mic drugs were pooled, and no beneficial effect has been demonstrated for calcium channel blockers.

The results of our coding of the recommendations of the experts writing the review articles and textbook chapters dealing with secondary prevention are presented on the right side of Figs 3A through 3G. In each instance in which the cumulative meta-analyses revealed the treatment to be effective in reducing the risk of dying, the majority of the clinical experts lagged behind in recommending an intervention by more years than could be explained by the usual publication delays. The most striking example was the antiplatelet drugs (Fig 3C) that did not begin to be recommended for routine use by more than half of the reviewers until 1986, 10 years after they could have been shown to be effective by cumulative meta-analyses, and 6 years after the first published meta-analysis. The majority of reviewers did begin to recommend β-blockers for either routine or specific use within 2 years of the first published meta-analyses, but it was 6 years after the time when a cumulative meta-analysis would have been positive. From 1988 on, the majority of authors still did not recommend cholesterol-lowering attempts despite evidence of a significant mortality-reducing effect. Rehabilitation programs (Fig 3E) started to be recommended well before the accumulating evidence on total mortality.

Recommendations for use of calcium channel blockers in specific patients may be based on a recent trial of diltiazem that reported a suggestive trend toward reduction of reinfarction rates but no effect on total mortality. Long-term use of type I antiarrhythmic drugs were recommended by three reviewers as late as 1990 and their risks are not mentioned by most authors. Yet, this class of drugs has been shown to cause an increased death rate after MI. 34, 35 Efficacy of long-term anticoagulant use did not become statistically significant until 1990, yet they have been recommended by some without qualification and clawed by others as controversial for the last 25 years.
years. Other authors still do not mention them.

COMMENT
Potential Causes of the Lack of Concordance Between the RCTs and the Recommendations of the Experts

These data have uncovered discrepancies between the timeliness of recommendations by clinical experts and the meta-analytic evidence obtained from pooling RCTs. We are not advocating that reviewers necessarily follow the conclusions of the experimental data or of the meta-analyses, an increasing number of which are appearing, but rather that they comment on the RCTs in the literature when formulating their opinions. Some reviewers have not mentioned effective therapies, while others continue to recommend those that are ineffective or possibly harmful. The discrepancies may be the result of a complex interplay of factors discussed below.

Volume of RCTs.—The volume of clinical trials in every specialty is too large for the clinical specialists to digest in an ongoing basis. (An average of 94 RCTs on treatment of acute MI are listed for each of the last 3 years in MEDLINE.) Even if the reviewers had the time to do the searching, the available methods of finding all the RCTs are too cumbersome for the average clinical expert who may be untrained in the art of searching the literature for every available trial. Time, money, and support personnel are necessary to bring a textbook chapter up to date in an active field such as acute MI. Textbook chapters and review articles also may lag behind clinical practice because of publication delays that may exceed 1 year. Of note, we found no significant differences in the distribution of recommendations between chapters and review articles.

"Negative" RCTs.—Some reviewers may not appreciate that a small trial whose result is not statistically significant is not necessarily a "negative" trial, suggesting that the treatment does not work. Instead, the RCT may merely lack the power to show a beneficial or detrimental effect. Alternatively, some experts may select a conservative approach by awaiting the publication of very large trials such as the GISSI and ISIS cooperative studies, even when statistically significant results were present in several smaller trials.

Limited Familiarity With Meta-analysis or Concerns Over the Techniques of Combining Data From Multiple Trials.—The biostatistical technique of meta-analysis has only recently become popularized in the clinical literature, and many reviewers may have limited familiarity with interpretation of meta-analytic results and/or may have personal reservations about the process of combining the results of multiple trials.

Reliance on Personal Experience, Problematic Because of Low Event Rates.—Another possible explanation for the discrepancy is illustrated by the contrast between the tendency to ignore the thrombolytics that had been proven to reduce mortality and to endorse about lidocaine that had not. In the former case, physicians could see the side effect of bleeding after treating only a few patients or hearing in the hospital corridors of only a few others. They would have had to have treated a thousand or compared them with thousands of randomized controls to have appreciated that the drugs were saving lives. Conversely, in the case of lidocaine, they could see ventricular arrhythmias that they considered harbingers of sudden death diminished by treatment in many patients. They would have had to study thousands of patients of individuals under carefully controlled conditions to appreciate that there was not only a decrease in mortality of patients treated with lidocaine, but there might even be an increase. Properly carrying out meta-analyses that overcome the small-size deficiencies of most published RCTs requires special training and expertise, and is sometimes misunderstood or looked on with suspicion by medical specialists.

Market Availability.—The availability of a drug on the market for other uses may have led to its recommendation for use in patients with acute MI even before definitive proof of a reduction in mortality was available. B-blockers are a good example of this concept. Twelve different B-blockers have been approved and advertised for use in a variety of cardiovascular conditions in the last 10 years. This may have contributed to the feature that the B-blocker recommendation rate was much higher than that for intravenous vasodilators and anticoagulants, two classes of drugs whose efficacy in reducing mortality was established several years before the B-blockers.

Effects on Other End Points.—Some experts may have been influenced by treatment effects on other end points than total mortality, such as the arrhythmias mentioned above and the effects of B-blockers on multiple cardiovascular end points. Other reviewers might take a conservative opinion as to which patients to apply the conclusions of multiple RCTs, because the trials vary greatly in their inclusion and exclusion criteria. However, one advantage of pooling multiple small trials is that differing criteria for inclusion and exclusion of patients add or diminish support for the consistency of the findings across different groups.

Drug Choices and Patient Selection.— Some reviewers may have not recommended certain therapies because of perceived unacceptable side effects (eg, stroke) despite efficacy in reducing mortality. Alternatively, some therapies may have been considered too costly, or alternative therapies available on the market were considered equally effective or better. Other experts may have recommended only those therapies that would be applicable to the majority of patients with MI seen in private practice and avoided recommending treatments they believed were applicable only to a highly selected subset of patients enrolled in a clinical trial. Finally, some reviewers may have felt that although a number of potentially helpful treatments have been individually identified, they were reluctant to make firm recommendations because little data are available on their relative merits or on the consequences of concurrent use of more than one treatment in the same patient. The effects on mortality might not be additive when two treatments that are independently shown to be helpful are combined in the same individual, because of drug interactions. Many of the treatments reviewed in this article were evaluated in the prethrombolytic era and their precise treatment effect may be different after adjusting for the effects of reperfusion. The limited data that are available from RCTs in the thrombolytic era, however, do suggest that beneficial mortality effects are seen with combinations of interventions. For example, in the cases of thrombolytic and antiplatelet drugs, the two interventions were combined in one study (ISIS-2) and the mortality reductions were found to be additive in the combined treatment group.

Food and Drug Administration Approval.—Finally, the reviewers may have been awaiting the announcement of approval by the Food and Drug Administration of the use of a particular drug for the routine treatment of MI that often did not occur until after the publication of two large-scale randomized trials for a given intervention. Evidence of approval by appearance of such a recommendation in the Physicians Desk Reference has often lagged behind the results of accumulated small trials and, in the instances of intravenous vasodilators and magnesium salts, has not
yet occurred. On the other hand, the recommendations for thrombolytic therapy followed quite quickly after the completion and publication of the GISSI trial. It should be pointed out that the Food and Drug Administration is not empowered to approve therapies unless requested to do so by the manufacturer.

Limitations

Some might object that we have restricted our analyses to total mortality and not considered other end points. One conceivable important end point that we have not reported is the effect of the therapies on quality of life. We have not reported data on quality of life in the survivors of MI for two reasons: the data are still too sparse and variable to permit reliable analysis, and, in the case of a postinfarction patient, a poor quality of life could only rarely be considered worse than premature death.

Trial design and patient characteristics (e.g., the degree of illness and risk of mortality) may have varied over time, possibly resulting in some minor fluctuation of the point estimates of the treatment effect and CIs as the cumulative meta-analyses evolved when more recently conducted trials were included in the analysis. Furthermore, differences in interpretation of the types of patients enrolled in the trials may have led to differences in the recommendations of the expert reviewers with regard to whether a treatment should be used routinely or only in selected patients. However, that does not explain the large number of authors who have not even mentioned many therapies that have been established as saving lives in at least some patients.

Performing a cumulative meta-analysis may have the appearance of a sequential study. One concern regarding bias in sequential studies comes from "optimal stopping," or stopping according to a rule that depends on outcomes, such as stopping as soon as one gets 10 successes. It is true that if the individual studies of the meta-analysis use sequential stopping rules, problems can occur. However, cumulative meta-analysis does not have biasing stopping rules since no stopping is occurring either; the data are being summarized up to the given moment.

As time passes, all aspects of medical care (hospitals, physician training, medications, adjuvant treatments, style of treatment) undergo change. Consequently, after a considerable period of time, a number of early trials may be included in the meta-analysis that no longer represent current practice. Ultimately, we may need to introduce a time lag or discount factor to the early trials in the performance of a cumulative meta-analysis, but this will require more experience with such a new methodology before recommendations are developed.

All of the problems mentioned above can be overcome with time and effort. The first and most important—making sure that authors of review articles and chapters have available to them updated listings of the RCTs and meta-analyses—will require a dedicated service and a suitable source of adequate funding that is not now available. A prototype is available to obstetricians and perinatologists. Electronic publication of continuously updated meta-analyses of controlled trials, as exemplified by the Oxford Database of Perinatal Trials has been shown to be practicable, but requires considerable organization for maintaining the database. There is no reason, in principle, why this approach should not be applied to other fields of medicine, such as the treatment and secondary prevention of acute MI, given the relatively modest resources required.

Confidence in meta-analysis as a means of portraying the message contained in multiple small trials may come with time and with improvements in the analyses and presentation of the data. More data needs to be gathered on the reliability and applicability of meta-analysis of many small trials as compared with the results of large cooperative studies with one fixed protocol to clarify whether the tradition of awaiting the results of at least two large-scale RCTs needs to be modified.

CONCLUSIONS

Although there is a temptation after reviewing these data on the transmission of clinical trial results to take the next step of making specific recommendations about the use of one or more of the therapies in the treatment of acute MI, that is not a purpose of this article. Our goal is to bring about more timely review articles and textbook chapters by calling for dissemination of clinical trial results in a format that will facilitate better published clinical guidelines.

Cumulative meta-analyses such as those used in the present study will be helpful for research directors and regulatory bodies when synthesizing the burgeoning cardiology literature to formulate recommendations for treatment of patients with MI. The practitioner will then have maximal guidance in choosing appropriate therapies from an ever-enlarging menu of options.

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