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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Do Current Clinical Trials Meet Society's Needs?

A Critical Review of Recent Evidence

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ABSTRACT

This paper describes some important controversies regarding the current state of clinical trials research in cardiology. Topics covered include the inadequacy of trial research on medical devices, problems with industry-sponsored trials, the lack of head-to-head trials of new effective treatments, the need for wiser handling of drug safety issues, the credibility (or lack thereof) of trial reports in medical journals, problems with globalization of trials, the role of personalized (stratified) medicine in trials, the need for new trials of old drugs, the need for trials of treatment withdrawal, the importance of pragmatic trials of treatment strategies, and the limitations of observational comparative effectiveness studies. All issues are illustrated by recent topical trials in cardiology. Overall, we explore the extent to which clinical trials, as currently practiced, are successful in meeting society's expectations. (J Am Coll Cardiol 2014;64:1615–28)
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Randomized clinical trials (RCTs) are accepted as the source of the highest level of evidence for assessing the efficacy and safety of potential new treatments by guidelines and regulatory authorities. Indeed, innumerable important advances in patient care, including the abandonment of biologically plausible but ineffective or unsafe treatments, have been based upon rigorous scrutiny from major pivotal RCTs.

Despite such successes, it is relevant to ask to what extent the whole field of clinical trials research as currently practiced does, in fact, meet society's needs.

Here we focus on several topical controversies from a cardiovascular (CV) perspective, each illustrated by recent clinical trials. The aim throughout is to note deficiencies and encourage improvements, thus enhancing what the public should expect in terms of the extent of clinically-relevant advances in treatment and health derived from RCTs.

PLACEBO EFFECT AND MEDICAL DEVICES

Until the recent SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) trial revealed its negative findings (1), there was much collective expectation that renal denervation could be a very effective intervention in resistant hypertension. In 2009, SYMPLICITY 1, an uncontrolled trial of 45 patients, found a marked decrease in systolic blood pressure (SBP) after 12 months (2). SYMPLICITY 1 was subsequently expanded to report a mean 22 mm Hg decrease in SBP at 6 months in 86 patients (3). In 2010, SYMPLICITY 2, a randomized, unblinded, controlled trial in 100 patients was equally positive, with mean 6-month SBP reductions

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CI = confidence interval

CV = cardiovascular

FDA = U.S. Food and Drug Administration

GPI = glycoprotein IIb/IIIa inhibitor

PCI = percutaneous coronary intervention

RCT = randomized clinical trial

SBP = systolic blood pressure

STEMI = ST-segment elevation myocardial infarction

of 32 and 1 mm Hg, respectively, in the renal denervation and control arms (4).

Because of the recognized potential for bias in these studies, to obtain more rigorous evidence and, specifically, to satisfy the U.S. Food and Drug Administration's (FDA's) regulatory requirements, SYMPLICITY 3 was a larger RCT comparing renal denervation with a sham procedure control group in a 2:1 randomization ratio: patients and those assessing outcomes were blinded as to who got what (1). In the renal denervation (n = 364) and sham procedure (n = 171) arms, mean 6-month SBP reductions were 14 and 12 mm Hg, respectively: a nonsignificant difference of only 2 mm Hg. The difference between SYMPLICITY 3 and the earlier findings is very marked (**Figure 1**).

Advocates of renal denervation are exploring possible deficiencies in SYMPLICITY 3. Did patients not truly have resistant hypertension? Are there specific subsets of patients with hypertension who would benefit? Was drug use different in the 2 arms? Were operators too inexperienced? Are better devices now available? The obvious explanation is that renal denervation appears to be insufficiently effective in reducing SBP in this population and that previous findings reflect a substantial placebo effect, regression to the mean, and the possibility that patients with "refractory hypertension" became adherent to drug therapy once enrolled into the trial. Additional trials would be helpful in establishing the role (or lack thereof) for renal denervation in hypertension. However, the story thus far indicates that the hype of an illusory breakthrough in management of resistant hypertension was perpetuated by inadequately-designed RCTs, which gave exaggerated findings and did not take into account the power of the placebo.

Another excellent example of the placebo effect arises from trials of permanent pacemakers in patients with vasovagal syncope (5). A meta-analysis of 9 trials demonstrated that in unblinded studies, active pacing resulted in a striking reduction in recurrent syncope (odds ratio: 0.09, 95% confidence interval [CI]: 0.04 to 0.22). Nonetheless, when patients with permanent pacemakers were blinded as to whether or not the pacing modes were activated, there was no significant effect (odds ratio: 0.83; 95% CI: 0.41 to 1.70).

These experiences have important wider implications for research into medical devices. Of particular note are the very undemanding requirements for medical device approval in Europe (6). The CE Mark needed to market a device in the European Community does not usually require evidence from RCTs; renal denervation is 1 such example. Relatively small, uncontrolled studies focusing on performance objectives, rather than valid evidence of efficacy and safety, are assessed by Notified Bodies, who are widely recognized as lacking appropriate scientific objectivity. Consequently, such an easy, nonrigorous approval process carries risks that patients could be exposed to ineffective and/or unsafe devices.

There is understandable frustration in the United States that new devices get approved much more slowly than in Europe. Thus, for coronary stents and transcatheter aortic valve replacements, there is the perception that U.S. patients have a substantial delay in access to effective new devices compared with Europeans. Although there may be room for a more expedited approval process within the FDA, critics of the current approach need to recognize that efficacy and safety can be truly determined only after the FDA-required RCTs are performed. The real problem lies in Europe: there is a need for radical reform of how medical devices get approved in Europe, both in terms of the currently inadequate process and the need for well-designed RCTs to be a fundamental part of the mandated evidence base.

PROBLEMS WITH PHARMACEUTICAL TRIALS: THE BIVALIRUDIN EXPERIENCE

The results of the HEAT PPCI (How Effective are Antithrombotic Therapies in Primpary PCI) trial (7), which compared bivalirudin with unfractionated heparin in 1,892 primary percutaneous coronary intervention (PCI) patients followed for 28 days, provoked considerable debate. The primary composite outcome (death, stroke, reinfarction, or unplanned target lesion revascularization) was higher in the bivalirudin group (8.7% vs. 5.7%; p = 0.01), as was stent thrombosis (3.4% vs. 0.9%; p = 0.001), whereas there was no evidence of a difference in major bleeding (3.5% vs. 3.1%; p = 0.59). The use of glycoprotein IIb/IIIa inhibitors (GPIs) was similarly low in both groups (13.5% vs. 15.5%).

This apparent inferiority of bivalirudin seems to contradict evidence from 3 previous trials, each claiming superiority of bivalirudin alone versus heparin + GPI. The ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial (8) in 13,819 patients with acute coronary syndrome showed bivalirudin to be noninferior for 30-day composite ischemia (death, myocardial infarction, and revascularization) (7.8% vs. 7.3%) and superior for major bleeding (3.0% vs. 5.7%). The HORIZONS-AMI