VIEWPOINT

Answers to complex questions cannot be derived from "simple" trials

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As we progress in the exciting area of treatment of acute myocardial infarction, two clinical trial methodologies coming from different philosophies and traditions must be considered. Smaller (200-3000 patient), detailed trials focusing on pathophysiology will be referred to as "mini-trials", while mammoth studies (10 000-50 000 patients) designed to measure mortality rates will be referred to as "mega-trials." In the field of coronary thrombolysis, examples of mini-trials include the continuing efforts of the Thrombolysis in Myocardial Infarction (TIMI) Group, the European Cooperative Study Group (ECSCG), and the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Group.¹⁻⁸ The major mega-trials have been conducted by the Gruppo Italiano Per Lo Studio Della Streptochinasi Nell' Infarto Miocardico (GISSI) and the International Studies of Infarct Survival (ISIS) Groups.⁹⁻¹¹ Both types of trials have proved to be essential to our understanding of thrombolytic intervention, and in most ways the two designs are quite complementary. In this paper, in contrasting the two designs, we will highlight the critical contribution of the mini-trials and then provide insight into the opportunity provided in an ongoing mega-trial to investigate the differences in the approaches (table).

General philosophy: mini-trials

Individual mini-trials are designed to provide a small piece in the overall puzzle of the mechanisms by which disease states operate and the mechanisms by which interventions affect the disease process. These trials are

particularly suited to the evaluation of new mechanical or pharmacological strategies while they are in evolution. The mini-trial strategy carefully measures the *intended* target of the treatment in patients receiving the intervention and in patients not receiving the intervention. The data are required with maximum precision by a pre-specified protocol and an effort is made to control all other confounding factors (ancillary therapy) except for the therapy being randomised. Entry criteria are restricted to the group of patients expected to benefit most by the purported mechanism of action of the intervention. Biological markers, such as coronary perfusion, left ventricular function or haemostatic indices are measured whenever possible. More global clinical outcomes are measured (mortality, cost, quality of life) to provide a context in which to judge the likely overall effect of the treatment. The individual data items are usually monitored by individuals independent of the clinical site to ensure that all data are accurate.

The mini-trial allows for a special exchange of ideas among a focused group of investigators. Protocols can be developed through round table discussions and frequent site visits can be made to improve the spirit of collaboration and common purpose. The data generated can be reviewed by all investigators, each of whom can have input into published papers and can achieve academic recognition. All of these characteristics foster a highly interactive and enjoyable working relationship among the investigators and research co-ordinators.

Problems have arisen with the interpretation of mini-trials when they have been used

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Summary of major features that distinguish two classes of clinical trials

Mega-trial	Mini-trial
Large population (> 10 000)	Small population (< 3000)
Large number of clinical sites (200-2000)	Limited number of sites (4-30)
Minimal data collected/patient	Maximal data collected/patient
Protocol algorithm simple	Algorithm more complex
Entry criteria wide	Entry criteria more restricted
Cannot control ancillary care, treatment	Complete protocolisation of care possible
Data not quality assured	Full quality assurance of data
Cannot assess advanced technology or avant-garde or high risk therapy	Can assess <i>any</i> technology or therapy
Cannot probe the mechanism of therapy (reductionist)	Mechanistic focus
Limited knowledge of safety data during study's progress (lag)	"On-line" assessment of safety parameters
Key end point is mortality reduction	Focus on many non-fatal, important outcomes (for example, stroke, reinfarction, revascularisation, cardiac function, economic, quality of life)
Have not been used to establish drug dosing	Excellent means of establishing drug dosing
Long obligatory time lag of initiation	Can be started expeditiously

to draw conclusions which their design could not support. First, the critical educational effort of the ISIS group has been instrumental in bringing the importance of sample size into the clinical consciousness.¹² Medical treatments that reduce mortality by more than 25% are rare, so that sample sizes of more than 8000 patients are needed for most trials in acute myocardial infarction in order reliably to detect treatment effects. Finding “no difference” in mortality in an individual mini-trial is not adequate evidence by itself that a treatment should be abandoned. Secondly, mini-trials are designed to evaluate the impact of therapy on *intended* targets of the intervention based on current understanding of pathophysiology. Published reports include many examples of how rapidly our understanding of pathophysiology can change as large enough trials are completed to measure the effect of therapy on the *unintended* target. Classic examples of this problem include the finding that suppression of arrhythmias could be achieved with certain “anti-arrhythmic” agents, but the rate of sudden death actually increased (Cardiac Arrhythmia Suppression Trial (CAST)) and the finding that although calcium channel blockers can improve diastolic dysfunction or prevent coronary vasospasm, mortality in patients with reduced left ventricular function is increased by these agents. Finally, the almost irresistible urge to evaluate small subgroups in mini-trials can lead to erroneous conclusions because of the play of chance. The exclusion of elderly patients and patients with inferior infarction from thrombolysis because of subgroup analysis provides an excellent example of the difficulty with this approach. The ISIS investigators have emphasised the fact that “quantitative” differences are common, but that qualitative differences are uncommon. Treatments that have a positive effect in a disease state rarely have detrimental effects in particular subgroups, but differences in the magnitude of treatment effects are common.

Angioplasty after thrombolysis

In 1985 before the landmark GISSI-1⁹ trial had been completed we launched the first multicentre TAMI trial in which we assumed that thrombolysis would be the mainstay of treatment, but that the roles of coronary revascularisation and adjunctive therapy would become the major foci of investigation. Indeed several trials investigated mechanical revascularisation including TAMI,¹⁻⁴ TIMI,^{5,6} the ECGS trial,^{7,8} and Should We Intervene Following Thrombolysis? (SWIFT).¹³ Collectively, these mini-trials indicated that routine coronary angioplasty is not necessary after thrombolysis on either an emergency or elective basis.^{15,6,8} These studies had a major impact on avoiding unnecessary angioplasty in the United States¹⁴ and helped to focus biomedical research on better methods of stabilising the unstable atherosclerotic plaque with antiplatelet and antithrombotic therapy.¹⁴

Because these trials evaluated an expensive,

evolving technology the requirement for universal availability of coronary angioplasty and angiography facilities would have prohibited the mega-trial networks from performing the trials. The documentation of coronary patency, detailed data collection, standardised ancillary medical treatment, and post-discharge functional evaluations provide a rich source of data to guide practice in various areas of importance to these patients.^{1-8,13,14} In particular, the detailed information about complications has led to new insight on risk factors for intracranial bleeding and the impact of reocclusion of the infarct-related artery.

General philosophy: mega-trials

The mega-trial philosophy rests on the general principles described above and the belief that large numbers of patients will obviate the need for detailed data collection, measurement of pathophysiologic end points, and specification of ancillary therapy. In fact, detailed and restrictive protocols are seen as impediments to the primary goal: large numbers of *randomised* patients. The sheer volume of data is expected to “average” out the random error effects of imprecise data collection and confounding treatment effects. The success and impact of the mega-trial concept are self-evident.

Overextending the bounds allowed by mega-trial methods, however, also leads to considerable problems. The mega-trial philosophy is by definition reductionist; the treatments administered must be universally available and the method of administration must be feasible in all centres. Thus the mega-trial alone cannot be taken as definitive documentation of the relative efficacy of a class of treatment, because different dosing and monitoring strategies can have a profound effect on biological and clinical outcomes. Voluminous data are now available to demonstrate that “high-tech” environments lead to low mortality in certain conditions, presumably because of the increased ability to regulate therapy based on informed monitoring. This issue has come to the forefront with regard to heparin co-administration with thrombolytic therapy.

The mega-trial methodology of simple data forms and no interference with clinical practice prevents direct investigation of pathophysiological mechanisms. In the ISIS-2 trial oral aspirin led to nearly the same mortality reduction as intravenous streptokinase (odds ratio 0.21 and 0.26, respectively).¹¹ However, the mechanism for this observation was left unexplained. Although the reported reinfarction rate in ISIS-2 was reduced nearly 50% from 4.2% to 2.4%, the low absolute event rates preclude this reduction in reinfarction rates from accounting for the striking reduction in mortality, especially since most reinfarction events did not lead to death. Was the mortality reduction afforded by aspirin due to more rapid coronary thrombolysis, less re-thrombosis, or an anti-inflammatory effect on the myocardium or infarct vessel wall? Such complex mechanistic issues, which must be understood if more effective therapy is to be developed, could only

be explored by a mini-trial in which all factors were systemically examined.

Just as the value of the mini-trial can be overextended, the mega-trial concept can lead to speculative assertions not supported by the methods. In general, end points other than mortality are probably under-reported in mega-trials because the data are not verified. This particularly becomes a problem when patients are transferred from one hospital to another and no mechanism is in place for continued data collection. Furthermore, the lack of precise definitions and absence of standardised methods of data collection (for example, collection protocols to detect reinfarction) preclude a confident estimate of the true rate of complications related to a treatment, although comparisons of relative event rates between treatments remain feasible. This issue becomes particularly important when differences in mortality are small, but outcomes affecting critical areas of quality of life, such as stroke, may occur with different frequency in different treatment groups. Estimated incidence rates from mega-trials must be regarded with scepticism when composite estimates of the overall effect of a treatment are constructed.

Interchange of trial designs

A mega-trial can be initiated only after mini-trials have laid the groundwork. If early trials had not proved that thrombolytic agents effectively achieved myocardial perfusion and improved left ventricular ejection fraction, mega-trials might not have been undertaken. Another example of the interchange is the question of whether to treat patients with thrombolytic agents beyond six hours from symptom onset. Subgroup analyses from large scale trials generally show a favourable risk to benefit ratio,^{11 15} but multiple subgroup analyses are fraught with potential incorrect conclusions, and the large GISSI-I trial found no evidence of benefit in patients treated late.⁹ Recently, a mechanistic placebo-controlled trial of tissue plasminogen activator showed that coronary thrombolysis can be achieved in these patients and that end diastolic left ventricular cavity size is preserved.^{4 5} Other observational studies suggest that malignant ventricular arrhythmias can be suppressed by delayed infarct vessel recanalisation. Although these data are encouraging, a meta-analysis by Honan and colleagues raised the concern that delayed thrombolytic intervention may be associated with an increased risk of cardiac rupture.¹⁶ The only method to determine where the balance lies between these mechanistic benefits and detrimental effects is through the completion of dedicated mega-trials such as the Estudio Multicentrio Estreptioquinas Republico Americano Sud (EMERAS) and Late Assessment of Thrombolytic Efficacy (LATE) trials. The independent relation of the mini and mega trials is evident in the investigation of this issue, with each component providing independent, pivotal information.

Global utilisation of streptokinase and tissue plasminogen activator in occluded coronary arteries (GUSTO)

After conducting pathophysiologically oriented mini-trials for several years, in collaboration with investigators from 14 countries we are in the midst of a trial in which we intend to enroll over 40 000 patients. The main objective is to determine whether achieving early reperfusion (speed) and preventing reocclusion (permanence) leads to improved clinical outcomes. In this new mega-trial we have tried to hybridise elements of quality control and pathophysiological investigation from the mini-trials and the protocol simplicity of the mega-trials. We hope that this approach will lead to a more accurate data set that will allow the primary question to be answered while providing a source for investigation of the most appropriate methods for future large trials.

Although the data forms have remained brief (three pages) by mini-trial standards, enough details are collected to evaluate differences in baseline characteristics and incidences of morbid events. Questions are formatted so that the presence or absence of the outcome must be specifically noted. Training meetings are being held to emphasise the specific definitions agreed by the steering committee. Of course, decisions about which data items to place on the form were made much easier by the pioneering work of the GISSI and ISIS investigators.

Many more data are being collected in several key ancillary studies that were identified by the steering committee before the start of the trial. A 2400 patient angiographic study is being conducted as part of the trial, providing GUSTO with the ability to correlate the perfusion status in the angiographic sub-study with the clinical outcomes in the much larger population. Because of the intense interest in these areas, special information is being collected on all patients with stroke, reinfarction, and cardiogenic shock. A large, randomly selected population is being followed to allow a better understanding of quality of life, including resource consumption. By integrating these data from representative samples of the population, we hope to provide the foundation upon which the pathophysiological basis and societal implications of the mortality results can rest.

An independent organisation has been employed to audit 10% of the case records on a random basis with stratification so that each hospital is audited at least once during the trial. This system will allow us to verify the accuracy of the data from a mega-trial and provide a basis for estimating the degree of auditing that would be desirable in future mega-trials. The current mini-trial standard of 100% audit of case records may be a waste of time and money. A system for reporting major adverse events via facsimile has been developed to allow careful tracking of the progress of the study at the coordinating centre.

The combination of "softer" end point data and mortality results will allow us to validate composite clinical end points.^{17 18} As our investment in biotechnology matures, trials will be needed to examine refinements in treatment,

which will involve more fine tuning than merely comparing intervention with placebo. Since a mega-trial cannot be used to investigate every issue and in many cases, differences in mortality could not be expected, such factors as cost, return to work, prevention of hospital readmission, and freedom from non-fatal, adverse clinical events will become more important. Soft endpoints have been difficult to accept without evidence that they are also directly related to mortality.

Conclusion

Both types of trials are needed to advance the clinical treatment of acute myocardial infarction. Mega-trials can provide definitive evidence about the mortality reduction afforded by a class of therapy so that broad changes in clinical practice can be justified. Mini-trials can explain why a treatment is effective to allow development of more effective approaches attacking the identified mechanisms. Furthermore, the rationale for mega-trials and the "fine-tuning" of minor adjustments in treatment will be the task of the mini-trials. If reasonable composite clinical end points can be validated within the context of a large, simple trial and accepted by regulatory authorities and clinicians in the future, it is hoped that issues requiring mega-trial populations can be focused to maximise the amount of useful clinical information generated.

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