A Comparison of Results of Meta-analyses of Randomized Control Trials and Recommendations of Clinical Experts

Treatments for Myocardial Infarction

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Objective.—To examine the temporal relationship between accumulating data from randomized control trials of treatments for myocardial infarction and the recommendations of clinical experts writing review articles and textbook chapters.

Data Sources.—(1) MEDLINE search from 1966 to present; search terms used were *myocardial infarction, clinical trials, multicenter studies, double-blind method, meta-analysis*, and the text word "random:"; (2) references from pertinent articles and books; and (3) all editions of English-language general medical texts and manuals and review articles on treatment of myocardial infarction.

Study Selection.—Randomized control trials of therapies for reducing the risk of total mortality in myocardial infarction (acute and secondary prevention). Review articles and textbook chapters dealing with the general clinical management of patients with myocardial infarction.

Data Extraction.—Two authors read the material and recorded the results; disagreements were resolved by conference.

Data Synthesis.—We used the technique of cumulative meta-analysis (performing a new meta-analysis when the results of a new clinical trial are published) and compared the results with the recommendations of the experts for various treatments for myocardial infarction. Discrepancies were detected between the meta-analytic patterns of effectiveness in the randomized trials and the recommendations of reviewers. Review articles often failed to mention important advances or exhibited delays in recommending effective preventive measures. In some cases, treatments that have no effect on mortality or are potentially harmful continued to be recommended by several clinical experts.

Conclusions.—Finding and analyzing all therapeutic trials in a given field has become such a difficult and specialized task that the clinical experts called on to summarize the evidence in a timely fashion need access to better databases and new statistical techniques to assist them in this important task.

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SHORTENING the time between medical research discoveries and clinical implementation of new technologies by practicing physicians has been a concern of the American public since Congress established the Heart, Cancer, and Stroke Program over 25 years ago.[1] An undesirable lag still exists, and overcoming it is one of the goals of the newly formed Agency for Health Care Policy and Research.[2] Expert reviewers, who serve as opinion leaders by writing in both the periodical literature and in textbooks, play an important role in the process of interpreting technological advances and transmitting the information to clinicians. The data in this article on treatments for myocardial infarction (MI) indicate that one potential source of delay in widespread adoption of new treatments are discrepancies between recommendations of reviewers and the results of randomized control trials (RCTs).

We have reported the routine application of cumulative meta-analysis, a technique that permits the identification of the year when the combined results of multiple RCTs first achieve a given level of statistical significance.[3] The technique also reveals whether the temporal trend seems to be toward superiority of one intervention or another, or whether little difference in treatment effect can be expected, and allows investigators to assess the impact of each new study on the pooled estimate of the treatment effect. When cumulative

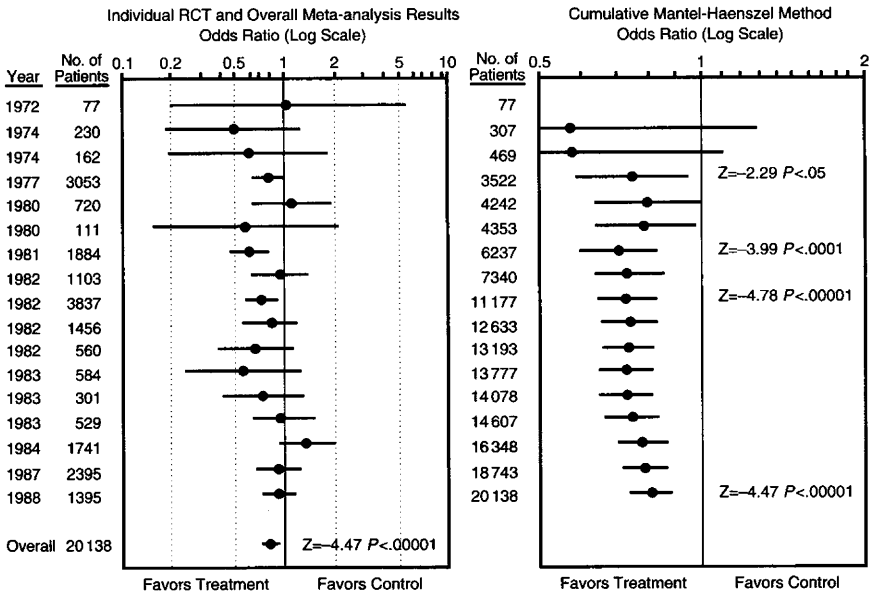

Fig 1.—Results of 17 randomized control trials (RCTs) of the effects of oral β-blockers for secondary prevention of mortality in patients surviving a myocardial infarction presented as two types of meta-analyses. On the left is the traditional one, revealing many trials with nonsignificant results but a highly significant estimate of the pooled results on the bottom of the panel. On the right, the same data are presented as cumulative meta-analyses, illustrating that the updated pooled estimate became statistically significant in 1977 and has remained so up to the present. Note that the scale is changed on the right graph to improve clarity of the confidence intervals.

meta-analysis is combined with a classification scheme of the treatment recommendations for MI found in review articles and textbook chapters, observations can be made on the timeliness of the translation of the results of RCTs into recommendations for clinical practice.

We found many discrepancies between the evidence contained in the RCTs and the timeliness of the recommendations of the expert reviewers, in the case of both effective and ineffective therapies. Emphasis on the time when cumulative meta-analyses would have indicated efficacy if they had been done is not meant as a criticism of the opinion leaders for not having implemented a technique not yet used widely. Rather, the relationships are presented as examples of the problems encountered when synthesizing a rapidly expanding segment of the medical literature now and in the future.

METHODS

Cumulative Meta-analysis

The technique requires the accumulation of published RCTs of the therapy in question and performing meta-analyses sequentially as the latest RCT is added to the cumulative results of the previous trials. As an example, the data from 17 RCTs of β-blockers for the prevention of death in the years following a MI are presented in Fig 1 as a traditional meta-analysis on the left (arbitrarily performed after 17 RCTs had been published) and a cumulative meta-analysis on the right (updating of the meta-analytic estimate of the treatment effect with the publication of each new RCT). (A bibliography of the included trials and articles is available from the National Auxiliary Publications Service [NAPS].) In the traditional meta-analysis, the individual trials are plotted as the odds ratios (ORs) of the treatment effect with their 95% confidence intervals (CIs); the pooled result is at the bottom. Three of the 17 RCTs had ORs favoring the control group, and only two of the remaining 14 RCTs had a statistically significant difference in mortality favoring the treatment group. In the cumulative meta-analysis on the right side of the graph, each OR and 95% CI now represent a new meta-analysis, the first a combination of the first two trials and the second the first three, and so forth.

Our literature search for meta-analyses and RCTs of treatments for MI involved a MEDLINE search as well as a detailed review of references in published RCTs. (Search terms used were *myocardial infarction, clinical trials, multicenter studies, double-blind method, meta-analysis,* and the text word "random:"). The results of this search led to a grouping of updated meta-analyses as follows:

1. Therapies for reducing the risk of mortality in acute MI: thrombolytic drugs,[4-13] intravenous vasodilators (nitroglycerin and nitroprusside),[14] intravenous or oral β-blockers,[15-18] anticoagulants,[19] aspirin,[20] lidocaine prophylaxis against primary ventricular fibrillation,[21-23] calcium channel blockers,[24] and intravenous magnesium salts.[25]

2. Therapies for reducing the risk of mortality following hospitalization for acute MI (secondary prevention): oral β-blockers,[15-18,26-31] anticoagulants,[32-34] antiplatelet drugs,[35-38] calcium channel blockers,[24] hypocholesterolemic treatments,[39,41] rehabilitation exercise regimens,[42-43] and type I antiarrhythmic drugs.[44]

Classification of the Opinions of Expert Reviewers

Review articles and textbook chapters were obtained from MEDLINE searches plus the authors' files and reference lists of other reviews, specifically focusing on discussions of the general management of patients with acute MI. Review articles and textbook chapters were excluded if they were concerned primarily with the cause or pathogenesis of acute MI with a single class of treatments, or if the treatments discussed were confined to a single manifestation of the disease rather than the overall clinical management of patients with MI.

A previously developed method of recording the opinions of expert reviewers with minimal bias[45] was modified as one of the authors (T.C.C.) first surveyed the opinions in an unblinded manner. After a suitable scale had been developed, the second observer (E.M.A.) independently classified all the articles and chapters after they had been blinded to the author, source, and date of publication. Differences between the two investigators (T.C.C., E.M.A.) were adjudicated from the blinded copies.

Recommendations of the expert authors were classified by us as follows:

1. Routine: The therapy should be used routinely unless there is a specific but not common contraindication. This would be exemplified by a recommendation to administer intravenous β-blockers to all patients with MI unless congestive heart failure, heart block, or bronchospasm were present.

2. Specific: The therapy should be used only in selected patients in whom there is a particular indication for treatment. An example would be a recommendation that anticoagulants be reserved for older patients with congestive heart failure who may not be am-

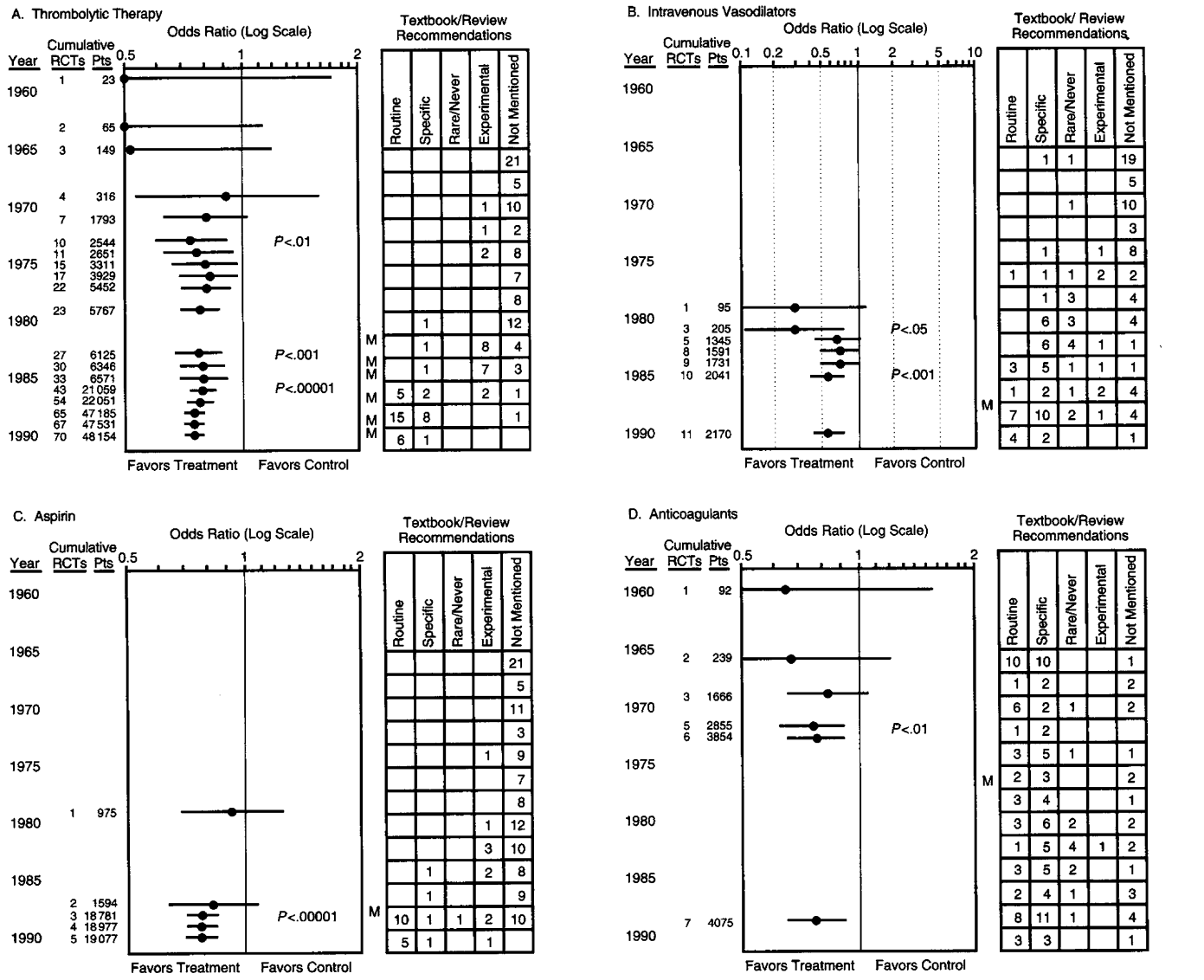

Fig 2.—A through H: For each treatment for acute myocardial infarction, the cumulative meta-analyses by year of publication of randomized control trials (RCTs) are presented on the left. The cumulative number of trials and patients (Pts) are also presented. On the right, the recommendations of the clinical expert reviewers are presented in 2-year segments; except for the entry in 1966, which represents all previous years. The letter M indicates that at least one meta-analysis was published that year; NS indicates not significant. See text for definition of categories.

bulated early.

3. Rare/Never: The therapy should never or only rarely be used.

4. Experimental: The treatment should not be used unless it is part of an ongoing investigation.

5. Not Mentioned: No mention of the treatment could be found in the article.

Independent duplicate determination of category of recommendation was an important aspect of our research because authors of the reviews were occasionally vague in their recommendations, and discussion between the two analysts facilitated a fair estimate of the original authors' intentions. It was not considered appropriate to write to the authors to determine what they meant. In reading the reviews, we assumed the role of a physician caring for patients with MI with a need to know how an expert or opinion leader would handle such patients.

RESULTS

Therapies for Acute MI

The results of 182 RCTs are included, and the recommendations in 43 review articles and 100 textbook chapters have been categorized. (A bibliography of the included trials and articles is available from NAPS.) The cumulative meta-analyses and recommendation surveys are presented in Figs 2A through 2H. The meta-analyses are plotted on a yearly basis and the recommendations are grouped in 2-year blocks. The letter "M" indicates that at least one meta-analysis was published that year. Reviews published in an odd-numbered year were combined with those in the preceding even-numbered year. Inspecting Fig 2A as an example, thrombolytic drugs were found to reduce total mortality significantly by 1973, at which time 2544 patients had been randomized in 10 studies. During 1986, 10 studies, including the GISSI trial,[46] brought the total number of patients randomized to 21 059, narrowing the CIs around the same mean effect. In 1988 the accumulated number of trials rose to 65 and the CI was narrowed still further, largely the

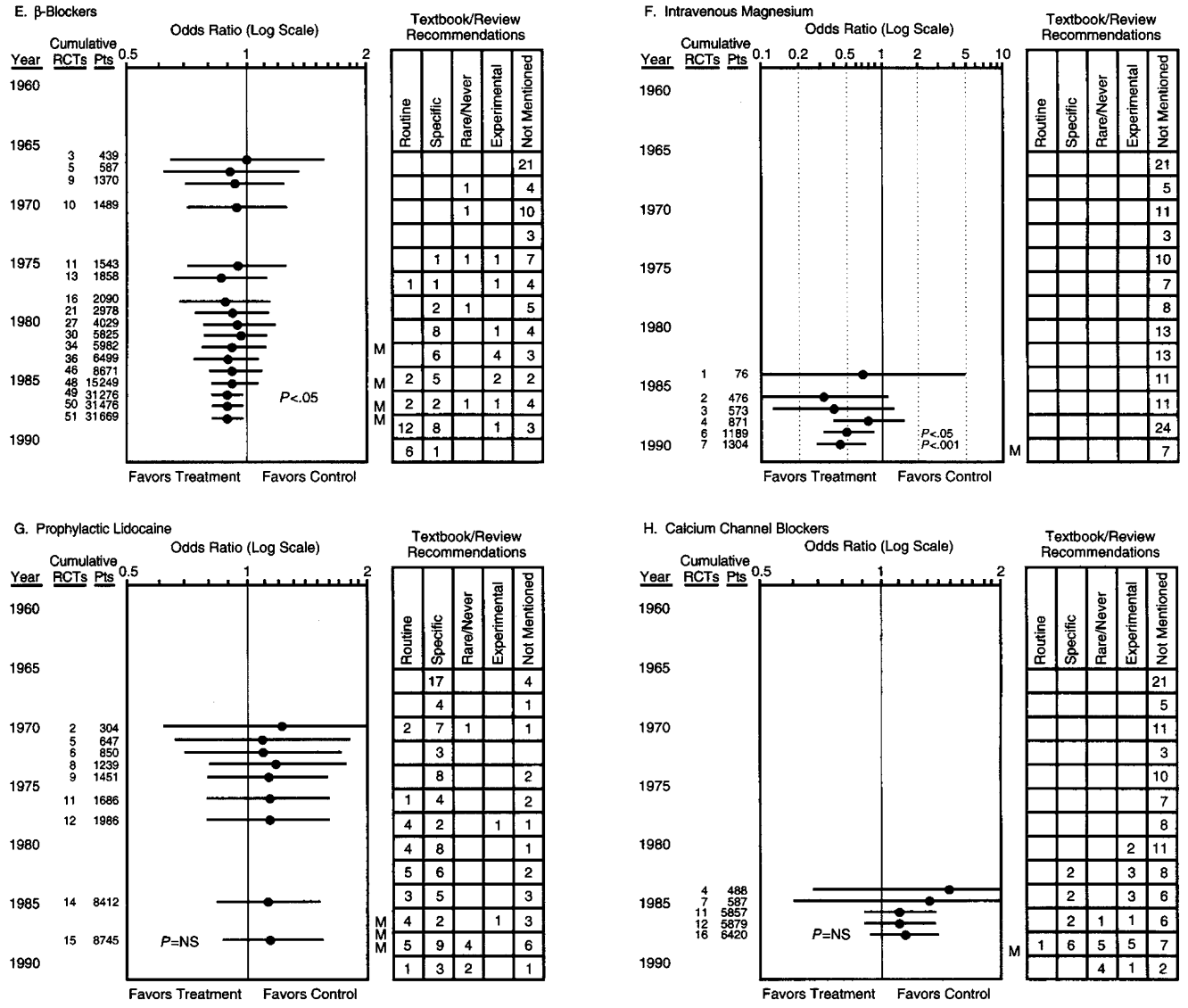

Fig 2.—Continued.

result of the ISIS-2 trial.[20]

Statistically significant reductions in mortality from acute MI were demonstrated for thrombolytic agents, intravenous vasodilators, antiplatelet agents, anticoagulants, intravenous magnesium salts, and β-blockers. In the cases of lidocaine and calcium channel blockers, the differences have not reached statistical significance; however, the current status suggests that these therapies are not effective and may actually be harmful.

The results of our coding of the recommendations of the experts writing the review articles and textbook chapters are also presented in Figs 2A through 2H. In five of the six instances in which the published RCTs and the cumulative meta-analyses revealed the treatment effect to be statistically significant in reducing hospital mortality, it was several years before the experts recommended the therapy with any consistency. An important example was the thrombolytic drugs that did not begin to be recommended even for specific indications by more than half the experts until 13 years after they could have been shown to be effective. Six years elapsed between the time the first meta-analysis showing an impressive reduction in mortality by thrombolytic therapy was published in a commonly read journal[4] and the time when the majority of reviewers recommended it for routine or specific use. Since 1985, when an approximately 20% reduction in the risk of death was established at the $P<.001$ level (OR, 0.78; 95% CI, 0.69 to 0.90), 14 reviews did not mention the treatment or felt it was still experimental.

Intravenous nitroglycerin and nitroprusside began to be recommended only for selected patients around the time the RCTs showed them to be routinely effective, and it was 9 years after that before the majority of authors recommended them for routine use. In the 2-year period of 1988 through 1989, 4 years after the cumulative meta-analyses could have demonstrated highly significant mortality reduction ($P<.001$ in 1985; OR, 0.54; 95% CI, 0.39 to 0.76), four of 24 authors did not mention them.

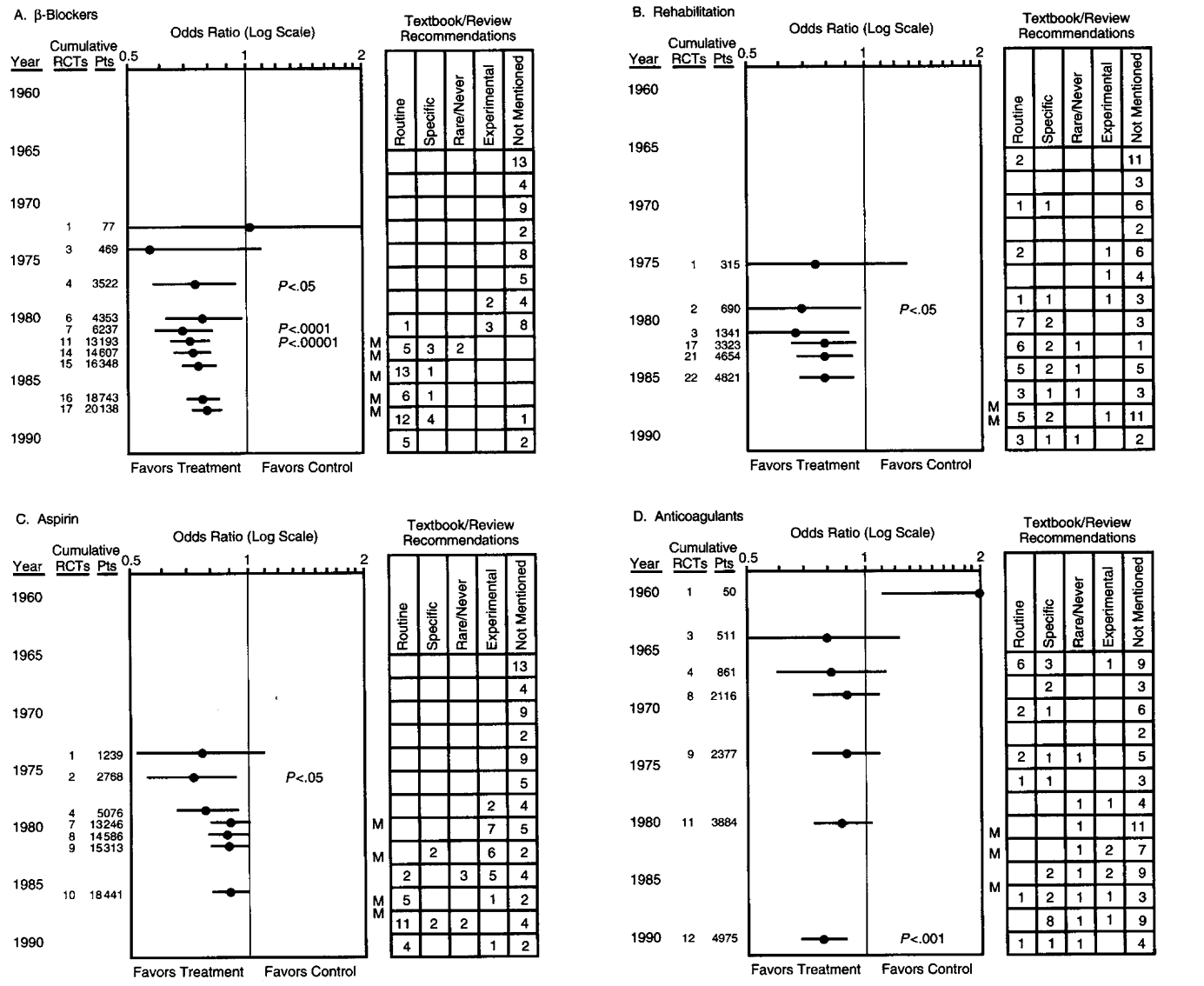

Fig 3.—A through G: For each therapy for secondary prevention of mortality following myocardial infarction, the cumulative meta-analyses by year of publication of randomized control trials (RCTs) are presented on the left. The cumulative number of trials and patients (Pts) are also presented. On the right, the recommendations of the clinical expert reviewers are presented in 2-year segments. The letter M indicates at least one meta-analysis was published that year; NS indicates not significant. See text for definition of categories.

On the other hand, β-blockers were recommended by some of the reviewers up to 12 years before the relative risk reduction in mortality of 11% (OR, 0.89; 95% CI, 0.80 to 0.99) reached the $P<.05$ level of statistical significance in 1986.

The aspirin data are sparse but highly significant because of the results of the very large ISIS-2 study[20] published in 1988. Anticoagulants could have been shown to be effective by 1973 and a meta-analysis was published in 1977.[19] Many reviewers recommended anticoagulants for routine use well before publication of the conclusive RCTs, while others continue up to this time not to mention their use. Administration of intravenous magnesium salts was shown to reduce mortality significantly by 1989, but the numbers of studies and patients randomized are small and no authors of reviews or textbook chapters had mentioned it by 1991.

The majority of authors have recommended lidocaine for prophylaxis against ventricular fibrillation throughout the last 25 years, yet there is no evidence of a mortality reduction in the controlled trials. Calcium channel blockers have begun to be recommended, although recent meta-analyses suggest increased mortality in the treated group.

Therapies for Secondary Prevention of Mortality

A total of 86 RCTs, 29 review articles, and 91 chapters of textbooks were analyzed. (A bibliography of the included trials and articles is available from the NAPS.) The meta-analyses accumulated by individual years are presented on the left-hand side of Figures 3A to 3G. Also, Figure 3 gives the number of patients randomized and number of RCTs published. Statistically significant reductions in long-term mortality, as shown by movement of the upper CI to a fraction less than one were demonstrated for β-blockers, rehabilitation exercise regimens, antiplatelet agents, pooled cholesterol-lowering measures (diet, drugs, and ileal bypass surgery), and oral anticoagulants, in that temporal order. There has been a significant adverse result when RCTs of type I antiarrhyth-

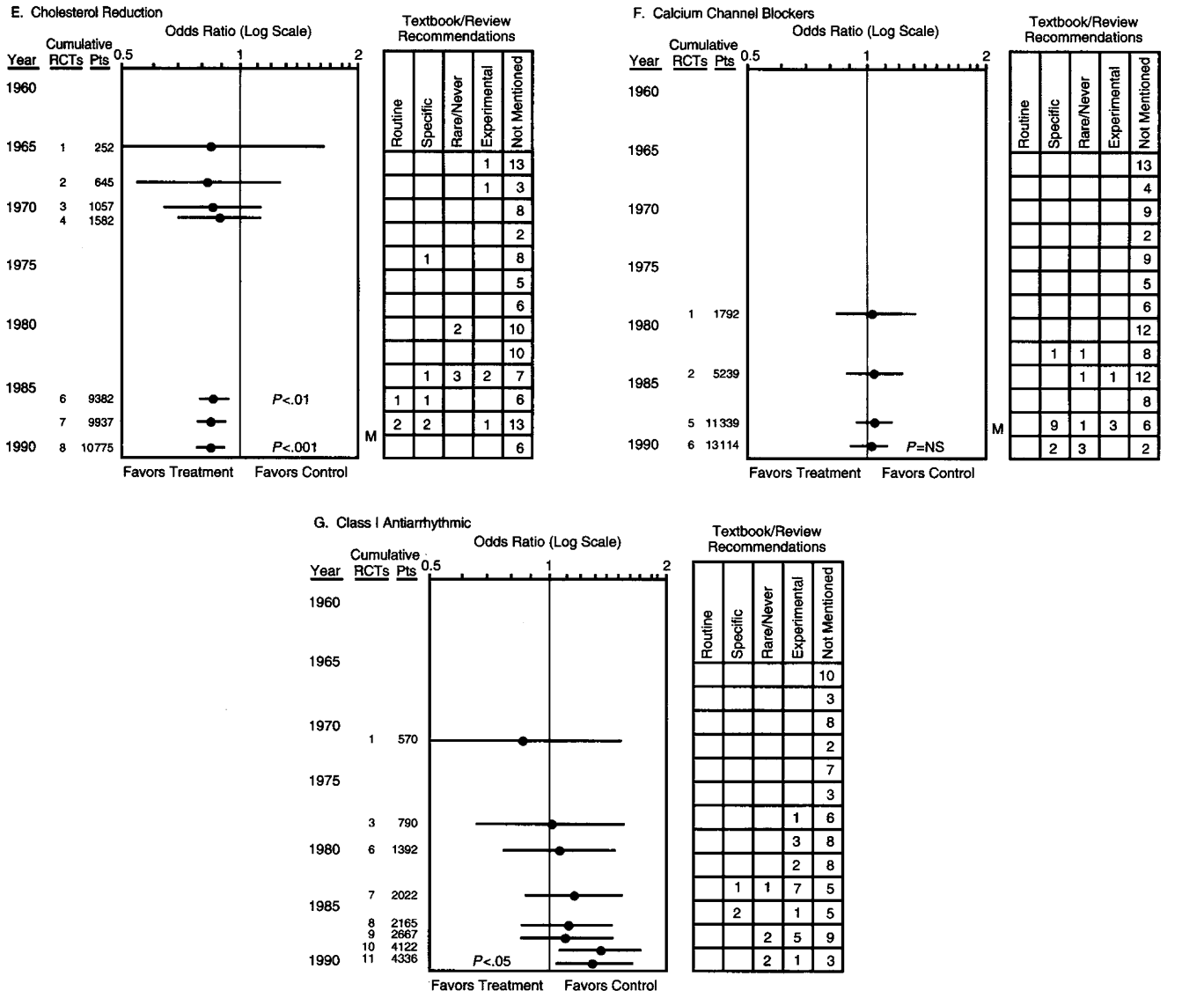

Fig 3.—Continued.

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.[35] 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,[26] 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 3B) 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.[47] 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.[44,48] Efficacy of long-term anticoagulant use did not become statistically significant until 1990, yet they have been recommended by some without qualification and classed by others as controversial for the last 25

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 yet 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 on an ongoing basis. (An average of 94 RCTs of the 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.[49] 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[46] and ISIS[20] cooperative studies, even when statistically significant results were present in several smaller trials.

Limited Familiarity With Meta-analysis or Concerns Over the Technique 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 enthuse 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 thousands and 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 no 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 β-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 β-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 β-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 β-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 dimisnish 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[20]) 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.[46] 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 conceivably 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 (eg, 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 "optional 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; rather, 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[50] 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.[51]

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 need 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 to clinical opinion leaders 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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