

ON JUMBO AND *JUNKIE* TRIALS: A FUMBLER AFFAIR, A JUNGLE, OR THE ULTIMATE SOLUTION?

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SUMMARY

Important Clinical trials conducted between 1980 and 1990 provided early leads to the community of practising cardiologists and general physicians on the fundamentals of the therapy of acute myocardial infarction. On the other hand trials like ISIS-III or GUSTO, the current giant among jumbo trials, could not solve the real problems arising in clinical practice. The large-scale clinical trials should be reserved for interventions that have been shown convincingly in smaller trials. The problem of restenosis after PTCA is discussed and the place of animal research is emphasized as the basis of the design of future clinical trials. These exciting data require a human study but with a scale that proves the efficacy of the intervention and substantiates the underlying hypothesis even in a small population.

RESUMO

Macro-ensaios: solução inapropriada, uma selva ou a derradeira opção

Ensaio Clínicos conduzidos entre 1980-1990 proporcionam dados científicos importantes no tratamento do enfarte agudo do miocárdio, que foram rapidamente postos à disposição de clínicos gerais e de cardiologistas. Por outro lado Ensaio Clínicos como o ISIS-III ou o GUSTO, verdadeiros JUMBOS, tal o número de doentes admitidos em cada Ensaio, não resolveram verdadeiramente problemas postos na prática clínica corrente. Os grandes Ensaio Clínicos devem ser reservados apenas para encontrar soluções que foram já convincentemente demonstrados em ensaios envolvendo populações reduzidas. A problemática da reestenose depois da angioplastia das coronárias (PTCA) é discutida, sendo apontado o papel dos achados em modelos animais como base para a estruturação de futuros Ensaio Clínicos nesta área. Os Estudos se forem planeados no homem a partir de objectivos baseados em dados científicos apropriados, derivados de premissas lógicas, são mais facilmente atingidos e demonstrados em pequenas populações.

This is a condensed version of our speech delivered to the University of Lisbon on the occasion of our Honorary Doctor's Degree. It deals with the vexing question of the value of clinical trials in Cardiology.

Let us not let Genie escape from the bottle, again! The author of that quote, Eugene Braunwald, used it in 1980 at the beginning of the New Thrombolytic Era¹, as a plea for order in the design of trials. Indeed, it seems as if the world has followed his advice because most thrombolytic trials conducted between 1980 and 1989 — on both sides of the Atlantic Ocean and in Australia and New Zealand — have been an example of how to conduct responsible clinic research. They provided early leads to the community of practising cardiologists and general physicians on how to fundamentally change the therapy of acute myocardial infarction and how to avoid excesses by not applying these therapies beyond where they are warranted. Compared to the earlier period between 1950 and 1980 when collectively more than 50,000 patients were subjected to investigations with streptokinase most of which were not informative, the trial designs since the 80's have successively and successfully cleared the air¹. Indeed, this time worldwide we seem to have handled the matter responsibly and with a minimum of overlap, wastage or excessive use of patient material. So, why didn't we stop here?

For example, do we really need an ISIS III or a GUSTO, the current giants among the JUMBO trials to prove whether rt-PA or streptokinase is better? Is it really necessary to subject more than 40,000 people to uncertainty, another informed consent (and the agonies of that decision, let alone the explanations by the investigator) when we know the outcome to be limited in its information, is not irrelevant. For

indeed, those physicians who do not want to pay the higher price of rt-PA anyway (look at some National Health care Policies in Europe, the Diagnostic Related Groups Philosophy in America or some Hospital Pharmacy Directives) will stay with the cheaper but less universally applicable product, streptokinase (SK). Then there are many of those who argue that, after previous SK administration, or in large infarcts with much tissue at issue, imminent shock, late arrival but viable tissue, impending surgical interventions, out hospital utilization³, etc. they will prescribe rt-PA anyway and will circumvent all of these financial restrictions for they want the *best* for their patients. Indeed, the prescription patterns world wide seem to substantiate that attitude.

So the lesson we expect to be confirmed, if the recent publication of GISSI II and ISIS III has not done this already, is that the profession will have made its mind up well before the answers of the last JUMBO trial can come in. There is nothing against the scientific questions that are being asked in those studies, nor against the notion that some Jumbo trials are necessary. It is just that physicians (for better or worse) use other arguments rather than results from such trials only. Often, they *have* to act before all the facts are in or definitive battles between pharmaceutical houses have been fought. Hence, should we not think of these giant trials as the Junk Bonds that are floating around on Wall Street these days in search of a new (unlikely) owner just as in a game of financial musical chairs? In short, do they really add to our fund of knowledge and are they worth the effort and a sound financial investment?

As argued earlier there is a need for large scale trials if, as Yusuf et al.⁴ state: ... *the identification of effective treatment is likely to be more 'important', if the disease to be studied is*

common than if it is rare, and studies of common conditions can be large, and... the identification of effective treatments for common diseases is likely to be more 'important' if the treatment is widely practicable than if it is so complex that it can be performed only in specialized centres, and treatment protocols for widely practical treatment can be simple. These statements per se are correct but do not constitute a *raison d'être*, let alone a dominant and exclusive position of the Jumbo in the clinical trial world.

Also, such large scale trials, if they are to clarify the issue in question should be launched quickly and effectively if they are to be helpful. They lead us into the Jungle however when they are used as Yusuf et al.⁴ state: *no matter what prognostic features are recorded at entry, the duration of survival, etc., among apparently similar patients is still likely to be rather unpredictable, so no great increase in statistical sensitivity is likely to be conferred by stratification and/or adjustment for such features. In other words, the reliability of the main treatment comparison is improved surprisingly little by adjustment for any initial imbalances in prognostic features, which suggests that entry protocols can be simple too.*

For, if these statements were to be true, they could not solve most outstanding clinical issues on an individual patient basis. Nor can their statement *that trials must be large to provide reliable answers* or the conclusion that *a number of important medical questions will be answered reliably in the next few years only if some ultra-simple, ultra-large, strictly randomized trials can be mounted.* We disagree as these issues can sometimes be better resolved by other means, such as small, properly designed, trials aimed at specific disease groups, disease stages or pathophysiologic questions (which can provide more specific, and quicker answers⁵, backed up by other non-experimental efficacy research. We propose in fact a juxtaposition of these approaches in which the JUMBO is reserved for specific public health issues only.

We would encourage this in-between position as was done by Brown et al.⁶ in their report on the FATS regression trial. Whilst agreeing with them that *large-scale clinical trials should be reserved for interventions that have been shown convincingly in smaller trials*, the evidence for such regression of atherosclerosis, or for that matter whatever intervention, should be substantiated considerably better before a recommendation for large-scale trials can be made with pure clinical endpoints. After all, however exciting the initial trials for the possible regression or retardation of the development of atherosclerosis in the coronary arteries may be, such as was shown recently in the INTACT trial with nifedipine⁷ and however encouraging the experimental evidence from animal models, it is the intermediary scale trial in which the role of quantitative arteriography should be given its maximal opportunity to prove efficacy of the intervention and to substantiate the underlying hypothesis. Thus, we agree with Brown et al. that no large scale clinical trial must be mounted until the underlying hypothesis is strong enough. But, we would side with Yusuf et al.⁴ that *the identification of effective treatments for common disease is likely to be more important, if the treatment is widely practicable, than if it is so complex that it can be performed only in specialised centres.* In short, a *Trident*, a three-levelled approach presents itself (as it always has been!) as the best solution to a given clinical dilemma. It is this approach which the practising cardiologist should insist upon before changing his therapy. First, the original observation, anecdotal or observational in limited series, the larger-scale, properly powered trial going for *surrogate* endpoints such as quantitative arteriography in atherosclerosis studies, or ventricular function in thrombolysis trials, to be ultimately substantiated by, if appropriate, the Jumbo-sized trial advocated by Yusuf et al. with simple clinical end points.

Let us now look at a vexing public health as well as scientific problem with these thoughts in mind, the problem of restenosis after PTCA. As we all know, Percutaneous Transluminal Coronary Angioplasty (PTCA) is now an established and important treatment for patients with coronary artery disease. Although the primary success rate is high, in the 95-100% range, one of the major limitations to its usefulness is the high incidence of restenosis. Depending on the lesion, and the technique employed restenosis occurs in 25% to 60% after dilatation⁸⁻¹². Thus for every successful PTCA's one or two will have to be repeated. With some 400.000 procedures worldwide that means 100.000 more every year! So a solution is needed, soon! Technological advances such as atherectomy and lasers have increased the likelihood of success of the procedure itself, however, they have not altered the occurrence of restenosis, on the contrary it has increased. The real cause of the excessive proliferation leading to restenosis is unclear, but factors such as platelet aggregation, formation of mural thrombi, various growth factors stimulating smooth-muscle cells from the artery's subintima, and coronary vasospasm are all important. Various treatments administered shortly before and up to 6 months after PTCA, such as aspirin, dipyridamole, warfarin or coumadin, all have failed to reduce the rate of restenosis¹³⁻¹⁷. Aspirin after PTCA is known to reduce only the occurrence of thrombo-embolic events. Chesebro et al. in a more recent article have provided a model of the factors involved in the restenosis process¹⁸. These concepts have led to a further series of experimental and clinical approaches including heparin¹⁹⁻²⁰, varying doses of aspirin²¹, the combination of aspirin and coumadin²², other anti-aggregatory agents²³⁻²⁴, newer calcium antagonists²⁵, derivatives of fish oil^{26,27}, varying doses of steroids and even anti-tumour agents and anti-platelet derived growth factors²⁸⁻³¹. None of these have worked in a significant manner.

Recent pre-clinical research however has demonstrated very promising results of cilizapril in reducing intimal proliferation after carotid artery wall injury³². These experiments are based on an exhaustive analysis of factors influencing experimental work over the past decade³³⁻³⁴. The experimental *ballooned-artery-rat-model* reproduces the histological findings (mainly intimal proliferation) which are observed as restenosis in patients following PTCA. Up to 82% inhibition of neo-intima formation could be demonstrated with a corresponding increase in the diameter of the artery's lumen. In various series of animals, both pretreatment as well as treatment at the time of vessel injury achieved a comparable effect with respect to the inhibition of neo-intima formation. Is this finally the solution? While some other animal models have confirmed these exciting data, it requires a human efficacy study to be certain.

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