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Viewpoint

Bayesian interim statistical analysis of randomised trials

James M Brophy, Lawrence Joseph

Uncertainty, although not always recognised, is pervasive in clinical medicine and, paradoxically, may be increasing despite advances in our knowledge.[1] Evidence-based medicine is a construct that attempts to formalise our knowledge, but its inability to cover all aspects of patient care has been recognised.[2] Randomised clinical trials have been championed as the best method to advance evidence-based medicine, but they are not always feasible because of, for example, cost and ethical issues. Furthermore, the stringent criteria used to select patients for trials may limit the generalisability of results to routine practice. Consequently, before embarking upon or continuing with a randomised trial it is important to ensure that the proposed research question is still relevant.

Further controversy may develop about the best approach to analyse a clinical trial. For example, the GUSTO thrombolytic trial[3] when analysed by standard frequentist statistical methods seemed to show the superiority of one agent over another (p=0·006), but a Bayesian analysis of the same data,[4] incorporating a range of prior information, suggests that considerable uncertainty should remain about the clinical significance of any difference between the agents. This finding is undoubtedly disconcerting to sponsors, physicians, and patients.

Bayesian analysis integrates the summation of our past knowledge (via the prior distribution) with the newly acquired data (through the likelihood function) by Bayes theorem to arrive at a newer understanding of the studied phenomena (summarised by the posterior distribution). Bayesian analysis will not always lead to increased uncertainty; indeed, these methods are criticised for their use of subjective priors, which, if inappropriately chosen, may give a false impression of reduced uncertainty. However, as the following example illustrates, Bayesian interim analysis of randomised clinical trials may occasionally provide a clearer interpretation of the data than standard statistical analysis and assist in the sometimes difficult task of deciding whether a trial should continue.

In the 1980s, angiotensin-converting-enzyme (ACE) inhibitors were shown to improve the morbidity and

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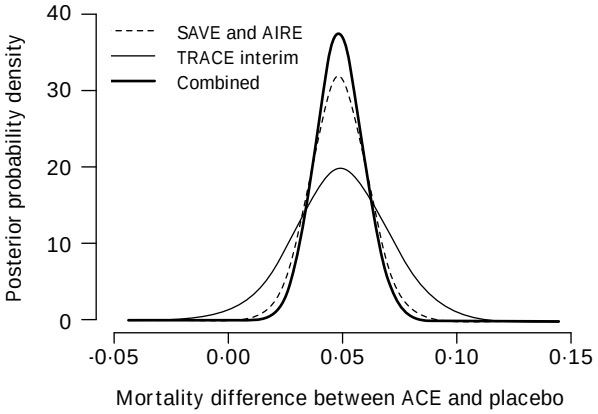
mortality of patients with established congestive heart failure. Consequently trials were planned to test the hypothesis that early administration of these drugs to post-myocardial-infarction patients would improve outcomes. The first results came from the SAVE investigators[5] and showed a 19% reduction in total mortality ($p<0·02$) in post-myocardial-infarction patients with significant left-ventricular dysfunction but no clinical signs of heart failure. The AIRE[6] study confirmed a reduction in total mortality (27%, $p<0·002$) in patients with clinical signs of heart failure following myocardial infarction.

The TRACE trial,[7] published in December 1995, was of patients with left-ventricular dysfunction after myocardial infarction randomised to trandolapril or placebo. This trial, like SAVE and AIRE, randomised only patients with significant left-ventricular dysfunction and confirmed results from other randomised trials[5,6,8–11] showing decreased mortality with ACE inhibitors. TRACE randomised patients from May 1, 1990, to July 7, 1992, with a 2 year minimum follow-up, implying that some patients received placebo until July, 1994. The SAVE results, published in September, 1992, are completely applicable to 40% of TRACE patients with left-ventricular dysfunction without signs of heart failure, and the AIRE results, published in October, 1993, are directly applicable to the other 60% of the TRACE population. Therefore, the publications of SAVE and AIRE raised ethical questions for the TRACE investigators. Should the TRACE patients be advised of their new results? Is a revised informed consent necessary? Should the TRACE trial be prematurely ended?

The TRACE safety committee received quarterly safety reports, did three interim analyses (the last in August, 1993), and recommended that the trial continue. It is not known if any statistical criteria were employed to assist in the decision to continue the trial or whether patients were advised of the other published trial results. TRACE mortality results at the final interim analysis are not given but may be inferred from a previous publication, giving an overall 1 year mortality of 23%,[12] or about 25% and 21% for placebo and trandolapril, respectively. Whereas a χ^2 test of these results ($p=0·03$) may not be statistically significant enough in an interim analysis to cause abandonment of the trial, incorporation of the SAVE and AIRE results with these interim results presents a different picture.

Since the SAVE and AIRE trials had similar entry criteria to TRACE, a Bayesian analysis, which permits the formal inclusion of these previous results, may have been helpful in deciding whether to continue the trial. Letting the results from SAVE and AIRE represent our prior knowledge and updating this knowledge with the interim TRACE results by Bayes theorem, reveals that the best estimate for the difference in mortality between treatment with ACE inhibitors and placebo is 4·9 lives saved per 100 patients treated. The 95% credible interval (the Bayesian analogue of a confidence interval) for this estimate is from three to seven lives saved per 100 patients treated. Furthermore, this analysis reveals that we are 99·8% certain that the benefit of ACE inhibition is at least two lives saved per 100 treated (figure). Thus, even without terminating the TRACE trial, it seems almost certain that a clinically significant benefit exists with active treatment.

Incidentally, a similar Bayesian analysis shows the necessity of continuing the TRACE trial at least until the publication of the AIRE results. An analysis limited to



Probability density plots of the mortality difference between placebo and ACE inhibitors in post-myocardial-infarction patients representing prior knowledge (SAVE and AIRE), new data (TRACE), and the updated posterior distribution

SAVE gives a point estimate of 4·2 lives saved per 100 treated for ACE inhibitors, but the credible interval is still wide and the probability that the benefit exceeds at least two lives saved per 100 treated (a reasonable starting point for clinical significance) is only 89%. Furthermore, the patient populations from these two trials, although very similar, are not totally identical and more knowledge was consequently desirable to be certain of the clinical benefit.

A Bayesian analysis combining data from SAVE, AIRE, and TRACE seems reasonable as all trials enrolled patients within 3–16 days of a confirmed myocardial infarction resulting in severe left-ventricular dysfunction, although the method of determining this dysfunction varied between the trials.

One must obviously be prudent not to prematurely halt a trial and thereby arrive at an inconclusive result, but in the case described here the relative uniformity in selection and homogeneity of results, and the large treatment effect, argue convincingly in favour of a Bayesian analysis (a similar conclusion would be reached by conventional meta-analysis). Consequently, the TRACE trial could have been halted in October, 1993, or possibly earlier and patients receiving placebo offered ACE inhibitors. This is not an isolated example and these observations may also be applicable to another recent trial of ACE inhibition following myocardial infarction.[11]

Clinical research remains a difficult proposition, at the same time balancing the quest for definitive scientific proof with our role as patient advocates. In this era, several clinical trials that address the same or very similar questions may be simultaneously undertaken, and it behooves us as clinical researchers to explore statistical techniques that permit the explicit integration of results. While randomised clinical trial methodology is well suited to increasing our knowledge of treatment effects, decision making based on this knowledge may be strengthened by Bayesian methodology during interim analyses and in making treatment choices.

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Bayesian interim statistical analysis of randomised trials: the case against

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Brophy and Joseph in this issue (p 1166) ask the intriguing question of whether interim analyses should be combined with knowledge from previous trials in a type of formalised progressive meta-analysis to provide guidelines for stopping trials. There may be situations where such an approach is helpful, but the method was inapplicable in the TRACE study, in which we participated.

The principal flaw in relation to SAVE,[1] AIRE,[2] and TRACE[3] is that acute myocardial infarction is not a chronic condition where the importance of advising patients of results of similar trials is always going to be relevant. We accept that a combined analysis of SAVE and AIRE would nowadays discourage randomising patients to placebo in a post-myocardial-infarction trial involving an angiotensin-converting-enzyme (ACE) inhibitor. However, when AIRE was published the last patients had been randomised in TRACE for over a year. Thus, a decision to stop placebo treatment in TRACE should not have been based on knowledge of how to act immediately after the infarction, but rather on wider knowledge arising from trials of chronic heart failure or chronic left-ventricular dysfunction, in particular CONSENSUS1[4] and the SOLVD[5,6] trials. This information was used, and eventually half the patients in TRACE were not on trial medication, in many cases because they were given open treatment with an ACE inhibitor.

We accept that there are similarities between SAVE, AIRE, and TRACE, but the differences are also important. There is more to a trial population than entry criteria. In the SAVE trial the 1-year mortality was around 10%, in the AIRE study 16%, and in TRACE 23%. Thus, even though these studies included patients following acute myocardial infarction with left-ventricular dysfunction (SAVE and TRACE) and signs of congestive heart failure (AIRE), the populations represented a range of risks. About 100 000 acute myocardial infarction patients were screened in order to randomise 2231 in the SAVE trial,[7] whereas the comparative figures for AIRE are 30 717 and 2006, and 6676 and 1749 for TRACE. The proportion of eligible patients randomised highlights major differences between the studies. Patients with ongoing ischaemia were excluded from the SAVE study but included in TRACE. Thus, pooling of results from SAVE and TRACE would be difficult and in some ways inappropriate.

The Bayesian method assumes that the effect of ACE inhibition is the same for all the different ACE inhibitors. This assumption eventually seems true, but only after similar results have been acquired with a range of ACE inhibitors, including trandolapril. It is dangerous to assume a class effect until wider experience becomes available.

The safety committee in TRACE had prespecified rules for stopping the trial, but it did not attempt to function merely as a computer. The committee was free to act on any knowledge, including the results of other trials. When the TRACE trial was conducted patients were stratified according to wall-motion index (WMI) less than 0·8 and from 0·8 to 1·2. Results were presented to the safety committee as A and B, the actual treatment code being semi-concealed. According to the first interim analysis (330 patients) there were 50 deaths in group A and 47 in group B. In the second interim analysis there were 91 deaths in group A and 104 in group B. However, treatments A and B behaved differently. In the low WMI group there were 28 deaths in group A and 19 in group B, whereas there were 63

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