Clinical trials and registries in cardiovascular disease: competitive or complementary?

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Online publish-ahead-of-print 20 January 2010

This editorial refers to ‘The role of cardiac registries in evidence-based medicine’, by A.K. Gitt et al. on page 525

‘My friend is not perfect—no more than I—and so we suit each other admirably.’

Alexander Pope

Mortality from cardiovascular disease continues to decrease in developed countries, due to a combination of factors including changes in socioeconomic status, reduction in risk factors, application of results from clinical trials defining effective treatments, and the ability and infrastructure to translate these findings into clinical practice. We are fortunate to have new therapies that have been proven in large pragmatic trials to reduce mortality and other important clinical outcomes, and these serve as the mainstay of evidence-based clinical practice. Although dissemination of new and proven therapies into clinical practice leaves considerable room for improvement, adherence to guidelines has been associated with substantial improvement in outcomes in registries such as GRACE and CRUSADE. Documentation and public reporting of hospital performance on quality indicators, such as use of aspirin following myocardial infarction and angiotensin-converting enzyme (ACE) inhibitors, aldosterone antagonists, and β-blockers for heart failure, has been an important part of a successful feedback loop in the ‘cycle of therapeutic development’.

Unfortunately, much of what we do in practice rests on less secure evidence. Even for ST elevation myocardial infarction, arguably the most thoroughly studied condition in all of cardiovascular medicine, only 13% of the recommendations in the ACC/AHA guidelines are based on ‘level A’ evidence, i.e. from multiple large randomized clinical trials.

An obvious solution is the performance of more practical clinical trials, but, aside from prohibitive cost, the lack of generalizability of clinical trial findings needs to be appreciated. Major limitations include restrictive inclusion and exclusion criteria leading to highly selected populations (entry bias), insufficient power to define effects in subgroups, and failure to compare new therapies with the best existing therapies. Even a well-conducted and internally valid trial but including a highly selected population under controlled conditions may not be externally valid, i.e. not generalizable. The complexity and cost of doing clinical research, in part related to privacy laws, government regulation, and contracting, has limited the ability of the general practice community to participate in research. This has been amplified by financial pressures and lack of adequate reimbursement for patients in research, particularly in certain countries. The clinical research enterprise is failing to fulfill its role. Some of these problems could be addressed by improvements in the methodology of clinical trials, including simplification to remove many of the unnecessary barriers to conducting large trials in general practice at a more reasonable cost.

Even if many of the difficulties surrounding clinical trials were resolved, there remains a secure place for prospective registries. The experience and lessons learned from high-quality European-based registry studies are reviewed by Gitt et al. They discuss methodological issues as well as the use of registries to assess the extrapolation of trial results into practice, to generate new hypotheses, and to improve quality of care. A major advantage of a registry is the ability to include the entire spectrum of the patient population with a particular disease or syndrome, including patients with many co-morbidities who are under-represented in trials, and who may be susceptible to increased risk, e.g. from dosing errors. The follow-up in registries is often considerably longer than that of initial clinical trials, and this may be very important in certain settings, e.g. to evaluate late stent thrombosis with drug-eluting stents.

This discussion comes at an important time of the recognition that while clinical trials are important, our biggest opportunity to improve care now may be in better application of what we already know. The Obama administration has earmarked US$1.1 billion to fund ‘comparative effectiveness research’ in the American Recovery and Reinvestment Act of 2009 to better inform decisions made by patients and clinicians. The Institute of Medicine has prioritized 100 research topics, of which half were reported by the evaluators
as best addressed with randomized clinical trials, and half with other methodologies including prospective registries. While some of the deficiencies of randomized trials can be addressed by registries (Figure 1), we should be mindful of the caveats and the potential pitfalls of relying upon observational analyses. Gitt et al. provide the example of fibrinolysis in the elderly, where a financial claims database analysis falsely concluded that there was no benefit in this population. The CAST trial provides another example of how drugs targeting a surrogate marker of mortality derived from observational studies (premature ventricular contractions) can paradoxically result in an increased mortality when subjected to the rigours of a controlled trial. Many treatments, such as hormone replacement therapy and vitamin E, appear to be beneficial in carefully conducted observational studies, only to be found to be neutral or harmful in definitive randomized trials. A recent careful analysis from Vancouver showed that statin adherence was strongly and independently associated with lower risk of motor vehicle accidents, accidents in the workplace, greater use of screening strategies, and lower mortality from other diseases. There is no biological explanation for these benefits from statin therapy. This serves as a cautionary reminder of the influence of unmeasured confounders that is the ‘Achilles heel’ of these types of analyses. Although multivariable analyses can provide adjustment, albeit imperfect, for differences in baseline variables, this is not possible for unmeasured variables. ‘Comparative effectiveness research’ is therefore at risk of ratiﬁying what may be more aptly termed ‘confounded observational analysis’. It of particular concern that comparative effectiveness research is expected to inform which subgroups of patients will benefit the most from certain treatments to guide personalized care, resulting in a dangerous multiplicity of errors from confounding and from subgroup analyses. Like any other evaluation of an intervention, comparative effectiveness is best assessed with large clinical trials, since randomization is the only method to control effectively for confounding factors between treatment groups.

In the end, as argued by Gitt et al., it is the combination of high quality clinical trials and prospective registries that is needed to best define and apply effective therapies. In order to make the best use of the available information, we need to be cognizant of the strengths and limitations of both forms of analyses; trials and registries provide answers to different questions and are complementary.

Conflict of interest: none declared.

References