The rt-PA Versus Streptokinase Controversy—IV

The probing and provocative editorial of Mourad (1) will undoubtedly be subjected to vigorous rebuttal. However, several of the issues raised in the editorial bespeak the useful application of the results of controlled clinical trials of cardiovascular interventions other than thrombolytic.

The purpose of such trials is to establish the clinical utility of a particular intervention, medication or procedure for the prevention of disease or for the relief of its consequences. The clinical significance (nature, magnitude and generalizability of response), logistics (ease of application) and overall cost (vs. no alternative therapies) collectively determine the broad value of medical practice to society. Logistical and cost issues are seldom included in the trial design but must enter into clinical decision-making. In acute myocardial infarction effective application of thrombolysis must be the responsibility of emergency room, family practice or internal medicine physicians. A simple, uncomplicated procedure is better than an elaborate or deferred to a specialist cardiologist with further undesirable delay.

The conclusions of the TIMI I trial, implying lack of thrombolytic efficacy of streptokinase and the potential for actual harm (2), were astonishing to me and my colleagues in 1985. But our early data (3,4) were uncontrolled and observational in nature. In that year the de facto endorsement by the NHLBI of rt-PA as the agent of choice—without regard to logistics and cost—and the funding of trials only if rt-PA was the lytic agent strongly discouraged use of other agents in the United States. Perhaps a lawyer would argue that selection of streptokinase was below the standard of care. Thus, many cardiology trainees in the second half of the last decade entered programs in which the superiority of rt-PA was established dogma and the detailed findings of TIMI and TAMI were required reading. These physicians have now entered clinical practice, are well trained in the application of rt-PA and provide the answer to the question on preferences by country raised in the accompanying editorial by Sherry and Marder (5).

It is not my intent to enter into the somewhat irrelevant debate regarding the intent to "prove" superiority of rt-PA, clearly an effective thrombolytic agent. However, to reject the findings of GISSI and ISIS—studies that reasonably resemble general clinical practice—undermines the relevancy of all controlled clinical trials. Indeed, in a program of the American College of Cardiology held at Lake Louise in March 1992, the respected cardiovascular epidemiologist, Salim Yusuf of the NHLBI poses the interesting title: "Impact of Clinical Trials on Thrombolytic Therapy in Clinical Practice: Science or Marketing?" Controlled clinical trials to refute prior controlled clinical trials, when funded in large part by commercial interests, are deserving of critical examination as to actual purpose. The hope to derive other interesting, perhaps important, insights is analogous to justifying the space program on the basis of the biology of weightlessness.

Optimal policy decisions with regard to funding must not be adversely affected by the singular opinions of powerful persons in the scientific or regulatory community. Thus research funding on atherogenesis has been directed at the lipid aspects of the process. The simplistic, outdated and incomplete hypothesis—that dietary fat intake and its marker, total serum cholesterol, determine adverse outcomes—now requires major revision to incorporate new knowledge regarding thrombosis, endothelial function, vascular reactivity and other complex, polygenic multifactorial mechanisms. A similar simplistic hypothesis—that an open artery at 90 min would automatically translate into superior clinical benefits—has now been shown to be false. Mourad's commentary, and the accompanying editorial by Sherry and Marder (5), are deserving of careful consideration.

Such issues are part of the substrate for the topic of the President's Page by Robert L. Frye, President of the ACC—"The Medicare Fee Schedule" (6). If, in the aggregate, expensive interventions supersede others of wider applicability and substantially less cost, health care cost containment cannot be achieved.

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References

Corrections
An error appeared in the article by Hirata et al. in the July 1991 issue of the Journal (Hirata K, Tripoploskidas P, Sparks E, Bowen J,