including patients treated very early or those treated later and those receiving or not receiving concomitant thrombolytic treatment. The trend towards increased mortality was perhaps due to the excess incidence of cardiogenic shock and heart failure in the magnesium group, which is in direct contrast to both the results and the suggested mechanism of benefit observed in LIMIT-2. In contrast to the findings in LIMIT-2, but consistent with the results of older trials and experimental data, there was a significant reduction in early ventricular fibrillation with magnesium in ISIS 4.

When the unexpected results of ISIS 4 were reported at a meeting of the American Heart Association in November 1993 critics of meta-analysis pointed to the lack of consistency among the results of the meta-analysis, LIMIT-2, and ISIS-4. Supporters of magnesium questioned whether the large simple trial itself was unreliable: perhaps the patients enrolled were those unlikely to benefit from treatment with magnesium or perhaps the timing of the magnesium regimen was inappropriate. All the comments and analyses will need careful examination.[8]

The lack of consistency between ISIS 4 and the meta-analysis of the small trials does not necessarily invalidate the technique. Firstly, the meta-analysis was based on a relatively small amount of data (only 78 deaths), and despite the extreme P value (0·001) the result may not necessarily have been "robust." The results of meta-analyses are subject to a number of biases that are not readily quantifiable. Traditionally, meta-analysis has been carried out on topics where the results are likely to be interesting. Indeed the decision to perform and publish a formal meta-analysis may itself be data derived. Although the LIMIT-2 trial seemed to confirm the results of the meta-analaysis, its own results were only just statistically significant (P=0·04) with wide confidence intervals.

One explanation is that delays in giving magnesium after thrombolytic treatment could have confounded the results of ISIS 4. While it is true that the experimental treatments were started after proved treatments (aspirin, β blockers, and thrombolytic drugs) had been given, further analysis of ISIS 4 indicates that there was no benefit even among the 10 252 patients randomised within three hours of the onset of symptoms. In these patients recanalisation of the coronary artery and the infusion of magnesium would probably have been almost simultaneous. Furthermore, in LIMIT-2 the benefits of magnesium were similar in those receiving and those not receiving thrombolytic treatment. In ISIS 4 there was no evidence of benefit of magnesium in either of these groups. No coherent explanation has been offered for the differing results.

What are the lessons to be learnt? Firstly, a meta-analysis of small trials is not a replacement for large, carefully conducted trials. Secondly, since most treatments produce either no effect or at least only moderate effects on major outcomes such as mortality, investigators should be sceptical if the results obtained deviate substantially from this expectation ("too good to be true"). Thirdly, definitive trials should demand levels of evidence that are statistically more reliable, with the lower confidence limits of the risk reductions representing a clinically worthwhile difference.

Until further research evidence is presented there are no grounds for the routine use of magnesium for patients with acute myocardial infarction.

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Misleading meta-analysis

Lessons from "an effective, safe, simple" intervention that wasn't

See p 751

A meta-analysis of treatments in myocardial infarction published in 1992 retrospectively showed that streptokinase was associated with a highly significant fall in mortality by 1977, after inclusion of 15 trials.[1] Thrombolysis was, however, not widely recommended until 10 years later—after the effect was confirmed in two mega trials.[1-3] In the case of magnesium, a substantial fall in mortality was evident by 1990, after inclusion of seven trials. In 1993, based on an updated meta-analysis it was argued that magnesium treatment represented an "effective, safe, simple and inexpensive" intervention that should be introduced into clinical practice without further delay.[4] The negative results of ISIS 4 (the fourth international study of infarct survival), published in last week's *Lancet*,[5] have dealt a blow to enthusiasm for both magnesium and meta-analysis.[6] As the findings of meta-analyses and systematic reviews are generally not tested in mega trials the situation regarding magnesium represents an opportunity to examine a false positive meta-analysis.

The table compares the meta-analyses of trials of magnesium and streptokinase after myocardial infarction. Trials were cumulatively included until the treatment effect was significant at P < 0·001. For magnesium, seven small trials whose results were published in the 1980s were sufficient to establish the effect. Although trials were larger in the case of fibrinolytic treatment, twice as many studies and two decades were necessary to reach the same level of significance. Until recently it could have been argued that this was due to the larger effect apparently associated with magnesium treatment, which should be detectable in a smaller number of trials. In the light of ISIS 4, however, another explanation must exist.

Could selective identification of positive studies have led to this finding? Trials that support a beneficial effect are cited

Comparison of two meta-analyses—of intravenous magnesium and streptokinase for acute myocardial infarction—refuted and confirmed by subsequent large randomised controlled trials

	Refuted by mega trial* (magnesium)	Confirmed by mega trial† (streptokinase)
Year of first publication	1984	1959
Year when $P<0.001$ achieved	1990	1977
Estimated reduction in mortality (%)	55	23
No of trials	7	15
Total No of deaths/patients	78/1301	926/4314
No of trials of size:		
10-99 Patients	3	4
100-199 Patients	1	3
200-499 Patients	3	4
500-999 Patients	—	4
Average No of patients per trial	186	288

*Refuted by ISIS-4.[5]
†Confirmed by GISSI 1 and ISIS 2.[2,3]
Trials were included cumulatively until $P<0.001$.

more frequently than unsupportive trials and are thus more likely to be located for meta-analysis.[7,8] We have addressed this hypothesis by hand searching relevant specialist journals and by extending the search to the literature in languages other than English. This has yielded another five small trials[9-13]; however, two of them showed a significant ($P<0.05$) reduction in total mortality[9,13] and the three others a non-significant trend in the same direction.

Publication bias is another possibility. Small positive trials are more likely to be published than negative ones, potentially distorting the findings of meta-analyses. If publication bias is operating one would thus expect that, of published studies, the larger ones report the smaller effects. This can be examined in funnel plots, in which the estimates of effect size obtained in the studies are plotted against the sample size. If there is no publication bias the plot should resemble a symmetrical inverted funnel with the results of smaller studies being more widely scattered than those of larger studies. The figure shows the funnel plots for the magnesium and streptokinase trials that appeared before the relevant mega trials with the mega trials added. The plot for the streptokinase trials is symmetrical, and the pooled estimate is in line with the results of the mega trials, GISSI, (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardio), and ISIS 2.[2,3]

This is clearly not the case for magnesium. The pooled estimate is at odds with the results of ISIS 4, and there is a gap in the bottom right of the funnel, which indicates the absence of negative small studies. Selective non-publication of negative trials thus seems to be a likely explanation for the discrepant findings of the magnesium meta-analysis. The possibility that negative trial results were turned into positive results by selective exclusion of patients from the analysis or other inadequate handling of data must also be considered. For example, a significantly ($P<0.05$) reduced mortality from cardiac causes was initially reported for the group treated with magnesium in one trial (A M Thogersen *et al*, VIth international magnesium symposium, Indore, India, 1991); when the results were later analysed on an intention to treat basis, however, this difference became non-significant.[12] Furthermore, 16 deaths due to non-cardiac causes were reported during nine months of follow up,[12] but only eight such deaths were mentioned in a later paper covering 22 months of follow up.[14]

Such biases are probably less likely to act in larger, well monitored trials and could thus produce the same asymmetrical pattern in funnel plots. It remains unclear to what extent publication bias and inadequate handling of data and analysis have contributed to this situation. Finally, it should be kept in mind that, with hundreds of meta-analyses being performed, a few will produce misleading results by chance alone—though this is unlikely in the present case. Indeed, the situation regarding magnesium is not unique. Reviews of the use of nitrates in myocardial infarction[15] and of aspirin in the prevention of pre-eclampsia[16] are further examples of meta-analyses that were based on small trials and whose positive results were later substantially modified by larger trials.[5,17]

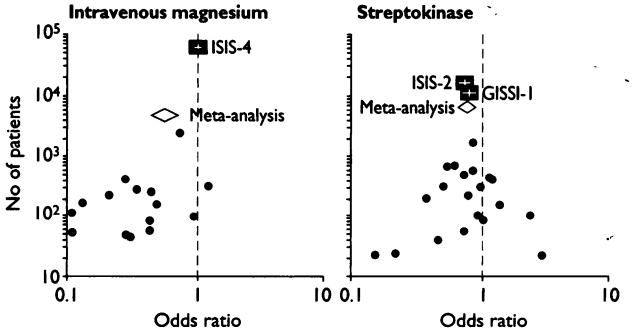
Evidence from mega trials will continue to be unavailable for most medical interventions, and in these situations systematic reviews that are based on meta-analyses of randomised controlled trials are clearly the best strategy for appraising the available evidence.[18] But to avoid this strategy becoming discredited several steps should be taken. Firstly, more research into the factors associated with misleading meta-analysis is needed. This research should focus on the process of identifying and selecting studies and on the refinement of methods to scrutinise results and should lead to a better estimate of the incidence of the problem. Secondly, registers of clinical trials should be established, with new studies being documented at inception. This is the most effective way of reducing the risk of negative trials disappearing from view. To ensure complete registration, ethics committees should link their approval to the requirement that trials are registered.[19]

Thirdly, in the meantime results of meta-analyses that are exclusively based on small trials should be distrusted—even if the combined effect is statistically highly significant. Several medium sized trials of high quality seem necessary to render results trustworthy.

Fourthly, the results of meta-analyses should always be subjected to careful sensitivity analyses to test the robustness of the findings. For example, the use of β blockers in secondary prevention after myocardial infarction is widely recommended, largely on the basis of a meta-analysis published in 1985.[1,20] The results of this meta-analysis are robust to the choice of the statistical methods used for combining the data and to the exclusion of trials of lesser quality or of studies terminated early. A symmetrical funnel plot suggests that publication bias did not distort the findings.

Such sensitivity analysis should be part of any article reporting the results of meta-analyses[21]—it could, in fact, have prevented the misleading conclusions drawn from the magnesium trials.[22] Therefore, finally, meta-analyses and systematic reviews published in print or electronically should

Funnel plots for meta-analyses refuted and confirmed by subsequent mega trials: intravenous magnesium (left) and streptokinase (right) in acute myocardial infarction.



Points indicate odds ratios from small and medium sized trials, diamonds indicate combined odds ratios with 95% confidence intervals from meta-analysis of these trials, and squares indicate odds ratios with 95% confidence intervals from mega trials.
(The list of trials is available from the authors)

be scrutinised carefully. Analyses based exclusively on small studies should be treated with caution.

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Abduction of infants from hospital

Vigilance and staff training are the keys to prevention

Abduction of infants from birth to the age of 6 months from hospitals by people who are not members of their family, such as the recent abductions in Nottingham and Wales, are rare. In Britain since 1990 roughly half a dozen infants have been reported to have been abducted from their natural parents by people who were not members of their family out of a total of 800 000 births a year. The experience of any one hospital or police force in Britain is therefore very limited.[1] Rabun, who is an authority on the abduction of infants from the National Center for Missing and Exploited Children in the United States, has analysed 77 abductions of infants from American hospitals between 1983 and 1992,[2,3] and the lessons of his analyses have to be relearnt each time an abduction occurs in Britain.

In Rabun's study all the abducted infants were 3 months old or younger (half were less than 1 week old) and 73 were returned safely within two weeks. In the typical case a woman impersonated a nurse. Almost all the abductors were female, and they were often overweight (making it easier to mimic pregnancy). The abduction usually occurred between 9 am and 3 pm, presumably because the abductor's partner must be out of the house at the time. The male partner must be naive enough to believe in the "immaculate birth" that has occurred in his absence. He rarely took part in the planning and execution of the crime, although he may have become an unwitting party to the crime after the event. The abductor rarely had a criminal record or an important documented psychiatric history, and claims of acute psychiatric illness at the time of abduction have rarely been sustained.[1,4,5]

The vicarious "birth" usually followed a period of "nesting" (decorating the nursery and the like) and a simulated pregnancy. These abductions are therefore rarely spontaneous copycat crimes or acts of impulse due to diminished responsibility. The abductor may have had a baby who died, have a history of recurrent miscarriages, or have faked previous pregnancies. She usually lived in the same community as the natural parents, and some abductors have had previous peripheral involvement with the health service. A stairwell or corridor was preferred for the escape rather than a lift, and the abduction was usually from a room that was less than 40 seconds' walk from the exit used by the abductor. A pram was never used.

Vigilance and training of staff are the keys to prevent the abduction of infants from hospitals.[6,7] Simple measures include attaching an identification band to the baby immediately after birth, requiring all staff to wear identity cards with their photograph on, having a written policy on hospital security, and ensuring that staff are educated about the risk of abduction of infants. All neonatal, paediatric, and maternity wards should have policies controlling access. Receptionists should ask all visitors their name and the name of the mother they are visiting. Anyone removing an infant from the ward for any test should show his or her identity card, which should be conspicuous, numbered, and legible. Prospective parents should be advised never to give their infant to anyone who cannot show hospital identification. The parents should know the nurse assigned to them and should challenge any unfamiliar person handling their infant.

All staff should be instructed to offer help to any stranger in the ward and report to hospital security if his or her behaviour is suspicious. No unaccompanied mother should be allowed to walk out of the maternity unit with a baby; a midwife should escort the baby from the ward to the waiting car.

More sophisticated security systems are not foolproof but act as a deterrent. No infant has been abducted from a hospital with an electronic security system in place. These systems, however, can be expensive, and one hospital has allegedly spent £250 000 on security.[8] Hospitals are public places and are difficult to render impregnable. An intimidating atmosphere and military style security would not be appropriate.

One of Nottingham's maternity units is sited within a