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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Fig 1.—Results of 17 randomized controlled 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, reporting many trials with nonsignificant results but a highly significant estimate of the pooled results on the bottom of the panel. On the right, the 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 be 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, intravenous vasodilators (nitroglycerin and nitroprusside), intravenous or oral β-blockers, anticoagulants, aspirin, lidocaine prophylaxis against primary ventricular fibrillation, calcium channel blockers, and intravenous magnesium salts.

2. Therapies for reducing the risk of mortality following hospitalization for acute MI (secondary prevention): oral β-blockers, anticoagulants, antithrombotic agents, calcium channel blockers, nitrates, hydralazine, and type I antithrombin.

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 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 bronchoconstriction 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-

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

4. Experimental: The therapy 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 48 review articles and 160 textbook chapters have been categorized. A bibliography of the included trials and articles is available from NAPS. The cumulative meta-analyses and recommendation analyses are presented in Figs 2A through 2E. 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; NS indicates not significant. See text for definition of categories.
result of the ISIS-2 trial.²⁰

Statistically significant reductions in mortality from acute MI were demonstrated for thrombolytic agents, intravenous vasodilators, antplatelet 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 journal⁴ and the time when the majority of reviewers recommended it for routine 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 5 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, 0.59 to 0.76), four of 24 authors did not mention them.
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 published in 1988. Anticoagulants could have been shown to be effective by 1978 and a meta-analysis was published in 1977. Many reviewers recommended anticoagulants for routine use well before publication of the constrictive 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 antiarrhythmic agents were compared with placebo.