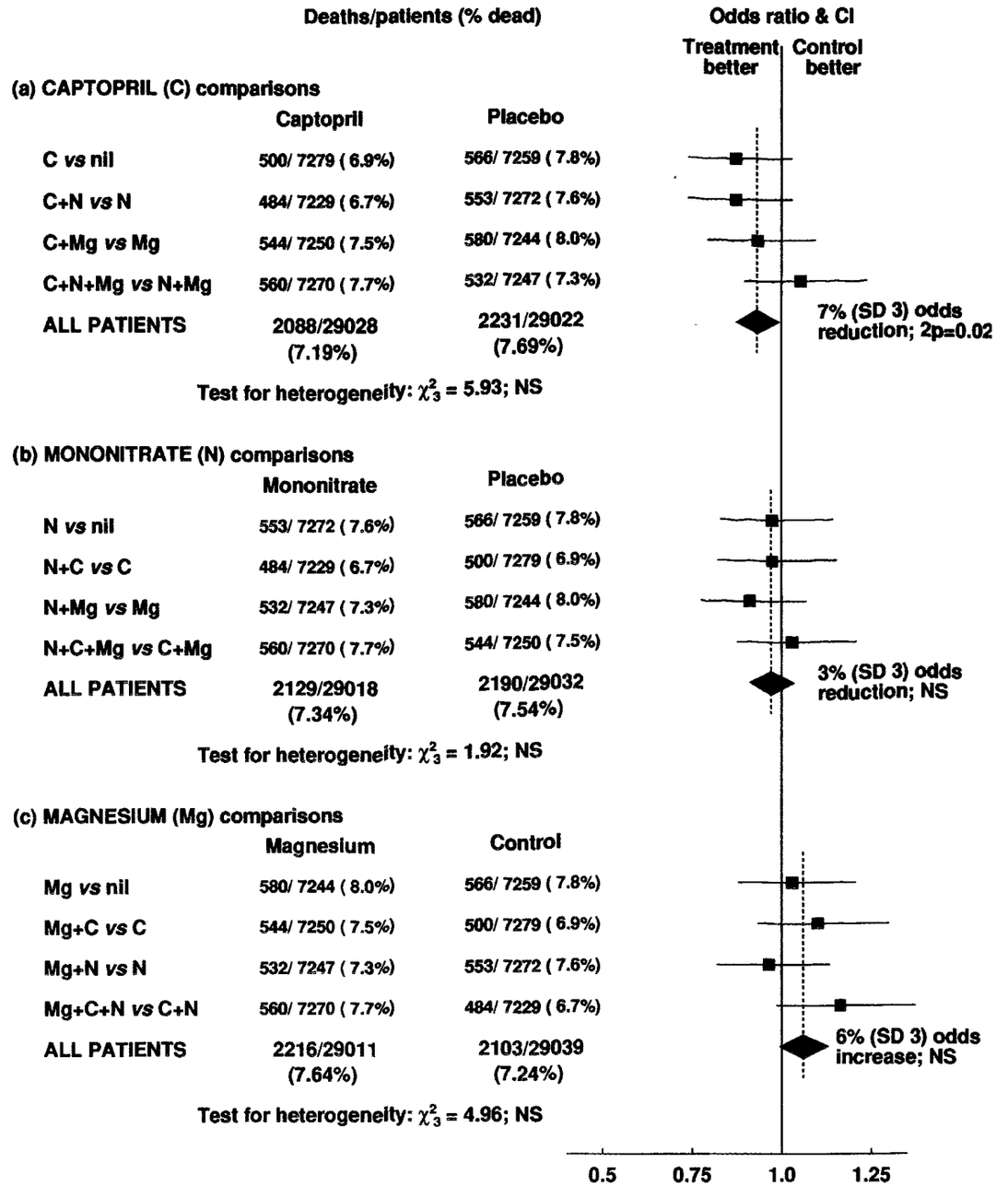

Figure 3: **Mortality in days 0-35 subdivided by other randomly allocated study treatments**
Comparisons (a), (b), and (c) as in figure 1. C=captopril, N=mononitrate, Mg=magnesium: so, for example, the subgroup assessment of captopril in the presence of mononitrate is denoted C+N *vs* N. Odds ratios (ORs: black squares with areas proportional to the amount of "statistical information" in each subdivision[60]) comparing the mortality among patients allocated the study treatment to that among patients allocated the relevant control are plotted for each of the treatment comparisons, subdivided by the other randomly allocated study treatments, along with their 99% confidence intervals (CIs: horizontal lines). For each of the three study treatment comparisons, the overall result and its 95% CI is represented by a diamond, with the overall proportional reduction (or increase) and statistical significance given alongside. Squares or diamonds to the left of the solid vertical line indicate benefit (significant at 2p<0·01 when the entire horizontal line is to the left of the vertical line and at 2p<0·05 when the diamond does not overlap the vertical line). Chi-square tests[60] for evidence of heterogeneity of the sizes of the ORs in the subdivisions are also given.

there was no excess of deaths on days 0–1 among patients with low blood pressure at entry (SBP <100 mm Hg: 41 [6·1%] *vs* 40 [6·0%]; SBP 100–104 mm Hg: 35 [2·4%] *vs* 42 [2·9%]).

Effects on other clinical events in hospital

Captopril was associated with a small increase in the proportion of patients in whom infarction was confirmed (table 1a), but this difference was only marginally significant for a subsidiary analysis (2p=0·01: see statistical methods). Despite previous concerns,[7] starting captopril early in acute MI was not associated with any significant increase in reported reinfarction. Unexpectedly, however, captopril was associated with a small, but significant, excess of second or third degree heart block (6 [SD 2] excess per 1000; 2p<0·001), mostly soon after the start of treatment (days 0–1: 5 [SD 1] per 1000). No significant difference in heart failure occurring in hospital was recorded. A small excess of cardiogenic shock was reported with captopril (5 [SD 2] excess per 1000; 2p <0·01), again mostly early (days 0–1: 4 [SD 1] per 1000), but there was no significant difference in deaths attributed to cardiogenic shock (1·48% captopril *vs* 1·40% placebo). There was an increase in hypotension considered severe enough to require termination of study treatment (10·0% captopril *vs* 4·8% placebo; 52 [SD 2] excess per 1000; 2p<0·0001), about half of which was observed early (days 0–1: 28 [SD 2] per 1000). This

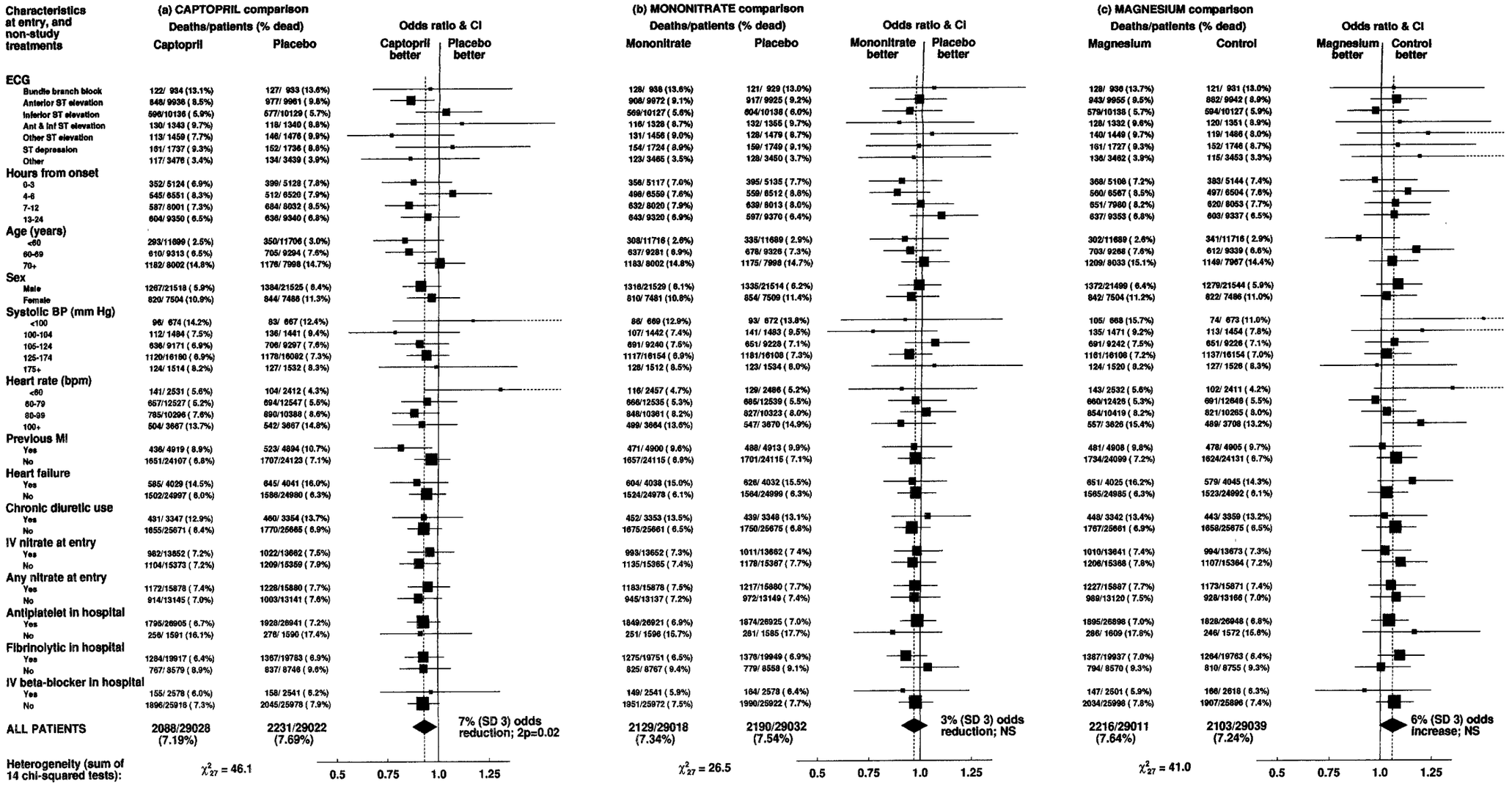

Figure 4: **Mortality in days 0-35 subdivided by presentation features and by non-study treatments**
Comparisons (a), (b), and (c) as in figure 1, and symbols and conventions as in figure 3. (The chi-square heterogeneity test results may be inflated since the baseline factors are not independent of each other.)

	(a) Captopril comparison		(b) Mononitrate comparison		(c) Magnesium comparison	
	Captopril n (%)	Placebo n (%)	Mononitrate n (%)	Placebo n (%)	Magnesium n (%)	Control n (%)
No randomised	29 028	29 022	29 018	29 032	29 011	29 039
No with discharge form	28 515	28 546	28 539	28 522	28 527	28 534
Infarction confirmed	26 322 (92·3)	26 193 (91·8)*	26 251 (92·0)	26 274 (92·1)	26 264 (92·1)	26 261 (92·0)
Post-infarction angina	4581 (16·1)	4517 (15·8)	4562 (16·0)	4536 (15·9)	4563 (16·0)	4535 (15·9)
Coronary artery graft (CABG) or angioplasty (PTCA)	1322 (4·6)	1288 (4·5)	1318 (4·6)	1292 (4·5)	1320 (4·6)	1290 (4·5)
Stroke	295 (1·0)	268 (0·9)	277 (1·0)	286 (1·0)	291 (1·0)	272 (1·0)
Pulmonary or systemic embolism	149 (0·5)	152 (0·5)	142 (0·5)	159 (0·6)	148 (0·5)	153 (0·5)
Reinfarction	1162 (4·1)	1101 (3·9)	1143 (4·0)	1120 (3·9)	1134 (4·0)	1129 (4·0)
Day 0–1	294 (1·0)	259 (0·9)	265 (0·9)	288 (1·0)	264 (0·9)	289 (1·0)
Day 2–35	868 (3·0)	842 (2·9)	878 (3·1)	832 (2·9)	870 (3·0)	840 (2·9)
Ventricular fibrillation	1031 (3·6)	1048 (3·7)	1060 (3·7)	1019 (3·6)	992 (3·5)	1087 (3·8)
Day 0–1	680 (2·4)	718 (2·5)	712 (2·5)	686 (2·4)	652 (2·3)	746 (2·6)
Day 2–35	351 (1·2)	330 (1·2)	348 (1·2)	333 (1·2)	340 (1·2)	341 (1·2)
Other cardiac arrest	844 (3·0)	901 (3·2)	866 (3·0)	879 (3·1)	916 (3·2)	829 (2·9)
Day 0–1	396 (1·4)	413 (1·4)	381 (1·3)	428 (1·5)	434 (1·5)	375 (1·3)
Day 2–35	448 (1·6)	488 (1·7)	485 (1·7)	451 (1·6)	482 (1·7)	454 (1·6)
2°/3° heart block	1179 (4·1)	1004 (3·5)†	1093 (3·8)	1090 (3·8)	1115 (3·9)	1068 (3·7)
Day 0–1	802 (2·8)	662 (2·3)†	720 (2·5)	744 (2·6)	775 (2·7)	689 (2·4)
Day 2–35	377 (1·3)	342 (1·2)	373 (1·3)	346 (1·2)	340 (1·2)	379 (1·3)
Heart failure	4847 (17·0)	4952 (17·3)	4930 (17·3)	4869 (17·1)	5069 (17·8)	4730 (16·6)†
Day 0–1	2871 (10·1)	2903 (10·2)	2865 (10·0)	2909 (10·2)	3079 (10·8)	2695 (9·4)‡
Day 2–35	1976 (6·9)	2049 (7·2)	2065 (7·2)	1960 (6·9)	1990 (7·0)	2035 (7·1)
Cardiogenic shock	1309 (4·6)	1170 (4·1)*	1233 (4·3)	1246 (4·4)	1306 (4·6)	1173 (4·1)*
Day 0–1	748 (2·6)	631 (2·2)*	669 (2·3)	710 (2·5)	741 (2·6)	638 (2·2)*
Day 2–35	561 (2·0)	539 (1·9)	564 (2·0)	536 (1·9)	565 (2·9)	535 (1·9)
Profound hypotension requiring termination of study treatment	2851 (10·0)	1368 (4·8)‡	2318 (8·1)	1901 (6·7)‡	2267 (7·9)	1952 (6·8)‡
Day 0–1	1501 (5·3)	717 (2·5)‡	1230 (4·3)	988 (3·5)‡	1265 (4·4)	953 (3·3)‡
Day 2–35	1350 (4·7)	651 (2·3)‡	1088 (3·8)	913 (3·2)‡	1002 (3·5)	999 (3·5)
Any profound hypotension	5951 (20·9)	3130 (11·0)‡	4970 (17·4)	4111 (14·4)‡	4781 (16·8)	4300 (15·1)‡
Median days in hospital of survivors (25 & 75 centile)	9 (7 & 15)	9 (6 & 15)	9 (6 & 15)	9 (6 & 15)	9 (7 & 15)	9 (6 & 15)

*2p<0·01; †2p<0·001; ‡2p<0·0001.

Table 1: **Clinical events in hospital (up to day 35 or earlier discharge)**

excess with captopril appeared to be particularly large among patients who presented with entry SBP <100 mm Hg (22·1% *vs* 10·4%; 117 [SD 20] excess per 1000), but not in any other group of patients studied (including, for example, those receiving study mononitrate: 59 [SD 3] excess per 1000).

Other adverse events occurring in hospital were not specifically asked about but were to be recorded on the discharge form. Table 2a indicates those reported significantly (2p<0·01) more or less commonly with captopril. Headache was slightly less common (in contrast to the mononitrate result) and dizziness associated with hypotension was slightly more common. There was, as in GISSI-3, a small excess of renal dysfunction (1·1% captopril *vs* 0·6% placebo; 5 [SD 1] per 1000) but most of these cases were not classified as severe (0·5 [SD 0·2] excess per 1000 of severe renal dysfunction). Complications associated with control of diabetes mellitus were recorded less commonly among patients allocated captopril.

Results: oral mononitrate versus placebo

Effects on mortality in first 5 weeks and later

During the first 5 weeks there were 2129 (7·34%) deaths recorded among 29 018 mononitrate-allocated patients compared with 2190 (7·54%) among 29 032 patients allocated matching placebo (figure 1b). This 3% (SD 3) proportional reduction in the odds of death during days 0–35 is not statistically significant (2p=0·3), and the 95% CI (9% reduction to 3% increase) completely excludes the large effects suggested by the previous small trials of short-term nitrate therapy. Follow-up to 1 year did not indicate any further divergence or convergence of the survival curves following one month of oral mononitrate (figure 2b: 1·8 [SD 2·8] fewer deaths per 1000 at 12 months; NS).

There appeared to be a greater effect early after starting treatment (deaths on days 0–1: 514 [1·77%] mononitrate *vs* 628 [2·16%] placebo; 2p<0·001). This emphasis on mortality on days 0–1 only was, however, an entirely "data-derived" analysis (with no particular cause of early death clearly prevented: data not shown). If this effect on early mortality is real, it would have been expected largely among those who were not already receiving non-study nitrates at the time of randomisation. Actually, the difference in deaths during days 0–1 among such patients (236 [1·80%] study mononitrate *vs* 305 [2·32%] placebo) was about the same as the overall result. Hence, although the overall benefit on days 0–1 does support the safety of early nitrate use, it does not clearly demonstrate efficacy.

There was no significant evidence that mononitrate had any effect on 5-week mortality in the presence or in the absence of the other study treatments (figure 3b). Nor did one month of oral mononitrate significantly reduce mortality in any of the other patient subgroups studied (figure 4b). In particular, there was no significant survival advantage among those treated early after the onset of symptoms, among those with heart failure at entry, or

among those not receiving intravenous or other non-study nitrates (which might have diluted any benefits of the oral mononitrate studied). The baseline characteristics of patients receiving and not receiving non-study nitrates were very similar (for example, 14·2% and 13·5%, respectively, had heart failure at entry)—an indication that non-study nitrate use may have been determined more by general policy than by clinical indications in particular patients. The use of non-study nitrates also varied substantially from country to country, but even in countries where they were not commonly used there was no evidence of any mortality benefit with the study mononitrate (for example, 911 [8·0%] study mononitrate deaths *vs* 921 [8·1%] placebo deaths in countries where only about one-quarter or less of patients [average of 17%] were on intravenous nitrates at entry; NS).

Effects on other clinical events in hospital

Mononitrate was not associated with any significant difference in the proportion of patients in whom infarction was confirmed, or in reinfarction rates (table 1b). Nor was there any apparent reduction in the number of patients reported to have had post-infarction angina at some time during the hospital stay (16·0% mononitrate *vs* 15·9% placebo). There was an increase in hypotension considered severe enough to require termination of study treatment (8·1% mononitrate *vs* 6·7% placebo; 15 [SD 2] excess per 1000; 2p<0·0001), about half of which occurred early after the start of treatment (days 0–1: 8 [SD 2] per 1000). This excess did not seem to be greater in any particular group of patients (including those receiving the other study treatments). No other differences in major clinical events were observed with mononitrate.

Table 2b indicates that, as might be expected, headache was recorded significantly (2p<0·0001) more commonly among those allocated mononitrate. Dizziness, both with or without hypotension, was only slightly more common with mononitrate.

	Events/patients (%)		Excess per 1000 (SD): active minus control
	Active treatment	Control treatment	
(a) Captopril comparison			
Headache	356 (1·25)	430 (1·51)	−2·6 (1·0)*
Dizziness	155 (0·54)	110 (0·39)	1·6 (0·6)*
With profound hypotension	83 (0·29)	30 (0·11)	1·9 (0·4)‡
Other dizziness	72 (0·25)	80 (0·28)	−0·3 (0·4)
Renal dysfunction	316 (1·11)	170 (0·60)	5·1 (0·8)‡
Mild	130 (0·46)	74 (0·26)	2·0 (0·5)‡
Moderate	68 (0·24)	23 (0 08)	1·6 (0·3)‡
Severe	26 (0·09)	13 (0·05)	0·5 (0·2)
Unknown severity	92 (0·32)	60 (0·21)	1·1 (0·4)*
Problems with diabetes control	1 (0·00)	12 (0·04)	−0·4 (0·1)*
(b) Mononitrate comparison			
Headache	660 (2·31)	126 (0·44)	18 7 (1·0)‡
Dizziness	156 (0·55)	109 (0·38)	1·6 (0·6)*
With profound hypotension	68 (0·24)	45 (0·16)	0·8 (0·4)
Other dizziness	88 (0·31)	64 (0·22)	0·8 (0·4)
(c) Magnesium comparison			
Bradycardia	211 (0·74)	133 (0·47)	2·7 (0·6)‡
Flushing/burning	89 (0·31)	12 (0·04)	2·7 (0·4)‡

*2p<0·01; ‡2p<0·0001.

Table 2: **Other clinical events reported in hospital (up to day 35 or earlier discharge) significantly more or less commonly in the active treatment groups**

Results: intravenous magnesium versus open control

Effects on mortality in first 5 weeks and later

During the first 5 weeks there were 2216 (7·64%) deaths recorded among 29 011 magnesium-allocated patients compared with 2103 (7·24%) among 29 039 patients allocated open control (figure 1c). This 6% (SD 3) proportional increase in the odds of death during days 0–35 is not statistically significant (2p=0·07), but the 95% CI (0% reduction to 12% increase) does completely exclude the large effects suggested by the previous small trials. Follow-up to 1 year did not indicate any further divergence or convergence of the survival curves (figure 2c: 3·6 [SD 2·8] more deaths per 1000 at 12 months; NS).

There was no significant evidence that magnesium had any effect on 5-week mortality in the presence or in the absence of the other study treatments (figure 3c). Nor did intravenous magnesium appear to reduce mortality in any of the other patient subgroups studied (figure 4c). In particular, there was no significant survival advantage among the more than 23 000 patients randomised within 6 h of the onset of symptoms (928 [7·9%] magnesium *vs* 880 [7·6%] control; NS), in whom the magnesium infusion seems generally to have been started soon after the start of any fibrinolytic therapy (and, hence, before reperfusion in a substantial proportion: see Methods). Nor was there any significant survival advantage among the more than 17 000 patients who, like the majority in all previous trials of magnesium, did not receive fibrinolytic therapy (794 [9·3%] magnesium *vs* 810 [9·3%] control): of these, 9000 were randomised in ISIS-4 within less than 12 h of the onset of symptoms (median of 7 h: ie, with about the same average delay as in the previous trials), but even among them there was no evidence of benefit (10·3% *vs* 10·5%). Indeed, the only marginally significant effects of magnesium in any subgroups are the apparent excesses of deaths among patients who presented with slow heart rate or low SBP. But these do not—because of the large number of comparisons that have been made—provide good evidence of hazard. Moreover, there was no net hazard in the first day or two after randomisation, which includes the whole period when the magnesium infusion was to be given (deaths on days 0–1: 571 [1·97%] magnesium *vs* 571 [1·97%] control).

Effects on other clinical events in hospital

The assessment of magnesium involved open control. As in the much smaller placebo-controlled LIMIT-2 trial[48] magnesium was not associated with any decrease in the proportion of patients in whom infarction was confirmed (table 1c). Slightly fewer patients allocated magnesium were recorded as having ventricular fibrillation (0·01<2p<0·05) but slightly more were recorded as having some other form of cardiac arrest (0·01<2p<0·05), so that there was no difference overall in cardiac arrest (6·7% *vs* 6·7%). Despite concerns that magnesium might delay conduction no overall increase in the incidence of second or third degree heart block was observed, although there was a slight but not convincingly significant (0·01<2p<0·05: see Statistical methods) excess during or just after the infusion. In contrast with the

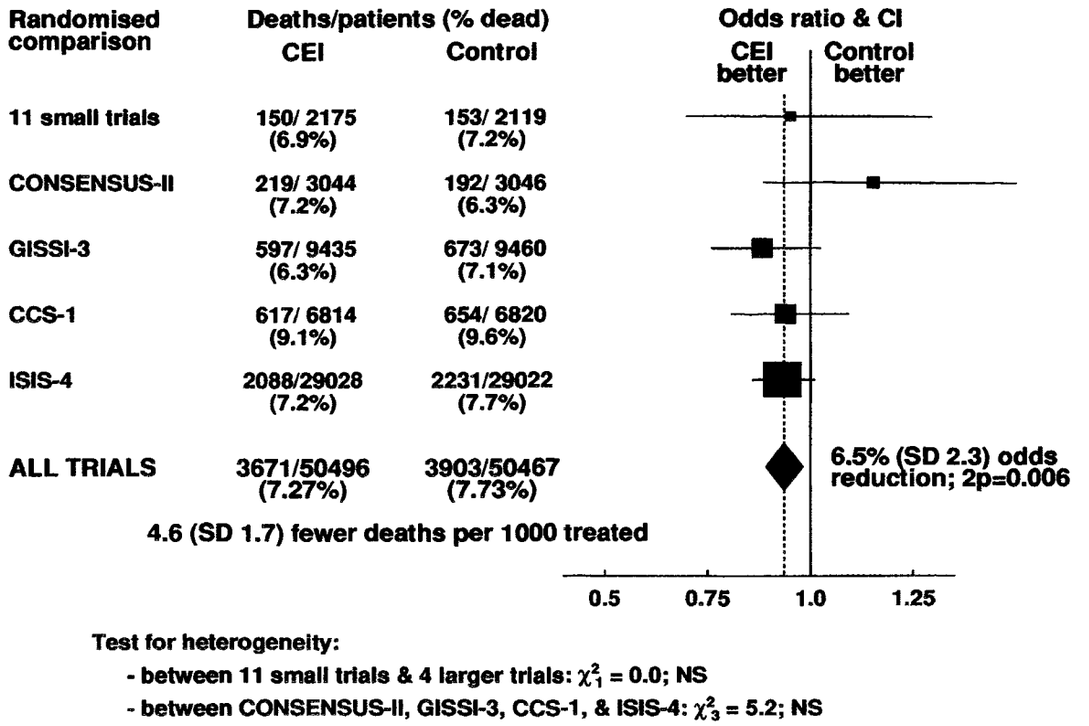

Figure 5: **Systematic overview of effects on short-term mortality of starting converting enzyme inhibitors (CEI) early in acute myocardial infarction**
Symbols and conventions as in figure 3. The results from the smaller trials were combined by use of standard overview methods[59,60] to yield the stratified OR that is plotted for these small trials. The overall OR for all trials is likewise stratified by trial, whereas the absolute mortality difference is unstratified. 99% CIs are used for the overview of small trials and for each of the larger trials, whereas a 95% CI, represented by a diamond, is used for the overall result.

results of some, but not all, previous trials,[45-48] intravenous magnesium was associated with small but significant increases in heart failure (12 [SD 3] per 1000; 2p<0·001), in cardiogenic shock (5 [SD 2] per 1000; 2p<0·01), and in deaths attributed to cardiogenic shock (1·62% magnesium *vs* 1·26% control; 2p<0·001). These excesses with magnesium mostly emerged during or just after the infusion period (heart failure on days 0–1: 13 [SD 3] per 1000; shock on days 0–1: 4 [SD 1] per 1000). There was a small increase in hypotension considered severe enough to require termination of study treatment (7·9% *vs* 6·8%; 11 [SD 2] excess per 1000; 2p<0·0001) that was observed early (days 0–1: 11 [SD 2] per 1000). This excess did not seem to be increased in any particular group of patients studied (including those receiving the other study treatments).

Bradycardia was recorded significantly (2p<0·0001) more commonly among those allocated intravenous magnesium (table 2c). Flushing was not systematically asked about and was rarely reported with the intravenous magnesium regimen studied—in which the initial 8 mmol bolus was given over about 15 min (compared with 5 min in LIMIT-2)—but still there was a small excess of such reports.

Discussion

Previous large randomised trials have shown that fibrinolytic and antiplatelet therapies can each improve survival substantially and that their effects are approximately additive.[59,60] Typically, fibrinolytic therapy in 1000 patients presenting with ST elevation or bundle branch block within less than 12 h of symptom onset prevents about 20–30 early deaths.[59] The addition of 1 month of medium-dose aspirin avoids about another 25 early deaths (as well as 10–15 non-fatal reinfarctions or strokes).[60] It is perhaps unrealistic to expect further mortality reductions of a few tens per 1000 with currently available treatments, but mortality reductions of "only" 10 lives saved per 1000 might well await discovery. Indeed, even a reduction from 8% mortality down to 7·5% (ie, 5 lives saved per 1000) by a widely practicable treatment with low toxicity could save thousands of lives each year. Reliable detection of such differences is not possible without randomised trials involving some thousands of deaths (to ensure that random errors are small in comparison with any such effects as may exist), together with systematic overviews of all relevant randomised trials that have assessed the same, or similar, treatments (to avoid biases due to selective emphasis of one or other extreme result in some particular trial or subset).[2,61] For these reasons, the results of ISIS-4 are discussed together with the other relevant randomised evidence.

Converting enzyme inhibitors started early in acute MI: about 5 lives saved per 1000 treated for 1 month

Previous trials of CEIs started a few weeks or months after MI in patients with evidence of impaired ventricular function and continued for some years have shown that such long-term therapy is protective,[19-21] saving about 2 lives per 1000 patients during each later month of treatment. Such long-term treatment also reduced the development of severe heart failure. Taken together, ISIS-4 and the other randomised trials of CEIs started early in the acute phase of infarction[24-33,57,58,62] now show that immediate treatment is safe and well tolerated (even when added to other treatments that also lower blood pressure, such as nitrates and fibrinolytic therapy) and that it

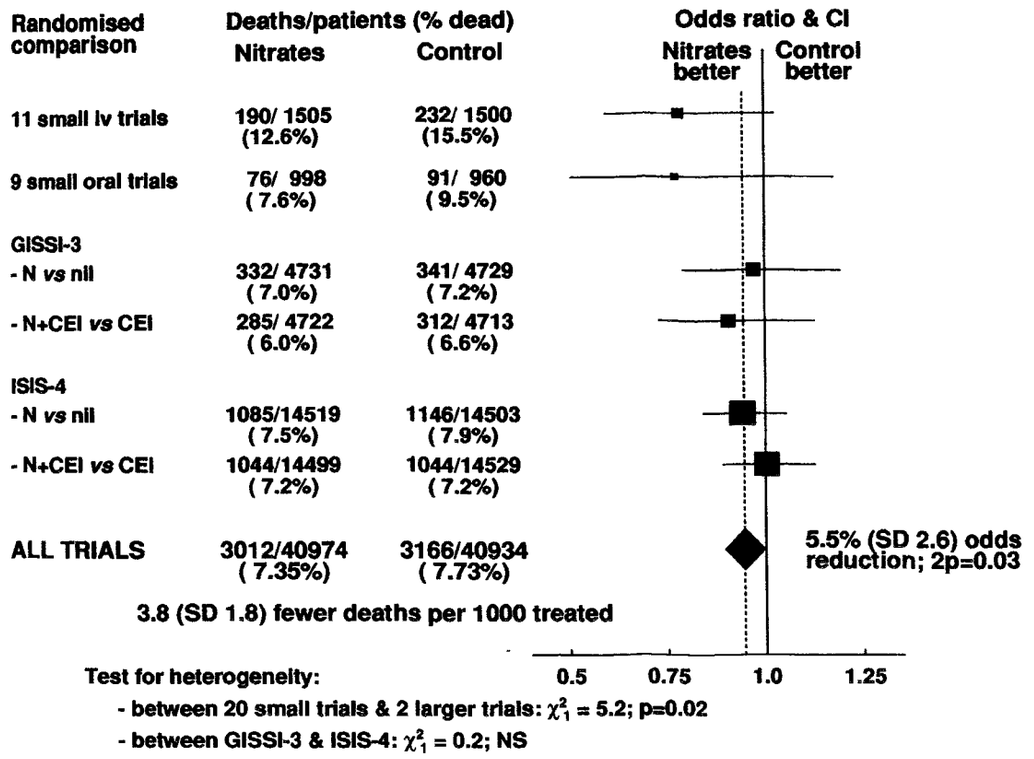

Figure 6: **Systematic overview of effects on short-term mortality of starting nitrates early in acute myocardial infarction**
Symbols and conventions as in figures 3 and 5.

produces a modest, but definite (2p=0·006), reduction in 1-month mortality (figure 5). ISIS-4 also indicates that the benefit from one month of treatment is maintained for at least 1 year (figure 2a). Neither in ISIS-4 (figure 3a) nor in GISSI-3 was there any significant evidence that the effect of CEI therapy was different in the presence or absence of the other study treatments. Typically, for a wide range of patients, about 5 extra lives were saved for every 1000 patients treated with CEIs early after the onset of acute MI, with somewhat greater absolute benefits—perhaps about 10 lives saved per 1000—in certain higher-risk groups, such as those presenting with a history of previous MI or with heart failure.

Discontinuation of CEIs because of hypotension was more common in patients who were already somewhat hypotensive (eg, SBP <100 mm Hg) before the start of treatment, but even among them this treatment was not associated with any increase in early death. In ISIS-4 and in GISSI-3[57] (though not in the much smaller CONSENSUS-II study[58]), CEI-associated hypotension carried a better short-term prognosis than placebo-associated hypotension. But this might be merely because CEI therapy has mixed some good-prognosis patients who would not otherwise have become hypotensive with the poor-prognosis patients who would have become hypotensive anyway. Arguments about the effects of treatment in subgroups that are defined by their hypotensive response to treatment can be completely misleading, and cannot reliably support claims of hazard[22] or of benefit, as it is not known which placebo-allocated

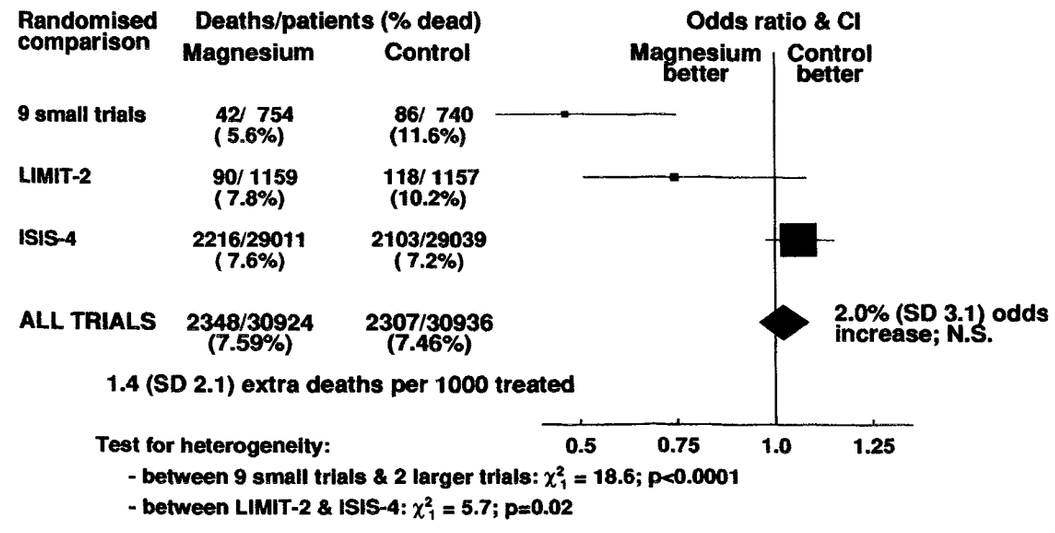

Figure 7: **Systematic overview of effects on short-term mortality of starting intravenous magnesium early in acute myocardial infarction**
Symbols and conventions as in figures 3 and 5.

patients should be compared with those who become hypotensive on active treatment. The only unbiased subgroup analyses are those defined by hypotension (or related factors) recorded before the start of study treatment, and for mortality these are generally reassuring in ISIS-4, GISSI-3, and CONSENSUS-II.[63] Hence, although for the routine use of CEI therapy in acute MI the lower SBP limit of 90–100 mm Hg that governed entry into ISIS-4 might be increased to 100 mm Hg or so (to avoid worries about hypotension), there is no evidence that it should be raised further. Apart from hypotension, a small excess of renal dysfunction was observed with CEIs in both ISIS-4 and GISSI-3, but in neither trial did this appear to be severe.

Nitrate therapy started early in acute MI: safe and well tolerated but no clear survival advantage

ISIS-4 tested, in almost 60 000 patients, 1 month of an oral controlled-release mononitrate regimen designed to avoid tolerance.[40] In addition, GISSI-3 has tested, in almost 20 000 patients, 24 h of intravenous glyceryl trinitrate (GTN) followed by six weeks of transdermal GTN.[57] Despite these large numbers, there is no clear evidence from these trials that nitrates improve survival, either overall (figure 6) or in any particular category of patient (including those that did not receive any non-study nitrate therapy). Nor is there any good evidence from these large trials (in contrast with previous suggestions[57]) that nitrates have a greater effect on mortality in patients receiving CEI therapy (figure 6). Another large randomised trial, ESPRIM, studied a different donor of endothelial nitric oxide (molsidomine given for 2 weeks) in 4000 patients, and again no significant survival advantage was observed (168 [8·4%] deaths among 2007 patients allocated molsidomine *vs* 176 [8·8%] deaths among 2010 controls).[64] Consequently, if there is any real mortality reduction with nitrates (or with this other nitric oxide donor), it is much less than the previous small nitrate trials had suggested (figure 6).[24,25,33,36,37] These nitrate regimens were, however, well tolerated in acute MI—indeed, on the first day or so there were somewhat fewer deaths in ISIS-4 among those allocated study nitrate, which is reassuring about the safety of nitrate use early in acute MI for symptomatic relief of angina or for left ventricular failure.

Intravenous magnesium in acute MI: no evidence of benefit overall or in any subgroup examined

Previously, eight very small trials of the intravenous infusion of magnesium, in a total of about 1000 patients with suspected acute MI, had collectively indicated a mortality reduction of about one-half[1,45,46] (figure 7: which also includes a recent small study[65]). Even if magnesium infusion could be shown to reduce mortality not by 50% but by "only" about 10%, this would still be clinically important with such an inexpensive and relatively simple treatment. The first study to test the hypothesis generated by the overview of small trials was LIMIT-2.[48-50] In that study, magnesium appeared to reduce early mortality by about one-quarter. There were, however, fewer than 200 deaths in the first month, so those results were statistically compatible both with a halving of mortality and with there being no benefit (figure 7). Now ISIS-4 has tested intravenous magnesium in nearly 60 000 patients with suspected acute MI (involving more than 4000 deaths), using a regimen very similar to that in LIMIT-2 (the only differences being that the initial 8 mmol bolus was to be given in ISIS-4 over about 15 min rather than about 5 min, and that the 24 h infusion was of 72 mmol rather than 68 mmol). In ISIS-4 alone or, more appropriately, in a combination of ISIS-4 with the previous trials, there is now no evidence of any beneficial effect of magnesium (figure 7).

Commentators on the preliminary results of ISIS-4 have expressed surprise at the perceived discrepancy with the results of the previous smaller trials. Proposed explanations for the lack of benefit in ISIS-4 include the initiation of magnesium infusion immediately after (rather than with) the initial "lytic" phase of fibrinolytic therapy, the late start of magnesium, and the relatively low overall control mortality.[49,66,67] However, few of the patients included in the overview of very small trials (which suggested a large benefit) would have received fibrinolytic therapy. Moreover, in LIMIT-2, where only about one-third of patients received fibrinolytic therapy, the investigators concluded—before the ISIS-4 results became available—that any effect of magnesium was independent of that of fibrinolytic or antiplatelet therapy and that it was not modified by the delay from symptom onset.[48] The very much larger numbers in ISIS-4 allow the various hypotheses that have been proposed to be addressed directly, and do not provide support for them. In particular, the ISIS-4 results remain non-significantly adverse for magnesium even among the 23 000 patients randomised within 6 h of the onset of symptoms, and remain adverse irrespective of whether or not the patients also received fibrinolytic or antiplatelet therapies. Nor could a high-risk subset of patients be identified in ISIS-4 in whom magnesium was beneficial (figure 4c), even after constructing a multivariate prognostic score and considering those at highest risk who were randomised within 6 h of symptom onset (deaths in days 0–35 in highest-risk quintile: 509 [20·0%] magnesium *vs* 453 [18·3%] control; NS). It has recently been suggested[66] that special trials of magnesium in acute MI are needed for subgroups of patients who are most likely to be magnesium-depleted (eg, the elderly, patients taking chronic diuretics, or those with heart failure), but the ISIS-4 results do not indicate any benefit whatever among such patients (figure 4c). Overall, there does not now seem to be any good clinical trial evidence for the routine use of magnesium in suspected acute MI.

Implications for research and clinical practice

Perhaps the most important finding for research and practice to come from ISIS-4, and the parallel GISSI-3, is the need for such large-scale randomised evidence. For when moderate benefits or negligibly small benefits are both much more plausible than extreme benefits, then a 2p=0·001 effect in a large trial or overview would provide much stronger evidence of benefit than the same significance level in a small trial, a small overview, or a small subgroup analysis.[2,61,68] Hence, it should not be particularly surprising to find the extreme benefits suggested by the small overviews of trials of magnesium or of nitrates or by the small LIMIT-2 study completely contradicted by the subsequent large-scale evidence from ISIS-4 and GISSI-3: and it is perfectly reasonable to trust the 3 standard deviation difference seen with 100 000 patients in the CEI trials (figure 5) while distrusting the 3 SD difference seen with only about 1000 patients in the early magnesium trials (top of figure 7). This underscores

the need to evaluate other treatments for acute MI (and for the many other conditions where only modest effects are likely to await discovery) in mega-trials involving some thousands of deaths, and for the removal of any unnecessary obstacles to such large numbers—for example, those that may be produced by the auditing and monitoring procedures currently being proposed by some bodies.[69]

Those who had trusted the results from previous small overviews and trials may be disappointed by the large-scale randomised evidence, which now shows that the routine use of magnesium has little or no effect on mortality in acute MI and that any effects of nitrates are far smaller than had previously been inferred. It is important, however, not to swing from excessive optimism to excessive pessimism. Over the past decade, large-scale randomised studies have demonstrated the benefits of immediate antiplatelet therapy for almost all patients with definite or suspected acute MI (or unstable angina) and of prompt fibrinolytic therapy for those presenting with ST elevation or bundle branch block who can be treated within at least 12 h of symptom onset.[59,60] Now ISIS-4, GISSI-3,[57] CONSENSUS-II,[58] CCS-1,[62] and the other studies (figure 5) have provided definite evidence of additional benefits from starting CEI therapy early in acute MI, and continuing for about 1 month. Typically, such treatment saves about 5 lives per 1000 treated—with somewhat greater benefits (ie, perhaps about 10 lives saved per 1000) in certain higher-risk groups of patient, and these benefits seem to persist for at least 1 year. (The UK drug costs are about £20, implying a "drug cost per life saved" of a few thousand pounds.) This complements the results of SOLVD,[19] SAVE,[20] and AIRE,[21] which demonstrated that continuing CEI therapy after the first few weeks or months in those who have evidence of ventricular dysfunction will produce a further mortality reduction of about 2 per 1000 patients per additional month of treatment following the first month.

It is therefore worth considering starting CEI therapy early in a wide range of patients with suspected acute MI, provided there is no clear contraindication (such as cardiogenic shock or persistent severe hypotension). Subsequently, after a few weeks, patients could be reviewed and treatment continued in those thought (on the basis of clinical heart failure, low ejection fraction, or other evidence of a large infarct) to be at particularly high risk of death or severe heart failure during the next few years. Although some clinicians might prefer to wait some days or weeks to identify and treat only those at highest risk, such a restrictive strategy may result in treatment being withheld from some whose early death could have been prevented.[70]

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Bodanese LC, Manenti E; das Clinicas, Porto Alegre Zago AJ, Chodosz HLK; Inst de Cardiologia do Rio Grande do Sul, Porto Alegre: Rodrigues R, Dutra OP, Santa Casa de Mis, Porto Alegre Leães PE, Blacher C; Oswaldo Cruz, Recife Cantarelli EL, Ribeiro CR; PROCARDIO-Urgências Cardiológicas de Pernambuco, Recife Markman Filho B, Montenegro ST; Real Português de Benef de Pernambuco, Recife: Victor EG, Silva MJR, UNICORDIS-Urgências Cardiológicas, Recife: Gonçalves FBW, Oliveira Jr W; das Clínicas, Ribeirão Preto Marin Neto JA, Almeida Filho OC; do Coração, Ribeirão Preto Papa MV, Grandini LC, Santa Casa de Mis, Ribeirão Preto· Lopes SLB, Muniz LEA, Associação de Caridade Sta Casa, Rio Grande: Capstein J, Fonseca MAM, Municipal Miguel Couto, Rio de Janeiro· Carvalho MLT, Soares VE; Municipal Salgado Filho, Rio de Janeiro Pinheiro CTM, Mirabeau GEO, Municipal Souza Aguiar, Rio de Janeiro Oliveira CC, Alhadas RM, Universitário Pedro Ernesto, Rio de Janeiro· Albuquerque DC, Campos LAM; de Cardiologia de Laranjeiras, Rio de Janeiro Scherr C, Loyola LH; dos Servidores do Estado, Rio de Janeiro: Carvalho MA, Escosteguy CC; Beneficencia Portuguesa, Rio de Janeiro. Mesquita ET, Montera MW, Universitário C Fraga Filho, Rio de Janeiro: Silva JAF, Pedrosa RC; da Lagoa, Rio de Janeiro: Pereira LSMM, Carvalho CRF; Português, Salvador: Esteves JP; Universitário Prof Edgard Santos, Salvador. Camara EJN, Robert W, e Maternidade Brasil, Santo André Jorge SC, Scalfo M, Sancor-Inst do Coração, Santos· Silva LFG, Teixeira EA; Santa Casa de Mis, Santos· Burgos FJC, Soares Neto MM, Soc Portuguesa de Benef, São Caetano do Sul: Sombra FB, Moraes SA; Santa Casa de Mis, São Carlos: Verzola RMM, Ribeiro LF, Inst de Card da Fundac Hospitalar de Sta Catarina, São José. Simão AF, Correa Filho H, Hospital Pio XII, Sao José do Campos Francisco RMGC, Santos EM; Policlin, São José do Campos· Magalhães CC, Zarur Jr J; Inst de Moléstias Cardiovasculares, São José do Rio Preto: Nicolau JC, Nogueira PR; PRONTOCOR-SERV de Pronto Socorro-CL Cirúrgica, São Luis Buhaten JB, Furtado RJC; UDI-CARDIO, São Luis: Melo Filho JX, Lobão MRL, São Cristovão, São Paulo: Massela CR, Aldrigui JR, Israelita Alberto Einstein, São Paulo. Bacuzzi ACA, Knobel E; Panamericano, São Paulo: Catani R, Santos LS, Hospital São Paulo Carvalho ACC, Gonçalvez Jr I, do Coracão da Assoc Sanatório Sirio, São Paulo: Romano ER, Barbosa MAO; do Servidor Público Municipal, São Paulo: Sales Filho EM, Novaretti JR, e Maternidade Leão XIII, Sao Paulo: Ghorayeb N, Oliveira AG, Inst do Coração-HCFMUSP, São Paulo Tranchesi Jr B, Kalil Filho R, Santa Casa de Mis, São Paulo. Franken RA, Golin V, Unicor, São Paulo· Silva LA, Ribeiro EE; Conjunto, Sorocaba Maiello JR, Almeida Filho JN; Escola de Faculdade de Medicina do Triang Mineiro, Uberaba Miziara LJ, Lopes MA, Santa Genoveva, Uberlandia Silva RWT, Ribeiro Jr JR; Universitário Cassiano Antonio de Moraes, Vitoria Barros FS, Pazolini CM; do Coração Ltda-SOCOR, Vitória Murad V, Costa AL

Canada (926; 29)—Hamilton General: Cairns J*, Turpie A*, Yusuf S*, Gill J, Kiperovic M; Brantford General: Bate L, Kott D, Joseph Brant Memorial, Burlington Carling L, Beare L, Cambridge Memorial Vizel S, Wilkinson D, Public General & St Joseph's, Chatham Harnarine C, Williston M, Easton P; Queensway General, Etobicoke: Sevitt B, Hood N; Guelph General· Raco DL, Eisen G; St Joseph's, Hamilton Sullivan M, Kennedy D; Henderson General, Hamilton Sealey J, Campbell J, McMaster University Med Centre, Hamilton Fallen E, McLeod M, Royal Inland, Kamloops Reid R, Prins J, St Mary's, Kitchener & Kitchener-Waterloo: Fowlis R, Schaefer B, Pallas P, Hotel Dieu de Montréal: Latour Y, Rondeau C, Greater Niagara General: Chan YK, Zaniol D; Oshawa General Bhargava R, Ellis M, Grey-Bruce RHC, Owen Sound Keeling CJ, Glass S, Penticton Regional Ashton T, Barr DM, Royal University, Saskatoon McMeekin J, Norfolk General, Simcoe. Chiu S, Szpakowski J, Stratford General Fuller DR, Smith P, Sudbury Memorial: Juma Z, Chorny L, Surrey Memorial: Kornder J, Mackie M; McKellar General, Thunder Bay: Leitrants P, MacLean S; Lion's Gate, Vancouver Imrie JR, Phillips P; St Paul's, Vancouver Thompson CR, McCarthy B, Heinrich D, North Branson, Willowdale: Teitelbaum E, Zafar N; St Boniface, Winnipeg: Smith H, Schillberg M

Chile (201; 8)—Cl Las Condes, Santiago Chamorro BH‡, Asistencia Publica, Santiago Chavez SE; Barros Luco T, Santiago. Ramirez CFJ, Dipreca, Santiago: Escobar CE; Fuerza Aerea, Santiago Matthei FR, JJ Aguirre, Santiago Yovanovich SJ; San Borja-Arriaran, Santiago Arriabada CA, del Salvador, Santiago: Manzur F.

Colombia (588, 18)—Bogota Estrada Espinosa G‡, Di Domenico R‡, Clínica San Rafael, Bogota. Olaya C; Clínica Shaio, Bogota: Suarez A, Isaza D; Clinica del Country, Bogota Eljaiek C; Fundación Santafe, Bogota: Jaramillo M, Militar, Bogota Eusse C, Orejaren H, Samaritana, Bogota· Garcia M; San Ignacio, Bogota: Pinzon JB, Saaibi F; de Kennedy, Bogota: Martinez F; Ramón Gonzalez Valencia, Bucaramanga: Castillo H, Universitario, Cali. Watemberg M, Narvaez JV; Inst de Seguros Sociales ISS, Cali· Caicedo B, Universitario, Cartagena. García del Rio C, Arteta D, Clínica Tolima, Ibague Acosta C, Cepeda C; Inst de Seguros Sociales ISS, Manizales Castaño O, Ocampo N, Fundación Sta Maria, Medellín Fernandez D, Inst de Seguros Sociales ISS, Medellín Llamas A; Inst de Seguros Sociales ISS, Pereira· Ramirez H

Estonia (287; 2)—Tallinn Mustamäe Hospital· Eha J, Voitk J, Tartu University Hospital: Teesalu R, Uuskula M

Finland (977, 20)—Maria, Helsinki: Kala R*, Pajari R, Nurmilaukas S; University Central, Helsinki· Heikkila J*; Ahtari District Maattanen J, Korpi E; Malmi, Helsinki: Kohvakka A, Rannikko C; Imatra District· Itkonen A, Kovanen H, Jokilaakso District Nyyssönen S, Myllys E, Kanta-Hame Central· Saksa M, Suuronen M, Keski-Pohjanmaa Central: Halkosaari M, Junell L; Lansi-Uusimaa District Lindström C-J, Rinne J, Lappi Central Raasakka T, Autio R, Lohja District Suhonen O, Lehtonen J; Lounais-Häme District Koskelainen J, Ryhta I, Malmska District· Nikus K, Pettersson M, Mikkeli Central Tarssanen L, Jaaskelainen H, Porvoo District· Harkonen M, Rask C; Raisio District: Karmakoski J, Paasipohja A, Rauma District: Saarelainen E, Valmunen H; Riihimaki District Tiukka T, Melin S, Selkameri District Tuunanen V, Leppamaki P; Vaasa Central: Jussila R, Kivela H, Penas-Rekola, Vantaa Hussi E, Rosti L

France (35, 5)— Hôpital Neuro-Cardiologique, Lyon· Leizorovicz A*, Boissel J-P*; Centre Hospitalier, Chalon sur Saône: Dellinger A, Centre Hospitalier Général, Guéret Bessède G, Mansour L, Hôpital d'Instruction des Armées Desgenettes, Lyon Palmier B, Brion R; Hôpital Central, Nancy: Zannad F, Sadoul N, Aliot E, Polyclinique de Courlancy, Reims: Carette B

Germany (5404, 100)—Klinikum Steglitz, Berlin Schroder R*, Schroder R, Pinkwart L, Luisenhospital, Aachen Ontyd J, KH Strausberg, Altlandsberg: Topp E; Herz-Kreislauf Klinik, Bad Bevensen· Notges A, Kreis-KH, Bad Homburg. Raisig S; Deister-Suntel Klinik, Bad Munder. Potthoff H-J, Mäckel P; Klinikum Bamberg Diamantis M, KH Belzig: Hessler M, Ev Wald KH, Berlin: Justiz R, Humboldt KH, Berlin. Menges M, KH Spandau, Berlin· Burbach H, KH Staaken, Berlin. Hampel D; St Gertrauden KH, Berlin. Ramdohr B, Becker B, Wenckebach KH, Berlin Kuckuck H; Malteser KH, Bonn. Muehlenberg K, Stadt KH, Brandenburg: Haase J; Rot-Kreuz KH, Bremen: Zschiedrich H, St Joseph-Hospital, Bremerhaven· Martin K, Zentral-KH Reinkenheide, Bremerhaven: Volkmann B, Stadt KH, Cottbus Kamke W, Elisabeth KH, Darmstadt Szappanos L, Stadt KH, Darmstadt Frederking H, Med Akademie, Dresden Weise M, KA Düren Simon H, Benrath, Dusseldorf: Schoppe WD, Nieradzik M, EVK Düsseldorf Asshoff D, Wald-KH Rudolf Elle, Eisenberg Schmolke G; Med Akademie, Erfurt Oltmans G, Franziskus KH, Essen Dorwald R, Knappschafts KH, Essen· Wittstamm FJ; Burgerhospital, Frankfurt/M· Sedlmeyer I, Nordwest KH, Frankfurt/M: Heller A, Klinikum Frankfurt/O. Zieger K, Burgerhospital, Friedberg Blum E, Kreis-KH, Furstenwalde Groschke KV, Kreis-KH, Gardelegen Schoof M, Bezirks-KH, Gera Bernhardt G; St Barbara-Hospital, Gladbeck· Graupner M, Kreis-KH, Glauchau· Meyer K, Kreis-KH, Gustrow. Duda S; Stadt KH, Gutersloh Bernsmeier R, KH St Salvator, Halberstadt Unger T; St Sixtus-Hospital, Haltern Beythien R; DRK/Freimaurer KH, Hamburg· Weiss B, EVK Hamm: Mosseler U, Siloah, Hannover von Leitner ER, Hackenjos B; St Josef KH, Heidelberg Stein U, KH Marienberg, Helmstedt: Schwartz BR; Paracelsus Klinik, Hemer Riebeling V, St Josef Hospital, Hilden Lipke M; Stadt KH, Hildesheim: Bodman K-F; Stadt KH, Itzehoe Willms E, Uniklinik, Jena-Lobeda: Thiele R; Malteser-St Elisabeth KH, Julich Jebens C; Reha-KH, Karlsbad Kutscher J, Elisabeth KH, Kassel: Hackethal G, Stadt KH, Kiel Polster H, KH Holweide, Koln· Saborowski F, KH Siebengebirge, Konigswinter. Kummerhoff PW; Kreis-KH, Konigs Wusterhausen· Schwarze B; Stadt KH, Korbach. Engelsing B, Städt KH, Landsberg: Perl R, Kreis-KH, Landshut Sauer E; Borromaus-Hospital, Leer Overbeck P, Med Uniklinik, Leipzig Hellmund F-D, Stadt KH, Leverkusen Jansen W, KH-Sud, Lubeck Krüger W, Med Uniklinik, Lubeck Mentzel H, Stift Bethlehem, Ludwigslust Korber H-G; Stadt KH, Luneburg: Werner HM, Niederstadt H, Bez KH, Magdeburg Siedentopf K, Med Akademie, Magdeburg Grund S; Heinrich-Lanz KH, Mannheim. Nissen P, Kreis-KH, Mayen Schubotz R, Kilp M; Kreis-KH, Mechernich Neuhaus J, Mohr P, EVK Mulheim/Ruhr Kotter V; KH Bogenhausen, München Delius W, Nowak EG; Rot-Kreuz KH, Munchen von Arnim Th; Kreis-KH, Naumburg· Beder E, Stadt KH, Nettetal Appenrodt H, Ruppiner KH, Neuruppin: Reichelt E, KH d Landkreises, Peine: Beck OA, KH

Ernst-v-Bergmann, Potsdam: Erkens R; Kreis-KH, Querfurt Kozarıszczuk G, Prosper Hospıtal, Recklınghausen Tenholt M, Tomsık H, Herz-Kreıslauf Klınık, Rotenburg/F Balı M, Diakonıe KH, Rotenburg/W· Bottjer H, Thüringenklınık, Saalfeld: Schmidt A, Wınterberg Klınıken, Saarbrucken: Zwırner K; Klınıkum Schwerın· Machıll K; St Marien KH, Siegen: Schuster P, Kreıs-KH, Springe: Besser N, Kantonspital, St Gallen Huber B, KH Am Sund, Stralsund. Müller-Esch G, Flor B, Elisabeth KH, Trıer Wertgen Th, KH Barmıh Brüder, Trıer Hauptmann K, Kreıs-KH, Waren. Volkmann J; Klinikum Wiesbaden Piper C, KH Bethesda, Wuppertal Wiebringhaus E; Klınıkum Elberfeld, Wuppertal: Hohler E.

Greece (1204; 17)—Hygeıa, Athens Karatzas N*, Pıpılıs A*, Alexandra, Athens. Moulopoulos S, Nanas S; Evangelismos, Athens: Anthopoulos L, Tsitouris G, Krespi P, Zarkos I, A Flemıng, Athens· Antonatos P, Chrısos D, Deliyannıs A, Kollios G; Laıko, Athens· Vogiatzi P, Hajızacharıas A, Makrıs T, IKA Pentelıs, Athens Papazoglou N, Pedıotides S; Soteria, Athens: Karides K, Kakouros S, Georgiades S, Universıty Hospıtal, Crete: Vardas P, Manıos M, General, Kalamata: Vasilopoulos I, General, Kavalla Tyrologos A, Simeonıdes D, Nikaia General, Piraeus. Papasteriades E, Petropoulos I; Tzanio, Piraeus. Cokkinos D, Pısımises E, Olımpios C; General, Serres Koutmerides M, Mikikes B; IKA, Thessalonika Papazachariou G, Kirpizides C, Ippokration, Thessalonika: Kontopoulos A, Avramides M; Panarkadikon, Tripolis: Stavrides A, Tsoukalis N; Achilopoulıon, Volos: Tsaknakis T, Malamos A; Asclepıon, Voula: Christakos S, Kifnides K

Hungary (1047, 25)—Hungarian Institute of Cardiology, Budapest: Keltai M*, Dékány P, Sitkei E, Borzáné SK, Bajcsy Zsilınszky, Budapest. Buday G, Páder K; HIETE, Budapest· Csányi E, Harsányi A; Hungarian National Emergency & Ambulance Service, Budapest· Lamboy L, Tury P; MÁV, Budapest· Asbót R, Szabóky F; Merényi, Budapest· Kárpáti P, Sebo J; Péterffy, Budapest. Kálmán I, Szauder I, Semmelweis Medical Universıty, Budapest· Váradi A, Kollár E, Jánoskuti L, Máte A, Fenyvesi T; St John's, Budapest. Jánosi A, Kiss B, Kovách G, Salamon F; St Margaret's, Budapest: Holló J, Ligeti J; St Steven's, Budapest· Keller L, Walton E; Toldy, Cegléd: Oze B, Kopaczné TI; Med Univ, Debrecen. Kovács P, Mohácsi A; Petz, Gyor· Lukácsy A, Vályi P, Kaposi, Kaposvár: Nyárady A, Keseru P; Bács-Kiskun County, Kecskemét· Király C, Timár S; Városi, Nagykanizsa: Heim T, Matolcsi A, Medical University, Pecs: Muhl D, Sárosi I; Szentgyorgyi Med Univ, Szeged: Högye M, Papp I; Fejér County, Székesfehérvár. Simon K, Turi T, Hetényi, Szolnok: Harmati L, Tolgyes A, Markusovszky, Szombathely Salamon A, Tarján J, Csolnoki, Veszprém: Csillag J, Gara A.

Ireland (300; 9)—Beaumont, Dublin: Horgan J*, O'Callaghan D*, Herlihy M; Bantry General: McCoy D, Kingston J; St Joseph's Medical, Clonmel O'Regan P, Cox B; Bons Secours, Cork: Kenny J; Our Lady of Lourdes, Drogheda: Muldoon C, Costello T, James Connolly Memorial, Dublin: Harte M, McDonnell M, Mullingar General: Quinlan C, Donovan M; Tullamore General: Taafe J, Quinn M, Monaghan General: McMahon B

Israel (428; 15)—Lady Davis Carmel, Haifa. Lewis BS*, Halon DA*, Emek, Afula: Rosenfeld T, Freedberg N; Barzilai, Ashkelon Reisin L, Jasari J; Soroka, Beer Sheba: Katz A; Bnei Zion, Haifa: Abinader EG, Goldhammer E; Carmel CCU, Haifa Palant A, Shapira C, Wolfson, Holon: Kishon Y; Meir, Kfar Saba. David D, Pausner H, Laniado, Natanya: Barash E, Kotler J; Scottish, Nazareth Shahin J; Hasharon, Petach Tikva. Zahavi I, Butto N, Kaplan, Rehovot Caspi A, Oettinger M, Rebecca Ziv, Safed: Marmor A, Sheba, Tel Hashomer: Hod H, Kaplinksy E; Poriya, Tiberias: Rudnik L, Reizler J.

Italy (GISSI liaison)—Mario Negri, Milan. Franzosi M-G*, Maggioni A*, Tognoni G*

Luxembourg (7, 1)—Centre Hospitalier, Luxembourg: Erpelding JR, Beissel J.

Mexico (334; 21)—Inst Nacional de Cardiologia, Mexico DF· Gil Moreno M‡, Martinez Rios M‡, Gaxiola E; Manuel Hidalgo, Aguascalientes Ramirez-Insuza JM, Ramirez JC; Cl del Parque, Chihuahua Guerrero J; General, Durango Gonzalez S, Santa Margarita, Guadalajara: Mayagoitia H; del Carmen, Guadalajara· Zuniga J, Civil, Guadalajara: Medina I; Cent Medicas del Edo de Veracruz, Jalapa: Lopez E; Gral de Leon SS, Leon Guerrero F, Fatima, Los Michis: Eng L; Cl de Mérida: Barrera M; Gral O'Haran, Mérida: Alejos R, Gral de Mexicali Medina A, Español, Mexico DF Carrillo L, Troitino C, Ingles ABC, Mexico DF: Martinez J, Sanchez G; ISan Jose, Monterrey: Manatou L, Univ J E Gonzalez, Monterrey. Bahena JH, C Medico Nac Noroeste IMM, Obregon· Quinteros R, Gral de Tampico: Duran P; Cl del ISSSTE de Nayarit, Tepic. Varela S.

Netherlands (771; 11)—Centre for Human Drug Research, Leiden· Cohen AF*, de Craen T, ten Kate-Roose MEC, Academisch Medisch Centrum, Amsterdam Koster RW*; ZH de Lichtenberg, Amersfoort· Wisse Smit J, St Gemini ZH, Den Helder de Porto AE; Diakonessenhuis, Eindhoven: Relik-van Wely L, Berte A; St Anna ZH, Geldrop. van der Horst MJ, Oosterschelde ZH, Goes· Roeters van Lennep HWO; Beatrix ZH, Gorinchem: van Rossum P, Elisabeth ZH, Haarlem: Kan G; Groot Ziekengasthuis, 'sHertogenbosch. van der Pol JMJ, Broeksteeg D, Zeeweg ZH, Ijmuiden: Kainama JJ, Kramer J; Canisius Wilhelmina ZH, Nijmegen· Lamfers EJP, St Laurentius ZH, Roermond Rook L.

New Zealand (537, 13)—Green Lane Hospital, Auckland: White H*, French JK, Scott M; Auckland Hospital: MacMahon S*, Sharpe N; Ashburton· Audeau FM, Bishop S; North Shore Hospital, Auckland: Frankish P, Hart H; Middlemore, Auckland: Williams M, Ko A, Wairau, Blenheim: Durham D, Johnston M; Memorial, Hastings· Luke R, Schmid D; Hutt Hospital, Lower Hutt. Mann S, Dewar J; Napier Hospital: Lewis G, Bent M; Nelson Hospital. Mylius A, Hawke J; Tauranga Hospital: Nairn L, Abernethy M; Wellington Hospital: Leslie P, O'Connell S; Northland Base, Whangarei: Rankin R.

Norway (1262, 24)—Rikshospitalet, Oslo Kjekshus J*, Midtvedt K; Sentralsjukehuset, i Sogn of Fjordane, Førde: Reikvam A*, Aarskog D, Buskerud, Drammen Larsen A; Farsund· Bjering E, Brodschøll T, Flekkefjord Omland T, Haavardstein V, Fylkessjukehuset, Florø: Sindre T, Houland B, Sentralsykehuset Per Ostfeld, Frederikstad: Holm T, Eide T; Hamar Haerem J, Risberg K; Hammerfest: Ingvaldsen P, Sandvik J; Ringerike, Hønefoss: Tenstad O, Strøm B; Horten: Baekkevar M; Fylkessjukehuset, Kristiansund Rognved G, Fylkessjukehuset, Laerdal von Euben F, Larvik Bru T, Urdahl D; Stensby, Minnesund Koss A; Rana, Mo: Drøpping O, Narvik: Njalla S, Zalmai A, Sentralsykehuset i Akershus: Nordbyhagen· Eriksen J, Hellman H; Notodden· Solheim S; Fylkessjukehuset, Odda: Abbasi I; Sandefjord Noer G, Nordlie K, Stokmarknes· Aas FL, Fylkessjukehuset, Volda Bae E, Fylkessjukehuset, Voss Bjørnstad H, Urheim S.

Poland (3491; 23)—Grochowski, Warsaw Ceremuzynski L*, Budaj A*, Cybulski J, Ptaszynska A, Cedro K; PSK AM, Bydgoszcz: Nartowicz E, Paczkowska B, ZOZ, Bydgoszcz: Poddany K, Kepski H; Zespolony, Kielce Janion M, Gutkowski W; I Klinika Kardiologii AM, Kraków· Kawecka-Jaszcz W, Lubaszewski W; J Dietla, Kraków. Maciejewicz J, Kurleto J, Narutowicza, Kraków: Smielak-Korombel W, Grzelewski J, ZOZ Chorób Pluc i Gruzlicy, Otwock: Nejman A, Swiatek P; Wojewódzki, Olsztyn: Dowgird M, Zach M, AM, Poznán Cieslinski A, Mularek T; Wojewódzki Zespolony I, Radom Ananko D, Achremczyk P, Wojewódzki Zespolony (II), Radom: Burski A, Iwaszczukiewicz W, Wojewódzki Zespolony, Skierniewice. Zambrzycki J, Kawka-Urbanek T; Wojewódzki, Zespolony, Torun Jaworska K, Mazurek W, ZOZ M Kopernika, Torun Dowbor B, Gessek J, Bielanski, Warsaw: Swidzinski M, Tomczak D, Bródnowski, Warsaw: Kuch J, Szczniecka O; Centralny Kolejowy, Warsaw Zaleska T, Mularczyk H, Czerniakowski, Warsaw: Kuczewska-Stanecka K, Jedrzejowski A, MSW, Warsaw: Zochowski R, Radowicka A, Pogotowia Ratunkowego, Warsaw: Dyduszynski A, Wasiutynska E, Wolski, Warsaw Wojtulewicz L, Komorowska M; ZOZ, Zyrardów Swiatek W, Gadzinski A.

Portugal (1413; 31)—Instituto do Coraçao, Hospital de Santa Cruz, Linda a Velha: Seabra-Gomes R*, Mendes M, Calqueiro J, Gonçalves N; Hospital Angra do Heroismo, Acores Coelho Gil JG, Dionisio Macedo AM; Hospital de Ponta Delgada, Açores· Pereira de Almeida L, Saenz del Castillo M; Hospital Garcia de Orta, Almada Carrageta M, Costa e Silva Z; Hospital Distrital de Aveiro· Leitao R, Nobre dos Santos JA, Hospital Distrital Barreiro Correa D'Almeida V, Caria R, Hospital Distrital de Beja· Serrano ML, Carlos Costa A, Hospital de S Marcos, Braga: Rodrigues P, Correia A, Centro Hospitalar de Coimbra: Fong FP, Macedo J; Hospitais Universidade Coimbra Providência L, Morais J, Hospital Distrital de Évora: Paiva Jara AJ, Valente Araújo FJ; Hospital Distrital de Faro· Camacho A, Amado J, Centro Hospitalar do Funchal Diniz M, Almada Cardoso A, Hospital Curry Cabral, Lisboa Castelbranco Mota JA, Guimarães R, Hospital Egas Moniz, Lisboa· Arroja I, Castanheira J, Hospital Militar Principal, Lisboa Ventura Estriga AJ, Gomes A, Hospital Distrital de Portimao, Lisboa: Coucello J, Moleiro J; Hospital S Francisco Xavier, Lisboa Lema Santos A, Mourão L, Hospital Pulido Valente, Lisboa Ramos MA, Rodrigues MJ, Hospital S José-UUM, Lisboa: Reis L, Salcher J; Hospital Santa Maria-UCIM, Lisboa: Lopes MG, Calçada Correia L, Hospital Santa Maria-UTIC. Diogo AN, Mestre C; Hospital Santa Marta, Lisboa Quininha J, Ferreira R, Hospital Distrital de Matosinhos Silva JA, Pinto da Fonseca A, Centro Hospitalar Vale do Sousa, Penafiel: Moura JM, Monteiro da Silva J; Hospital Distrital de Portalegre: Baeta C, Menezes A, Hospital Geral Santo António, Porto Pimenta A, Gomes JL, Hospital de S João, Porto: Correia dos Santos J, Santos Mendes J; Hospital Distrital de Setubal: Forjaz Lacerda A, Inês L, Hospital Vila Franca de Xira: Rabaçal C, Santos Rio M; Centro Hospitalar de Gaia, Vila Nova de Gaia: Simoes L, Fazendeiro Matos J, Hospital Distrital de Viseu Rufino E, Angelo F.

South Africa (675; 8)—Johannesburg Hospital: Meyer T*, Landless P*, Addington Hospital, Durban Cassim S, Universitas Hospital, Bloemfontein Marx D, Frere Hospital, East London. Sole T; Groote Schuur Hospital, Cape Town: Commerford P, Tygerberg Hospital, Cape Town: Weich H; Victoria Hospital, Cape Town· Regensberg L, Livingstone Hospital, Port Elizabeth Behari R.

Spain (2189; 30)—Dr Peset Alexandre, Valencia Valentin V*, Miralles L, Valls F, San Juan, Alicante: Colomina F, Bertomeu V, Virgen de los Lirios, Alicante: Amorós F, Villajoyosa, Alicante: Fuster M, de Alba L, Infanta Cristina, Badajoz: Garcia Guerrero J, Merchan A; Creu Roja, Barcelona: Rovira A, Roca J; Manresa, Barcelona: Jodar L, Corrons J, General Yague, Burgos: Monton A, Santamaria A; Guerra Zunzunegui, Cadiz. de las Peñas J, General Castellón: Ferrandiz A, Rodriguez MT; Gran Via, Castellón. Boix H, Aznar O, Alarcos, Ciudad Real. Ortega J, Universitario Granada: Aracil C; Insalud de Leon: Garcia Calabozo R, Simarro E; 12 de Octubre, Madrid. Carbonell A; Carlos Haya, Malaga: Vera A, Torrado E; Univ Virgen Victoria, Malaga: Garcia Alcantara A, de la Torre MV; Clinica Planas, Mallorca: Orellana J, Munroy N; General, Murcia: Mira E, Segura J, Santa Maria del Rosell, Cartagena: Jimenez F, Vignote G; Virgen de la Arrixaca, Murcia: Torres G, Rodriguez P; Central de Asturias, Oviedo: Rodriguez Llorian A, Cortina A; Can Misses, Ibiza Segui J, Santana A; Soria: López O, Gobernado M, Arnau de Vilanova, Valencia Fajarnes F, Hervás A; General Valencia: Echanove I, Francisco de Borja, Gandia: Mazza S, Lafuente M; Lluis Alcanys, Xativa Rodriguez M, Garcia López L, Sagunto, Valencia: Tormo C; Policlinico Vigo· Noriega F

Sweden (2467; 34)—Östra, Goteborg: Wilhelmsen L*†, Thorin M, Hudiksvall Lundkvist L*, Ångman K, Avesta. Perers G, Irwing P; Bollnäs. Hammarstrom E; Borås Wettervik C, Enkoping: Karlsson L; Malarsjukhuset Eskilstuna: Stjerna A, Hedqvist M; Fagersta Akrawi S, Nilsson H; Falkoping Viidas K, Hård G; Gallivare: Stenberg K, Lehto A, Harnosand: Hemmingson LO, Hassleholm. Wedberg P, Karlskoga: Engstrom B; Kiruna: Erkstam G, Johansen S, Messner T; Koping: Malmros B, Nicol P; Ljungby Fredholm O, Grundahl B; Lycksele· Bjurman A; Molndal: Holmberg H; Mora. Aronson D, Hedlund H; Motala. Rosenqvist U, Ahlstrom P; Nacka: Sjogren A, Loogna A; Norrtalje. Svenson G, Nykoping: Dahlberg A; Ornskoldsvik· Lovheim O; Sabbatsberg: Liljefors I, Wennerström L, Sandviken: Ellström J, Brodersson M; Simrishamn· Lindvall P, Gisselsson A, Kärnsjukhuset Skovde Ejdeback J, Lundstrom T, Ståhl L; Soderhamn. Mohaupt D, Sollefteå: Fagerström I; Södersjukhuset, Stockholm· Hulting J, Amanullah A; Sundsvall Moller BH, Wallner G; Trelleborg: Bachmann R, Wegbratt A; Trollhatten: Redfors A, Andersson M; Visby Hoffstedt E.

Switzerland (820; 36)—Ospedale Civico, Lugano: Moccetti T*, Lechuga S; Ospedale San Giovanni, Bellinzona Malacrida R*; Universitätspital, Zurich Genoni M*, Altstatten Hangartner P; Hôpital de la Glâne, Billens: Rime F, Regionalspital, Burgdorf. Gerber A; Kreuzspital, Chur: Wuscher V; Bezirksspital, Dornach Koelz A; Flawil: Schonenberger E, Hôpital Cantonal, Fribourg: Moser V, Mottet J; Kantonsspital, Glarus Wojtyna W, Rhyner K; Grenchen: Schlup P, Bezirksspital, Grosshochstetten: Burger H, Regionalspital, Herisau: Herzer H; Bezirksspital, Herzogenbuchsee: Bosshrad H, Regional, Lachen. Mader A, Kreisspital, Mannedorf· Strebel U; Ospedale Beata Vergine, Mendrisio Noseda G, Reiner M; Hôpital de la Zone, Montreux. Weber J; Hôpital de la Zone, Morges: Christeler P, Bezirksspital, Munsingen. Repond F, Kantonsspital, Munsterlingen. Biedermann H, Bezirksspital, Murten Amberg H, Hôpital des Cadolles, Neuchâtel: Enrico J; Hôpital Régional, Porrentruy: Bernhardt J; Regionalspital, Rheinfelden Iselin H, Kantonales Spital, Rorschach. Pfister M; Kantonsspital, Schaffhausen: Frey R; Limmattalspital, Schlieren: Caduff B; KH, Thusis. Veragut U; Hôpital du Samaritain, Vevey· Berger J; Ospedale Italiano, Viganello· Beretta-Piccoli C, Wadenswil: Garzoli G, Kantonales Spital, Walenstadt Schmidt D, Wil: Müller T; Kantonales Spital, Wolhusen. Rosli R; Neumunsterspital, Zollikerberg Siegrist P, Stäubli M, Schweiz Pflegerinnenschule, Zurich: Maire R, Federmann M

United Kingdom (15 929, 112)—Clinical Trial Service Unit, University of Oxford, and John Radcliffe Hospital, Oxford: Collins R*, Sleight P*, Peto R*, Parish S*, Flather M*, Conway M*, Pipilis A* , Baigent C*, Keech A*, Doll R†, Jayne K, Barton J, Jackson D & Halls H (administrators), Appleby P, Lloyd P & Foster S (programmers), Dove P* (medical illustration), Irish A (renal reviewer), Doulalas A, Foster C, Hudd J, King M, Knight S, Marsden C, Mead G, Murphy K, Radley A, Crowther J, Wilberforce S, Owers A, Leicester Royal Infirmary: Barnett D*, Woods K*, Woollacott G, University of Oxford. Armitage P†; Royal Sussex, Brighton: Chamberlain D†, National Heart, London. Fox K†, British Heart Foundation· Julian D†, Aberdeen RI. Kenmure ACF, Crombie M; Nevill Hall, Abergavenny Hutchison S, Goodchild R, Bronglais General, Aberystwyth: Davies AG, Chakraborty TK; Monklands General, Airdrie: Rodger JC, Perkins S, Cambridge Military, Aldershot: World M, Greenwood S, Vale of Leven District General, Alexandria. McCruden DC, Hunter E; Amersham General: Regan RJ, Cooper D, William Harvey, Ashford Wilson IV, Cowley A, Tameside General, Ashton-under-Lyne. Husaini M, Callaghan J, Ysbyty Gwynedd, Bangor Maxwell RT, Roberts S; Barnet General: Gray KE, Kavanagh M; Basingstoke District Fowler JM, Alves E; Bedford Cooper I, Flisher D; Birmingham General: MacIver DH, Lamb L, Bishop Auckland General. Bateson MC, Smith L, Bolton General. Bhalla KK, Kaneen A, Bolton General (Geriatrics): Adams KRH; Pilgrim, Boston: Nyman CR, Rix A; Bradford RI: Morrison G, Long L, Bromley Harris P, West Suffolk, Bury St Edmunds· Siklos P, Edwards C, Law, Carluke Baxter RH, Zachary J, St Helier, Carshalton. Pumphrey C, Jacob R, Colchester General: Handley AJ; Coleraine Finnegan O, McCusker K; Shotley Bridge General, Consett: Simpson G, Amos S; Crawley· Gossage A, Boolaky M; Dewsbury District. Kemp TM, Ahir S, Dorset County, Dorchester. Ashfield R; Noble's, Douglas (Isle of Man): Bourdillon RH, Ball M, Buckland, Dover: Wilson IV, Titterton R; Russells Hall, Dudley: Flint J, Joshi M; Nimewells, Dundee· Pringle TH, McKie S; General Register Office, Edinburgh· Campbell A, Lodge T; Edinburgh Royal Infirmary. Boon N, Flint L; Western General, Edinburgh· Starkey IR, Lochhead H; Epsom District· Robb GH, Easton P; Falkirk & District RI: McSorley PD, Campbell J; Farnborough· Wharton CFP, Ramsey Y; Queen Elizabeth, Gateshead Jones CTA, Naylor P, Southern General, Glasgow. Fyfe T, McGowan J; Royal Naval, Gosport: Hedger N; Grantham: Wijayawardhana UD, Armstrong S, James Paget, Great Yarmouth: Grabau WJ, Biddle S, Royal Surrey County, Guildford Foley TH, Simpson M, Princess Alexandra, Harlow. Milne JR, Blanchard H; Hartlepool General: Tildesley G, Elder P; The Conquest, Hastings Wray R, Coxon H; Hinchingbrooke, Huntingdon. Borland CDR, Wingfield T, Raigmore, Inverness· Kerr F, Calder G, Kettering General· Baines G, White M; Kidderminster General. Summers GD, Fadlon A, Royal Lancaster Infirmary Brown AK, Williams A; Ysbyty Llandudno: Vaterlaws AL, Preston C, Brook General, London: Foran J, Central Middlesex, London Dancy M, Joshi D, Edgware General, London Greenbaum R, Maher E, North Middlesex, London. Banim S, Rushworth R, Luton & Dunstable Stodell M, Newman J; Macclesfield District General: Davies ETL, Lomas M; Trafford General, Manchester Stephens WP, Smith K; Thanet District General, Margate: Morgan ADM, Hucey D; Middlesbrough General. McCormack P, Currie Y; Milton Keynes General Gwilt DJ, Long A; Royal Gwent, Newport Davies J, Wivell N, Whiteabbey, Newtownabbey· Crowe PF, Pyper M; Friarage, Northallerton Fisken RA, Burnside C; George Eliot, Nuneaton: Hollinrake K, Perry G, County, Oban: Henderson AK, MacKenzie F; Royal Oldham: Ahmed EM, Jaunbocus K; Orpington Wharton CFP, Royal Alexandra, Paisley Findlay IN, Gibson C; West Cornwall, Penzance Gibbons D, Sims D, Perth Royal Infirmary: Gray W, Fraser S, Pontefract General Infirmary Lewis R, Gibson CG; Whiston, Prescot Macmillan RR, Browne D, Royal Preston: Watt DAL, Golder M, East Surrey, Redhill Lyons JP, King N; Glan Clwyd, Rhyl Green GJ, Lynch E; Halton General, Runcorn: Mallya RK, Lewis R, Salisbury District. Jones AL, Winter S, Scarborough: Clark RS, Caunt J, Scunthorpe General: Batson GA, Robinson S; Northern General, Sheffield: Campbell S, Field P, Royal Shrewsbury Simmons ME, Webb C, Solihull. Burge S, Attwood J, Royal South Hants, Southampton Waller DG, Jones V; Southend General. Mellor J, Burgess K; Southport District General: Fox JP, Black R, OPCS, Southport Harris DP, Clayton T, Thomlinson L; Stepping Hill, Stockport Martin MA, Waldron K, Stonehouse Matthews DM, Wiseman D; Corbett, Stourbridge. Flint J, Henley M; Kings Mill, Sutton-in-Ashfield Rowley JM, Minich S; Taunton & Somerset Sanderson JE, Manning R, Princess Royal, Telford: Heber ME, Turner A, Torbay, Torquay: Dewhurst NG, Bennion R; Royal Cornwall (Treliske), Truro Mourant AJ, Garside C; Manor, Walsall: Cunnington A, Ishak S, Queen Elizabeth II, Welwyn Garden City: Keir PM, Engel M; Weymouth & District Ashfield R, West Cumberland, Whitehaven: Thomson C, Robinson N, Wigan RI Naqvi N, Belshaw M; Arrowe Park, Clatterbridge, Wirral. Silas JH, Halewood S, New Cross, Wolverhampton Pidgeon JW, Poole G; Worcester Royal Infirmary: Tibbutt DA, Lloyd A; Bassetlaw District General, Worksop Blandford RL, Ball E; Wrexham Maelor Sissons CE, Jones M; Princess Alexandra, Wroughton Amrolwalla FK, Cousins S, Wycombe General: Regan RJ, Houghton J

United States (3928; 164)—Brigham & Women's, Boston Hennekens C*, Ridker P*, Bilodeau C, Buring J, Clemente C, Lulejian C, University Hospital, Boston. Ryan T*, Columbia University, New York: Meier P† Akron City Josephson RA, Jasso D, Akron General Medical Center. Heiselman DE, Hudock DK, Allentown Osteopathic Medical Center. Starr HT, Scott L; Apple River, Amery: Johnson CT, Hegge C; Anderson Area Medical Center: Morse HG, Spoon D, Blackburn S, St Joseph Mercy, Ann Arbor Genovese B, Smith MJ, Athens-Limestone Scherff AH, Wilson C; Atlantic City Medical Center Nascimento TR, Solomon EA, Pomona, Atlantic City Ardire L, University, Augusta: Chandler AB Jr, Edwards M; Good Samaritan, Baltimore Fonda JN, Greene JE, Maryland General, Baltimore: Goldscher D, Connell D; Sinai Hospital of Baltimore Effron MB, Harrison T, DiFurio S, Bay Medical Center, Bay City: Shrestha DD, Huston C, Beaufort Memorial· Gambla KM, Neal C; University, Boston Ruocco NA, Hankin BR; Braddock Medical Center: Silver SJ, Brettschneider L, Harrison Memorial, Bremerton. Lee A, Eyer M; Brockton: Polansky BJ, Clements PJ, Kriegel A, Lahey Clinic, Burlington. Labib SB, Woodhead G; Casa Grande Regional Medical Center Nath HGY, De Leon OC; Mercy Medical Center & St Luke's, Cedar Rapids Rater D, Murrah E, Soukup M, Chandler Regional: Singh S, Landgraff T, Cerney-Powell V, Chelsea Community. Yarows SA, Bravo P; Loretto, Chicago. Kumar VP, Palutsis DM, Weiss Memorial, Chicago Chua KG, Schneider J; Fairview General,

Cleveland· Watts R, Camp B; Cloquet Community Memorial Swenson OP, Stevens N, USAF Academy, Colorado: Hansen JE, Hansen SR; Fayette Memorial, Connersville. Chandra SN, Anderson P, Cortland Memorial· Gillim SW, Rodgers K, Good Samaritan, Corvallis Marker TL, Veliotes C; Newton General, Covington Crews T, Hughes M, Scott A; VAMC-Dayton. Suryaprasad AG, Webb C, Griffin, Derby· Schwartz KV, Shah J, Romano M; Henry Ford, Detroit. Borzak S, Cruz T; Kent General, Dover· Jarrell TN, Moyer C; St Mary's Medical Center, Duluth. Thompson JI, Gressman A; R E Thomason General, El Paso· DiNardo-Ekery D, Gardea RM; Sun Towers, El Paso: Alvarez S, Ramirez C, William Beaumont Army Medical Center, El Paso: Mock GP, Sallee L, St John's Queens, Elmhurst Macina G, Kikel M, St John's Episcopal, S Shore, Far Rockaway Burnett V, Larosch K, VAMC-Fargo: Lim SP, Fogel VR; Parkland Health Center, Farmington: Grix GJ, St Gemme S, Cape Fear Valley Medical Center, Fayetteville Popio KA, McDonald K, Ballard L, Fort Madison Community: Cook TH, Lampe JA; Parkview Memorial, Fort Wayne Heger JJ, Richmond J, Dague D, Osteopathic Medical Center of Texas, Fort Worth Brooks LW Jr, Wright D, Southwest Florida Regional Medical Center, Ft Myers West SR, Bradley D; St Jude Medical Center, Fullerton Choe AM, Kerr B; Shands, Gainesville Conti CR, Handberg E, Edwards K, Addison Gilbert, Gloucester Arsenian MA, Cain B; St Francis Medical Center, Grand Island: Morse AK, Stines C, Community Memorial, Hamilton Muller RT, Putnam A; Margaret R Pardee Memorial, Hendersonville Goodfield P, Goodfield T, Hershey Medical Center Gilchrist IC, Glass S, Mesabi Regional Medical Center, Hibbing Bieging JK, Olson L; Bath County Community, Hot Springs Redington JF, Howell B, Ryder Memorial, Humacao. Rios ML, Sanchez R, VAMC-Huntington· Touchon RC, Peart K; Community East, Indianapolis Ziperman DB, Adams C; Falls Memorial, International Falls Johnson D, Nicholson G, Jersey City Medical Center Wong P, Kozlowski K; Castle Medical Center, Kailua Palma J, Johnson M, Bronson Methodist, Kalamazoo: Carrillo AP, Hearns P; Truman Medical Center - West, Kansas City Forker AD, Tertel K, Zimmerschied M; University of Kansas Medical Center, Kansas City· Wilson DB, Haffey K; Lower Florida Keys Health System, Key West· Calleja JF, Rogan N; Kingman Regional Medical Center· Bokhari SI, Wadsworth S, Crum C, Benedictine, Kingston: Lader EW, Bouren L; Preston Memorial, Kingwood. Shannon CK, Stump C, University of Tennessee Medical Center, Knoxville Scott JC, Reynolds FW; St Francis Medical Center, La Crosse· Santolin CJ, Peterson RM, Wilford Hall Medical Center, Lackland AFB Laveau PJ, Burns MJ, Lakes Region General, Laconia Rosenfeld AS, Waldron K; Rusk County Memorial, Ladysmith Charipar RM, Gustafson A; Lakeland Regional Medical Center Gleason W, O'Connor H, EW Sparrow, Lansing: Armstrong JR, Jupp K, Southwestern Medical Center & Comanche County Memorial, Lawton: Chun PKC, Whetzal J, Cottrell S, Welsh D; Beebe Medical Center, Lewes: Bolourchi H, Lane CG, Central Maine Medical Center & St Mary's, Lewiston Weiss RJ, Ridley C, Rauscher A; Lewistown. Suthar AL,Tussey S, St Elizabeth Community Health Center, Lincoln. Weaver WF, Mahaffey T, Littleton Pollak EM Jr, Buxton L; VAMC-Long Beach: Olson HG, Rousseue C; Monmouth Medical Center, Long Branch. Ferri DP, Lee K; Kaiser-LA, Los Angeles Kotlewski A, Browning R, Stauffer R; University of Wisconsin Hospital & Clinics, Madison: Ende DJ, Wiederholt P, North Shore University, Manhasset Morrison J, Ward M; The McDowell, Marion. Whisenant MN, Teaster Brown S; Gottlieb, Melrose Park Shanes JG, O'Connor PM; Mt Sinai Medical Center, Miami Beach: Korn D, Bordenave G; Lakewood, Morgan City: Blereau RP, Henry L, Copley, Morrisville. Buckley B, Shaw L, VAMC-Mountain Home. Richards SD, Downs C; Frick Community Health Center, Mt Pleasant· Lynn RE, Kubasky MJ, Muscatine General: Kwirant J, Waring P; VA Medical Center, Muskogee Danisa K, Wescott BL, Jersey Shore Medical Center, Neptune· Rubinstein R, Thornton DA, Carrero L; St Raphael, New Haven Jacoby SS, Wheeler P; LSU Medical Center, New Orleans: Subramaniam PN, New Rochelle Medical Center Gitler B, Miele MB, Beth Israel Medical Center, New York Strain JE, Kelly A; Harlem, New York City: Hodges D, Onwuanyi A, Sherzoy AA; Hoag Memorial, Newport Beach Kennelly BM, Meister F, Laurie N, Memorial, North Conway· Brewster W, Estey K, Norwalk: Cohen IS, McNamara GE; Community Memorial, Oconto Falls: Artwich R, Bartel A; Wright-Patterson AFB Medical Center, Ohio Broderick G, Pangborn L, Collins G, Marks R, Ojai Valley Community. McManus J, Bender L, Smith J, AMI St Joseph, Omaha Del Core MG, Stengel LA; University of Nebraska Medical Center, Omaha Meyer DG, Siebler J, East Alabama Medical Center, Opelika: Ingram RF, Stegall G, Oroville Fine MN, Mallette M, McCullough Hyde Memorial, Oxford Hunt TG,Williams N, Combs J; Raritan Bay Medical Center, Perth Amboy· Chiaramida AJ, Gaven R, St Francis Medical Center, Pittsburgh George JM, Byrnes M, St Margaret Memorial, Pittsburgh. George JM, Segaline J, Scavina JM, Damas, Ponce: Jovane JR, Medina L, St Luke's Episcopal, Ponce Torres-Aguiar R, Quisones R, Castleview, Price: Nichols D, Fisher K, Jefferson Memorial, Ranson Webb RF, Christie K; Frisbie Memorial, Rochester· Reeves DM, Gallot SH, Wuesthoff Memorial, Rockledge: Palaniyandi RB, Woodbury J, Lantz M, William Beaumont, Royal Oak Timmis GC, Tollis CA, Jones D; Salem VA Medical Center: Jarmukli N, Helms B, VAMC-Salisbury Khan MN, Zirt J; LDS, Salt Lake City: Anderson JL, Allen A, Moffitt-Long, San Francisco Wolfe CL, Akin J; University, San Juan: Cox RA, Rivera C, Firelands Community & Providence, Sandusky Young DJ, Dendinger L, Pulizzi MB, Wise M, Reising J, LSU Medical Center, Shreveport Sheridan FM, Gillespie L, Illini,Silvis: Mundodi B, Boelens D, Royal C Johnson Veterans Memorial, Sioux Falls Davis JB, Duncan L, Williams L, VAMC Spokane Brodersen A, Clark M, Dixie Regional Medical Center, St George: McDonnell MA, Musser L, United, St Paul Tschida V, Kolb RP, Staten Island University. Lefkevic L, Veneziano P; Olive View Medical Center, Sylmar Altamirano J, Rendon ES, Syosset Community Levine RH, Moran T, Angelone C; Titusville Area. Denlinger LE, Faunce TL; Parrish Medical Center, Titusville Modi KR, Morgan D; Medical College of Ohio, Toledo· Fraker TD Jr, Hinis S, Tooele Valley Regional Medical Center Sullivan WK, Sloan L; William Beaumont,Troy Smiley WH III, Brait DC, Tyler Memorial, Tunkhannock· Benner JN, Watkins D, Mother Frances, Tyler Sigal SL, LeBoeuf RM, Westchester County Medical Center, Valhalla. Weiss M, Kanakaraj A, Pollack B; Virginia Regional Medical Center Jamal K, Wingness V; Wahiawa Dang W Jr, Luke B; Jones Memorial,Wellsville· Sale MK, Benedict E, Winter Haven· Willard E, Schreiber MJ; Winthrop· Schulman CL, Demers P; University of Massachusetts Medical Center, Worcester: Becker RC, Ball S; Wythe County Community, Wytheville: McConnell JJ, Jones MS; St Elizabeth, Youngstown. Hill PE, Siverling EA, Bethesda & Good Samaritan Medical Center, Zanesville. Frerking T, Boehme E, McInturf E

Uruguay (132; 5)—Sociedad Uruguaya de Cardiologia, Montevideo: Sandoya E‡, Asoc Española de Montevideo Lluberas R; CASMU, Montevideo. Terra J; Español, Montevideo· Cobas J, Militar, Montevideo Dini A, COMERO, Rocha: Casanyes D

Venezuela (230, 8)—Dr Domingo Luciani, Caracas Isea Perez JE‡, Gomez R; Central, Acarigua: Gonzalez N, Despujos J; Universitario, Barcelona Marrero C, Arreza M, Ascardio, Barquisimeto· Garcia E, Torres W, José Gregorio Hernandez, Caracas Cataldo MT; Miguel Perez Carreño, Caracas: Rodriguez F, Espinoza R; Universitario, Maracaibo· Pena J, Vergara G; Central de Valencia: Marino P, Petrola I.