intrinsic difficulties deter continued commitment to implementation and evaluation of effectiveness.

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Randomised controlled trials in cardiovascular medicine: past achievements, future challenges

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Clinical trials have played a crucial role in the development of treatment strategies for cardiovascular disease: the earliest trials were conducted in the 1950s, but it was not until the 1970-80s that the results of clinical trials had a major impact on the choice of treatments. Relieving symptoms and improving quality of life have always been treatment goals. Over the centuries, the choice of treatment has evolved through several periods (box 1). The approaches are not necessarily distinct from each other, and current treatment strategies for cardiovascular disease are based on a mixture of goals aimed at the improvement of symptoms (for example, breathlessness), correcting markers of disease (improved ventricular function, etc), and improving clinical outcomes (fewer admissions to hospital, prolonged survival, etc). What characterises the current era is the expectation that theory, observations in animals, and human physiological studies alone are not enough to determine the value of a treatment. Rather, these observations should be verified by providing unequivocal evidence of net clinical benefit on the basis of reliable studies using the methods of randomised controlled trials.

Summary points

- Reliable knowledge (derived from well designed randomised controlled trials) of which treatments do or do not work has become the basis for evidence based practice
- Unbiased randomisation is the key methodological basis of randomised controlled trials
- Other major methodological advances that make randomised controlled trials efficient are extreme simplicity (which makes large trials feasible) and factorial designs (which enable the testing of more than one hypothesis simultaneously)
- Large trials and meta-analyses have both contributed to the reliable evaluation of treatments
- Future challenges are the conduct of studies in developing countries and among neglected high risk groups, minimisation of unnecessary bureaucracy, waste, and high costs in conducting trials, and the conduct of more trials of generic issues—for example, population based prevention strategies and other societally important strategies

The increasing impact of trials

Over the past 40 years, the results of randomised controlled trials have had an increasing impact on treatment choices (box 2). Firstly, the design and conduct of trials have improved so that results have become more reliable.[1–3] Secondly, the increasing acceptance of meta-analysis as a valid and useful methodology has meant that data from all trials, even trials too small to be reliable on their own, could contribute usefully towards the overall evidence.[4] Thirdly, better designed trials and well conducted meta-analyses have established that many existing simple and inexpensive treatments are effective in reducing mortality and morbidity. Equally important, these trials and meta-analyses showed that many commonly used treatments were either useless or harmful, despite promising data

Box 1—Evolution of treatment choices

- Arbitrary and blind beliefs in the efficacy of treatments such as blood letting
- Modification of the outward clinical manifestations of a disease (for example, foxglove to reduce oedema in dropsy)
- Rationalisation on the basis of correction of presumed pathophysiological abnormalities (prolonged bed rest for acute myocardial infarction in the belief that it would assist in the healing of myocardial scars, for example)
- Modification of disease markers (suppression of symptom free ventricular premature beats with antiarrhythmic drugs, etc)
- Emphasis that treatments should have a favourable (or at least a neutral) impact on mortality and morbidity and, where appropriate, an alleviation of symptoms

from experimental studies, epidemiological observations, or small trials indicating a favourable impact on surrogate outcomes. Fourthly, over the past 40-50 years a vigorous effort by the pharmaceutical industry has led to the development of numerous compounds, which have been subject to rigorous randomised controlled trials—partly to satisfy the requirements for regulatory approval and partly because the medical community has demanded reliable evidence that only such trials could provide. Consequently in many countries the payers (drug benefit plans funded by private insurance or governments) have demanded not only evidence of benefit with an acceptable safety profile but also that costs matched effectiveness. The increasing reliance on randomised controlled trials for evaluating treatments was due to several factors: sound methodological principles, the need to translate discoveries in basic science reliably and rapidly to improve clinical outcomes, and social forces such as regulatory and economic factors.

Making trials more reliable

The most fundamental advance that has made trials more reliable is randomisation. This has allowed similarities in measured, unmeasured, and unknown risk factors to be identified between active and comparator groups. Any difference in outcomes (provided it was measured in an unbiased way) was then due to differences in the treatments compared. In the 1970-80s, rediscovery that these principles were the dominant aspects of the validity of controlled trials suggested that substantial simplicity was possible in a trial's design (minimal data collection, and little or no standardisation as variations in other factors balanced themselves out between the groups) without compromising the main goals of the study. Also, acceptance that moderately sized differences in treatment (for example, a reduction in risk of one fifth or one sixth), major morbidity (for example, myocardial infarction or strokes), or mortality were likely and worthwhile made the detection of such differences important. Detecting such differences required larger studies in which several hundred or even a thousand events were observed. If the trial design was simple, large trials could be conducted at an affordable cost thereby making the evaluation of the treatments more efficient and reliable.[5] One of the first large, simple randomised controlled trials was the US polio vaccine trial in the 1950s, which included 400 000 children, and which showed in one season the efficacy of the vaccine.[6] Key aspects of this trial were the lack of detailed data collection on each subject, and only passive ascertainment of cases of paralytic polio when those children who had been randomised were admitted to hospital. Simplification made this large study practical at a comparatively modest cost. The value of the polio vaccine could only be established reliably by such a large trial, and the global impact of the vaccine in preventing morbidity and mortality from polio has been profound.

In cardiology, the principles of large trial sizes and simplicity were first applied to the ISIS (international study of infarct survival) and GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico) series of trials.[7–9] These trials, which showed the value of β blocking drugs, aspirin, thrombolytic therapy, and angiotensin converting enzyme inhibitors in acute myocardial infarction, have altered the management of patients with this condition. Large trial sizes and simplicity have been adapted and applied to long term trials in heart failure (for example, the studies of left ventricular dysfunction (SOLVD)[10] and Digitalis Investigation Group (DIG) trials[11]), in secondary prevention (for example, the long term intervention with pravastatin in ischaemic disease (LIPID)[12] and the heart outcomes prevention evaluation (HOPE) trials[13]), and in primary prevention.[14–16]

Another major advance is the use of a factorial design whereby more than one intervention is

Box 2—Treatments discovered through randomised controlled trials

Treatments that reduce mortality or morbidity

- Acute myocardial infarction: thrombolytics, aspirin (and other antiplatelet agents such as the thienopyridines), β blockers, angiotensin converting enzyme inhibitors, lipid lowering drugs, warfarin (in the absence of aspirin), direct angioplasty (highly suggestive, but not conclusive, evidence)
- Unstable angina: aspirin, new antiplatelet agents, thrombin inhibitors
- Heart failure: angiotensin converting enzyme inhibitors, β blockers, spironolactone, digoxin
- Surgery: coronary artery bypass graft surgery or carotid endarterectomy in patients at high risk
- Devices: implantable defibrillators
- Primary prevention: lipid lowering drugs, blood pressure lowering drugs, aspirin (suggestive, but not conclusive, evidence)

Treatments that are harmful or useless

- Acute myocardial infarction: prolonged bed rest, magnesium, class I antiarrhythmics, calcium channel blockers
- Heart failure: phosphodiesterase inhibitor inotropes, direct vasodilators
- Surgery: extracranial-intracranial bypass
- Prevention: β carotene, hormone replacement therapy (highly suggestive, but not conclusive, evidence)

evaluated within a trial. This strategy has been successfully used several times in cardiology, and it allows the simultaneous evaluation of generic, inexpensive treatments (for example, aspirin[17] or a vitamin[13] or generic intervention[18] for which there may not be significant funding), and newer compounds (for which there may be funding from the pharmaceutical industry). Despite concerns about "interactions" when more than one treatment is simultaneously evaluated, these have not been commonly observed—partly because drugs that may interact are not tested in the same trial and most patients are already on multiple drugs, and partly because interactions, even if they exist, may be only moderate in size.

The development of principles and methods of meta-analysis have also had a major impact.[19] Meta-analysis shares two key principles with large simple trials: large numbers of events are needed to reliably detect moderately sized differences, and assessment of only key data, random allocation, and unbiased outcomes are essential. Meta-analysis also emphasises the importance of making decisions on the data or outcomes from randomised controlled trials. Both large trials and meta-analyses have had a major impact on cardiovascular disease because they have provided persuasive answers that were not available by other means. Meta-analyses of existing trials showed that aspirin was effective in preventing vascular deaths, myocardial infarctions, and strokes in high risk patients.[20–22] In other situations meta-analysis emphasised what was apparent in some, but not all, trials viewed in isolation (for example, β blockers after myocardial infarction)[19] or led to renewed interest in old treatments (thrombolytic therapy, for example),[23] which were confirmed by further well designed randomised trials.[24] In other cases the results of meta-analysis led to large trials that disproved hypotheses, such as the value of magnesium in myocardial infarction.[25 26]

Although randomised controlled trials have contributed substantially to improving the management of patients, large simple trials have some limitations. By themselves they cannot shed light on the mechanisms by which an intervention works. Therefore large trials should be complemented by other forms of mechanistic research and small physiological studies. Also, many trials include only a small proportion of patients with the disease of interest, so that the applicability of results to a broad group of patients is sometimes uncertain. Trials should be designed to be more relevant by including a broad range of patients with the disease of interest and excluding only those with clear indications or contraindications for the treatment being evaluated.[27] Indeed the relevance of randomised controlled trials to clinical practice may be enhanced by minimising details of inclusion and exclusion criteria, and leaving substantial judgment to participating physicians. As long as a reasonable description of the characteristics of those in the trial is available, such a simple and flexible approach to patient entry will enhance the value of the trial by mimicking the "real world" and including a broader range of patients. Individual trials have generally had only a modest impact on clinical practice, and it usually takes several studies with the same result to convince practitioners to adopt a new treatment or abandon a commonly used treatment. Even after several trials with favourable results, the adoption into clinical practice is often slow.[28] Progress in reducing the care gap—that is, the gap between those eligible for a treatment and those actually receiving it—is critical to ensuring that patients benefit fully.

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Future challenges

Randomised controlled trials in cardiovascular disease face many new challenges. Currently, 60% of cardiovascular disease occurs in developing countries, and by the year 2020 this is expected to increase to 80%.[29] There is a major need to conduct trials of simple widely applicable treatments in these populations.

Many current trials have tended to underrepresent or even exclude elderly people (the mean age of patients with heart failure in the community is 70 to 75 years, yet in most trials the mean age of participants has been 60 to 65 years). Elderly people usually have the worst prognosis and are also likely to be at the greatest risk of adverse events. Given that elderly people are the fastest growing segment of the population and that they have high rates of cardiovascular disease and related drug use, future trials should facilitate enrolment of large numbers of such patients.

As advances in treatment continue, the potential for incremental benefit from new treatments tends to decline, the potential for side effects tends to increase, and there is a greater likelihood of drug interactions because patients are receiving several drugs. These factors may stimulate more emphasis on the concept of "primordial prevention" whereby societal and lifestyle factors could be modified to prevent the development of risk factors for common disease. Hypotheses regarding approaches to primordial prevention strategies at the community level will need evaluation in randomised trials conducted over decades and therefore require innovative study designs such as cluster randomisation, low intensity interventions, and passive ascertainment of outcomes.

A major impetus for randomised controlled trials in evaluating cardiovascular treatments has been the roles of regulatory bodies (by insisting on data from well designed trials for regulatory approval) and phar-

Box 3—Wasteful practices in clinical trials, which are often "required" by regulatory bodies or companies

- Extensive monitoring and routine verification of data items with "source" (contrary to the principles of randomised trials, where variations "randomise out")
- Adverse event reporting of individual events, which includes reporting any event, even those that occur during the natural course of the illness (these data are not reviewed by groups conducting the trials, and so it is often impossible to ascertain if the events are drug related)
- Overstandardisation of outcomes by use of extensive adjudication processes (most clinically important events are easily defined and ascertained)
- Complex consent procedures that confuse patients rather than inform them

maceutical companies (by developing new compounds and funding trials). These same influences, however, now also pose the greatest dangers to progress in cardiovascular treatments. The bureaucratisation of the conduct of clinical trials has made trials so expensive that the really large trials that are often required may never be done (box 3). These regulations have spawned huge bureaucracies within regulatory bodies, companies, and organisations of clinical trials, with very little scientific or medical value and little improvement in the reliability and validity of controlled trials. Multiple checks were designed in response to the rare instance of fraud, but have never been shown to reduce fraud or improve the reliability of trials. This has led to a culture of blind "rule followers," rather than a community that understands the critical principles of good trial design.

A second major unfavourable impact has been the overcommercialisation of trials. Although the reasonable costs of conducting any research should be met, the increasingly large per patient reimbursements that pharmaceutical companies provide and some investigators demand have made participation by some investigators more of a business than a scientific or medical endeavour. Conduct of less expensive trials of cheap generic treatments, such as a vitamin or a drug at the end of its patent life, are in jeopardy because the amount of compensation that investigators expect corresponds to commercial rates, which no peer review body—for example, the National Institutes of Health or the Medical Research Council—can justify. These two influences could potentially lead to the decline of randomised trials as they become unrealistically expensive. These problems can, however, be avoided by simplification of government regulations and by their implementation by pharmaceutical companies. With this reduction in complexity, investigators should be prepared to participate both in trials that are commercially driven—where they are well rewarded—and in trials of important scientific questions funded at more modest levels by peer review bodies. Forging partnerships between government, academia, and industry to facilitate the conduct of more trials with factorial designs will allow efficient and simultaneous evaluation of generic questions that are of societal importance.

Conclusion

As the next millennium approaches and we are poised to make substantial further advances in treating and preventing diseases using the gains from emerging technologies and molecular biology, we will need to rely increasingly on well designed and efficient randomised trials to distinguish between worthwhile, useless, and harmful interventions. We must support the conduct of important trials of good questions of relevance to public health by ensuring adequate support from both government and industry; by making randomised controlled trials more efficient by reducing waste, unnecessary bureaucracy, and regulatory demands; and, as investigators, by being willing to participate for fair or little financial compensation. Such an approach will ensure continuing progress in the battle against cardiovascular disease and other diseases, and will ensure that the fruits of basic science can be rapidly applied to human populations.

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Contribution of randomised controlled trials to understanding and management of early breast cancer

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The randomised controlled trial has become the gold standard for evidence based medicine; through the unbiased comparison of competing treatments it is possible to accurately quantify the cost-benefits and harm of individual treatments. This allows clinicians to offer patients an informed choice and provides the data on which purchasing authorities can make financial decisions. We, of course, subscribe to this view but also recognise this as a gross oversimplification of the power of the randomised controlled trial. The randomised controlled trial is the expression of deductive science in clinical medicine. Not only is it the most powerful tool we have for subjecting therapeutic hypotheses to the hazard of refutation[1] but also the biological fallout from such trials should allow clinical scientists to refine biological hypotheses. Trials of treatments for breast cancer have, at least twice, contributed substantially to a paradigm shift in our understanding of the disease.[2]

Summary points

- Clinical trials allow clinicians to accurately inform patients with breast cancer of the benefits and harm of different treatments
- Breast conserving techniques produce equivalent survival outcomes as more radical operations, but without the anticipated improvement in psychosocial morbidity
- The introduction of adjuvant systemic treatments has been associated with a significant fall in mortality from breast cancer in all age groups antedating the start of the national breast screening programme
- Counterintuitive results from clinical trials are being incorporated into an emerging conceptual model of the disease

Trials of local therapy

Postoperative radiotherapy

The first randomised trial in the management of early breast cancer can be credited to the Christie Hospital in Manchester. Patients undergoing radical mastectomy were randomised to receive postoperative radiotherapy or not.[3] The study found no difference in survival, although the morbidity of the combined procedure was substantial, with 30% of patients who received radiotherapy suffering lymphoedema. It took nearly two decades for the biological importance of those observations to be appreciated and for two trials to seriously challenge the prevailing belief of the centrifugal, mechanistic spread of breast cancer.[4 5] The more radical treatments in these trials (surgery plus radiotherapy) were associated with a reduced rate of local relapse, but failure to treat the axillary nodes either by surgery or radiotherapy left the long term survival unchanged.

More mature follow up of the early radiotherapy trials, together with later meta-analysis, provided another curious and unexpected result that might be considered part of the biological fallout of the deductive process. An excess mortality from cardiovascular events, particularly in those patients with left sided breast cancer, compensated for a modest reduction in mortality from breast cancer.[6] Two recent studies of postoperative radiotherapy for patients with poor prognosis support these observations, which challenge the contemporary belief of biological predeterminism[7 8] (more of this later).

Surgery

The first randomised controlled trial of breast conserving surgery compared with classical radical mastectomy