Commentary
Bridging case–control studies and randomized trials
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Abstract

Randomized trials and observational studies, such as case–control studies, are often seen as opposing approaches. However, in many instances results obtained by different designs may complement each other. For instance, case–control studies on aetiology of disease may help to give the direction of future trials. In this commentary, the author discusses the purpose of randomization and observation, and under which conditions one design may be preferred to another. Randomization is useful to combat 'confounding by indication', and is therefore the design of choice for most therapeutic trials. When this confounding is not an issue, as in studies of genetic risk factors or side-effects, then case–control studies are preferred.

Keywords case–control studies, genetics, randomization, side-effects, therapeutics

In this issue of *Current Controlled Trials in Cardiovascular Medicine*, Ray *et al* [1] report the results of a study on genetic and acquired risk factors for venous thrombosis in women. This paper is remarkable, not only because it focuses on women, but also because it is an observational, case–control study rather than a randomized trial.

In their editorial in the first issue of the journal, editors-in-chief Curt Furberg and Bertram Pitt did not explicitly mention randomized trials – they spoke of a journal for 'clinical trials' [2]. This suggests experimental rather than observational studies, but does not necessarily imply randomization. Nevertheless, by encouraging prospective authors to report trial results according to the Consolidated Standards of Reporting Trials guidelines [3], they implicitly made it clear that the journal was aimed at reporting randomized clinical trials.

Does this publication therefore represent a major change in policy? Did it take only a handful of issues before the editors decided to 'lower' their standards? I think not. Sir Austin Bradford Hill is credited with performing the first properly randomized trial in 1948 [4], although studies with some form of random treatment allocation antedated it by at least 50 years [5]. When we read his *Principles of Medical Statistics*, from the first edition in 1937 [6] to the last post-humous edition of 1984 [7], we see an increasing emphasis on randomization, the use of placebo controls and double blinding. However, even as a strong advocate for experimentation, he defined a clinical trial as a study in which we learn from a patient; up to the 12th edition he continued to quote the 1949 Presidential Address to the Royal Society of Medicine by Sir George Pickering, who argued that all that happened to a patient should be recorded.

Randomization is a tool, not a goal in and of itself. The goal of clinical research is to obtain an answer that is valid and precise, and the ultimate goal is to prevent and treat disease in the best way. Each study design has indications and contraindications. The main threats to validity in treatment studies are regression to the mean (ie improvement due to the natural course of a disorder) and 'confounding by indication' (ie incomparability of groups when the risk profile affects the choice of drug). Control groups are included to address regression to the mean, whereas randomization is aimed at creating groups with similar prognosis to combat confounding by indication. In clinical practice, physicians tailor treatment to a patient's prognosis, and so a simple comparison of patients treated with different regimens will often be biased. Because of the need to counter this confounding by indication, randomization has become nearly synonymous with good

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research into medical therapies. Many have broadened this to the belief that randomization is synonymous with good research, and have created a hierarchy of study designs. This is a mistake. First, randomized trials do have drawbacks. Secondly, they are not always possible, or, for that matter, ethical.

One important drawback of randomized trials is that they typically involve patients who were considered fit to enter, were likely to finish the trial, and believed, or even shown during a run-in phase, to comply with the medications. This population is quite different from the patients in the waiting room. Another important drawback is that, because the precision of an estimate is dependent on the number of patients experiencing an event, randomized trials, unless they are very large, will seldom be precise. A third drawback is that in all prospective studies, including randomized trials, it is seldom possible to relate the outcome of interest to determinants that occurred immediately before that outcome, and that might even have interacted in producing it (for instance lifestyle factors, intercurrent disease). In some cases, randomization is simply not possible, as in aetiological studies of genetic variants. Also, even for nongenetic risk factors, randomization would often lead to ethical problems (for instance, studies on the effects of alcohol).

Case–control studies, such as the one on venous thrombosis published in the present issue [1], have other indications and contraindications. In this type of study, patients with the outcome of interest are contrasted to those without, and therefore the precision of the estimate is much greater. Ideally, all patients in a certain geographical region are included, so generalizibility is better. Finally, in contrast to randomized trials and other cohort studies, patients can be seen shortly after the event and recent risk factors can be recorded.

Case–control studies also have drawbacks; if the disease changes the risk factor measurement, then inference becomes difficult (for instance, varicose veins are often seen after a deep vein thrombosis, but are probably not a cause of venous thrombosis). In studies of treatments, case–control studies, like all observational studies, may be subject to bias through confounding by indication. It is important to make a distinction between expected or intended effects (efficacy), and unintended or unexpected effects (side effects). Although in the case of efficacy confounding by indication is a likely source of bias, this is not so in the case of side effects. If physicians or patients neither intend nor expect a certain effect of a drug, then the presence of risk factors for that effect is unlikely to affect prescription, and therefore groups using and not using the drug will be comparable, and estimates will be unbiased. This can be illustrated with the effects of hormone replacement therapy. A large observational study

(the Nurses' Health study) showed a strong protective effect on coronary heart disease [8] that was not confirmed in a randomized trial [9]. Both studies found very similar relative risks of venous thrombosis, which was an unexpected side effect [10,11].

Genetic studies on the aetiology of disease and side effects of drugs are needed to direct or complement randomized trials of therapies. For both such study types the case–control design is the best choice. It is therefore appropriate that case–control studies and randomized controlled trials are published side by side, in order to serve our ultimate goal of improving patient care.

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