Moving the Goalposts Into Unblinded Territory

The Larger Lessons of DEFER and FAME 2 and Their Implications for Shifting End Points in ISCHEMIA

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At its conception, a randomized controlled trial is carefully designed to detect a significant effect of an intervention on a prespecified primary end point. Each aspect of a trial is deliberately constructed to allow it to answer this principal question. From the moment the first patient is recruited, the primary end point is fixed, and all other outcomes are considered secondary.

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial was designed around a clear primary end point: cardiovascular death and nonfatal myocardial infarction (MI).[1] It was on this basis that $84 million of United States National Heart, Lung, and Blood Institute (US NHLBI) funding was awarded, and >5000 patients signed informed consent to participate. However, on January 17, 2018, over 99% of the way through the recruitment period,[2] an amendment was made to the clinicaltrials.gov website.[3] This indicated that the primary end point for ISCHEMIA was to be altered to cardiovascular death, nonfatal MI, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure.[3] This Perspective discusses the implications of this in light of what other trials teach us, and why readers should retain their focus on the primary end point that was pre-specified and not one that was post-specified.

END POINTS MATTER IN CLINICAL TRIALS

Cardiovascular death and nonfatal MI are largely objective, dichotomous events. Their measurement is resistant to bias, and they are therefore often called hard clinical end points. Although both commonly occur in clinical practice, they may be less frequent in trial populations. Patients enrolled in trials tend to be younger, have fewer comorbidities, and are closely supported by trial clinicians. However, more important than this is the powerful influence of motivation and interest in health: patients who refuse to discuss clinical trials have ≈2-fold higher mortality than those who do not, a factor which rises to 3-fold after adjusting for measured covariates.[4]

Infrequent events mean larger trials are required to detect a significant difference between groups. With very large studies, the cost of running a trial and reporting the results within a meaningful time frame becomes prohibitive. Consequently, trialists are often tempted to include more common events, such as hospitalization and repeat revascularization, into the primary end point. A consequence—which may be unintended—is the incorporation of events that rely heavily on perceptions of both the patient and their healthcare provider. Severity of angina, perception of heart failure, and admission to hospital are examples of these soft end points.

THE MEANING OF BLINDING

Although soft end points are unquestionably important in clinical practice, in unblinded trials they are susceptible to unintended bias because they are reliant on

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interpretation by physicians and patients and are vulnerable to the physicians' drive to do something. The long-established remedy to bias in the measurement of these end points is blinding.

The term blinding means different things to different people. It can refer to blinding of patient and provider to treatment allocation—that is, the use of a placebo control—or it can refer to blinding during the adjudication of events after a treatment has been delivered. Given the difficulty in using placebo control for procedural interventions, randomized controlled trials of these therapies frequently rely on independent clinical event committees, blinded to treatment allocation, for unbiased adjudication that the clinical events actually did happen. In many landmark trials of percutaneous coronary intervention (PCI), these committees retrospectively review medical records to confirm the evidence of death, MI, or revascularization.

But what does blinding of these committees actually achieve? It can prevent malicious or intentional bias. For cardiovascular death and nonfatal MI, such committees may deliver unbiased quantification of the difference between arms, as these events do not require the subjective perceptions of patients or providers. Unfortunately, for symptom-mediated events, application of blinding at this stage can give a false appearance of freedom from bias. Symptom-mediated events have already been adjudicated by the clinician at the patient's bedside. Clinicians are quite rightly trained to use knowledge of the patient's history (including past treatments) to help interpret symptoms and come to treatment decisions. Clinical trials in which clinicians caring for patients are unblinded do not prevent this happening and affecting the subsequent event rates. The adjudication committee cannot undo this bias (even if it was allowed to) because its role is simply to confirm that, for instance, the patient was indeed admitted to hospital because of symptoms. Here, blinding the adjudication committee can make matters worse by providing an illusion of resistance to bias.

Indeed, we have found that some experts incorrectly think that a blinded adjudication committee somehow undoes this bias. For instance, 1 grant body reviewer rejected funding for ORBITA (Objective Randomized Blinded Investigaton with optimal medical Therapy or Angioplasty in stable angina),[5] the first truly blinded randomized controlled trial of PCI, because another trial had used an impartial end point committee:

> *"The applicants have dismissed prior randomised trials (including those with blinded endpoint adjudication) … In RITA 2, 1018 patients were randomised and follow up has been reported to 7 years. An independent and blinded endpoint committee examined and adjudicated the endpoints. Significant differences in angina, breathlessness and exercise performance were identified (in favour of revascularisation) …"*
>
> —Funding reviewer recommending rejection of the ORBITA trial

THE POWER OF TELLING: FAITH HEALING

Is there evidence that unblinded assessments can bias subjective end points? Some of the most startling findings in the Deferral of PTCA Versus Performance of PTCA (DEFER)[6] and Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2)[7] trials received surprisingly little attention. Both studies provided a fascinating insight into what happens to unblinded patients when they are told that they do not need coronary intervention.

The DEFER trial randomized patients with stable coronary disease and a stenosis of fractional flow reserve (FFR) ≥0.75, to either PCI or conservative therapy. The physicians were confident that FFR ≥0.75 was not hemodynamically significant and may well have conveyed this confidence to the patients in the conservative arm. The most remarkable finding, although not emphasized by the authors, was that the simple act of telling a patient that the physiology test shows no significant ischemia dramatically improved symptoms. In 2001, when invasive physiology was relatively new, the DEFER physicians, through this simple act of telling, were eliminating symptoms in more than one third of patients. At 1-month follow-up, without any protocol-directed changes to medical therapy, the proportion of patients with chest pain fell from 88% to 54%, a relative risk reduction of 39% (Figure 1, upper).[6]

A decade later, experience had grown and, with it, confidence. The FAME 2 trial randomized patients with FFR ≤0.8 but also reported the fascinating results of patients not eligible for randomization because their FFR was >0.8. In these patients, the FAME 2 physicians achieved a 77% relative risk reduction of Canadian Cardiovascular Society (CCS) II to IV angina at 30 days. Antianginal prescribing was effectively unchanged, and there had been no PCI: these patients had received nothing other than the reassurance of a negative test (Figure 1, lower).[7]

Just learning that FFR is above threshold allows you to confidently reassure the patient and may color your interpretation of later symptom assessment.

Even in patients who do receive PCI, the faith healing element is important. In ORBITA, most patients continued to have angina after PCI.[5] In contrast, enthusiastic unblinded investigators, who personally eradicated the lesion by PCI, witnessed the immediate hemodynamic resolution and subsequent normalization of ischemia tests, achieved not the borderline angina relief of ORBITA, but elimination of chest pain with 100% effectiveness.[8]

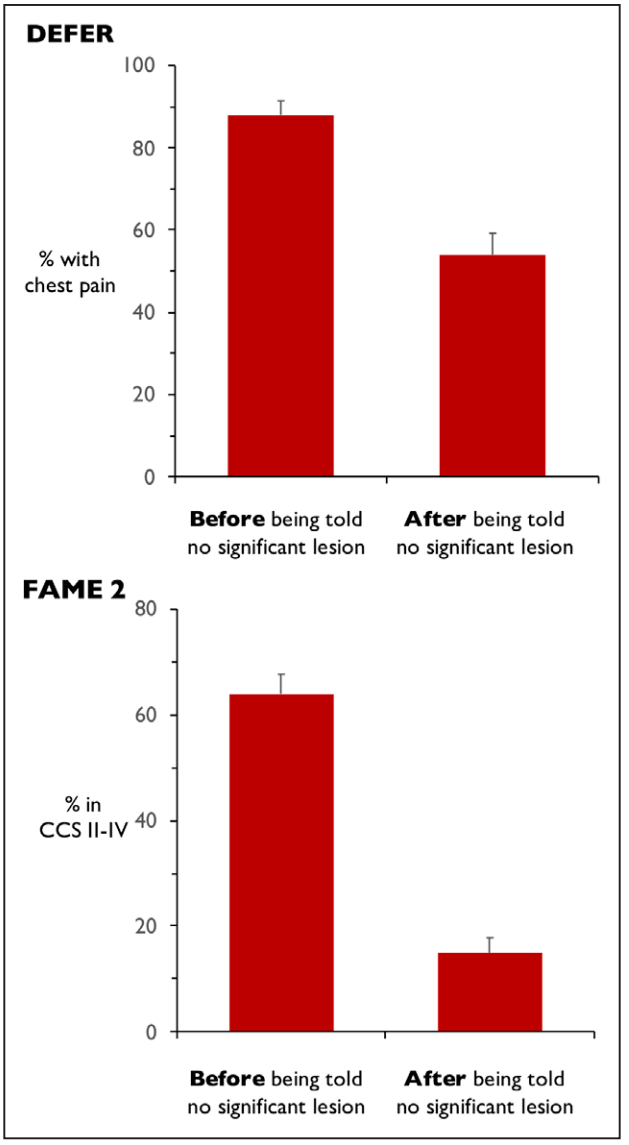

Figure 1. The proportion of patients experiencing chest pain in conservatively managed groups of the DEFER trial[6] (FFR ≥0.75, upper) and the FAME 2[7] registry (FFR >0.8, lower).
Patients were assessed at baseline and 30 days after being told there is no significant lesion.

We should use power of faith healing unashamedly in clinical practice but should not allow it to color scientific research.

THE POWER OF KNOWING: SUBTRACTION ANXIETY

Unblinded physicians are no less vulnerable than patients to the influence of bias. The only method to prove the efficacy of a treatment is to withhold it in a trial, even if symptoms seem to warrant intervention. Physicians are trained to act with beneficence, and consequently, withholding treatment thought to be of benefit causes a conflict of interest. This is not a problem for blinded medication trials because in both arms, the patient is receiving something from the doctor.

But for most procedural interventions, especially those that are routine and listed in guidelines, patients and their physicians in the control arm may experience anxiety from the knowledge that the intervention is being experimentally subtracted. This anxiety causes a time-limited enhancement of awareness of symptoms that can be so distressing (to patient and doctor) that they need to relieve the tension by taking action.

The tendency of physicians to take action means that with knowledge of a coronary stenosis which has been left untreated, the presence of symptoms, whether angina or not, will often trigger a series of events resulting in an urgent revascularization event. The characteristic feature of decision events mediated by subtraction anxiety is that they are magnified in the immediate aftermath of discovering that the intervention is being subtracted from the conventional clinical care plan. With time, the anxiety diminishes.

FAME 2 demonstrates this phenomenon perfectly once the revascularization events are stratified by their triggers into biomarker positive (ie, nonfatal MI), ECG positive/biomarker negative, and symptom only.[9] In stable coronary artery disease, events tend to accumulate steadily with time. This can be seen in 5 of the 6 graphs of Figure 2. However, when PCI is subtracted from clinical care, revascularization based on symptoms alone is not only overwhelmingly more numerous than all other events but is also enormously clustered in the first few months (Figure 2, top right).

Subtraction anxiety is a potent force in the control arm of unblinded trials of interventions already considered beneficial.

A DEFINITIVE TRIAL WITH DEFINITIVE DESIGN: ISCHEMIA

The ISCHEMIA trial set out to eliminate the temptation to inflate the efficacy of revascularization and in doing so end what was considered 'community equipoise' about its role in stable coronary disease. Rather than perform a trial with a placebo-controlled arm, it did this by specifying an incontrovertible primary end point invulnerable to the bias of unblinded adjudication: cardiovascular death and MI.[1,3,10]

The ISCHEMIA investigators wrote that the explicit goal of the trial was to overcome limitations of earlier trials by "being adequately powered to demonstrate whether routine revascularization reduces cardiovascular death or nonfatal MI in patients with SIHD and at least moderate ischemia".[1] The study design prespecified 8000 patients (although this was subsequently reduced) and was conducted internationally to support

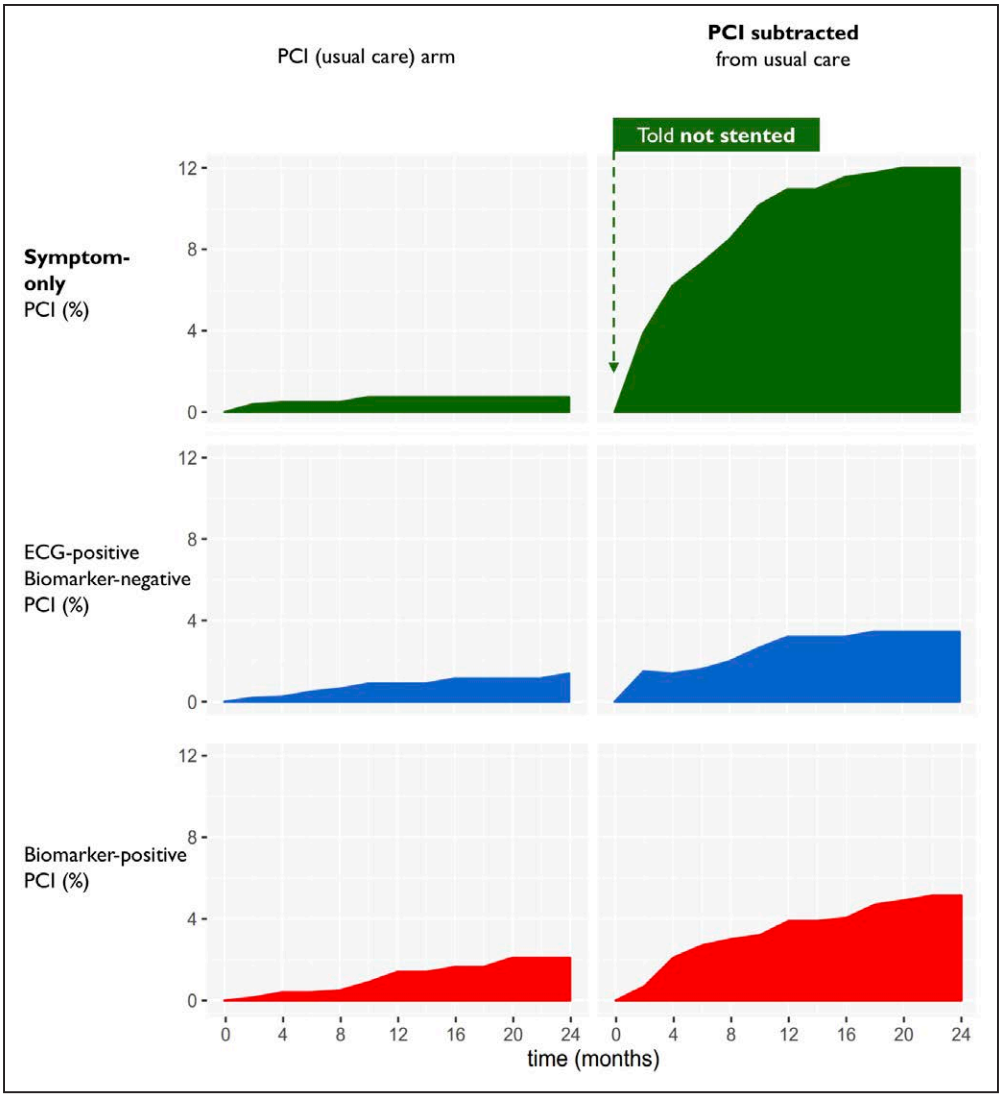

Figure 2. Early revascularization in the FAME 2 trial stratified by the trigger for revascularization.
PCI indicates percutaneous coronary intervention. Data derived from De Bruyne et al.[9]

its external validity. An extensive set of exclusion criteria have been specified to maintain purity of the study population. The trial closed to recruitment on January 31, 2018, and is expected to report within the next few months.[2]

With such clear emphasis on bias-resistant end points[2] throughout the many years of recruitment, it is disappointing to learn, just days before closure, of the intention to insert into the primary end point events which are vulnerable to bias in an unblinded trial.[3] Most damaging to the stated aim of the trial is the inclusion of hospitalization for unstable angina and heart failure. This will certainly fully allow the powers of telling and knowing to alter the meaning of the trial.

Inflation of events by adding these bias-prone outcomes will undermine the value of this well-designed study.[3] When the trial reports, we suggest that readers focus on the primary end point pre-specified, not any versions edited near trial end when the great majority of events will have already accumulated. We suggest readers disregard additional events decided on by doctors and patients unblinded to treatment allocation.

Looking beyond ISCHEMIA, the community must now focus their attention on two wider issues. First, symptoms are important, but unblinded trials of symptoms are as harmful for the study of procedural interventions as they are for the study of medications. Without full blinding of patients, providers *and* adjudication committees, end points reliant on physician or patient perception should not be incorporated with hard outcomes into a primary composite end point. Use of placebo control in PCI is achievable, as demonstrated in ORBITA.[5] Importantly, ethical concerns, which limited follow-up to 6 weeks in this trial, are less and less pressing with the accumulating evidence of prognostic neutrality of PCI. With longer follow-up, a broader range of end points could be assessed and the uncertain role of PCI in stable coronary disease may finally be defined.

Second, we must reflect on the whether there is any meaning to the term primary end point if these goalposts can be moved at will after a trial has begun recruiting—and especially if a very prominent trial does so shortly before reporting its result. We must learn to accept the results of trials even if they are not as we hoped. True scientists do experiments for the potential to surprise. The thousands of patients who volunteered to participate, and even more importantly the millions whose care will be informed by the reported trial results, deserve nothing less.

DISCLOSURES

Dr Nijjer is on the speakers' bureau for Philips Volcano. R. Al-Lamee has received speaker's honorarium from Philips Volcano. The other authors report no conflicts.

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FOOTNOTES

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