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SPECIAL ARTICLE

Authors' Self-Declared Financial Conflicts of Interest Do Not Impact the Results of Major Cardiovascular Trials

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Objectives This study assessed whether the results of major, potentially practice-altering cardiovascular trials were influenced by the authors' self-declared financial conflicts of interest (FCOI). Secondary objectives included assessment of trial outcomes by source of funding, by FCOI subtype, and by trial endpoints.

Background Financial conflicts of interest, ubiquitous in cardiovascular medicine because of significant investigator-industry collaborations, potentially can influence trial outcomes.

Methods A MEDLINE search was performed using the MeSH term *cardiovascular disease* limited to randomized controlled trials and clinical trials published from January 1, 2000, through April 15, 2008, in 3 high-impact journals. Two reviewers independently abstracted data from the published article. Chi-square tests, Fisher exact tests, and multivariate logistic regression were used to assess the associations between FCOI and study characteristics and between FCOI and trial outcomes.

Results Of the 550 articles reviewed, 51.1% satisfied FCOI criteria, including at least one of the following: stock ownership, employee, speaker's bureau, and consultant). Of the 538 articles providing sponsorship information, 34.6% reported funding solely by nonprofit organizations, 48.3% reported funding solely by industry, and 17.1% reported funding by a combination. Prevalence of FCOI significantly increased with level of industry funding: 21.5% (none), 50.0% (shared), 75.0% (industry solely, $n = 281$, $p < 0.0001$). However, no differences in reporting of favorable results were detected when articles were analyzed by self-declared FCOI (60.5% vs. 59.5% in those with and without, odds ratio: 1.04, $p = 0.81$). This result was upheld in multivariate analysis.

Conclusions Authors' self-declared FCOI and source of funding do not seem to impact outcomes in major cardiovascular clinical trials. (J Am Coll Cardiol 2013;61:1137–43) © 2013 by the American College of Cardiology Foundation

The Institute of Medicine in its 2009 position statement defined conflicts of interest as "circumstances that create a risk that professional judgments or actions regarding a primary interest will be unduly influenced by a secondary interest" (1). Collaboration between academic medicine and industry has produced revolutionary treatments that have contributed significantly to improvements in public health. The influence of this academia–industry collaboration on the integrity of research is debated actively and is subjected to appropriate scrutiny in the public domain because of perceptions that the outcomes of some high-impact clinical trials may be influenced by financial conflicts of interest (FCOI). Financial conflicts of interest are very important because of their potential for undue influence on the judgments of institutions and individuals, along with potentially threatening the integrity of scientific investigation, objectivity of medical education, and quality of patient care, all of which can lead to erosion of vital public trust (1).

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Abbreviation and Acronym

FCOI = financial conflicts of interest

Indeed, a recent systematic review revealed patients' belief that financial transactions affect physician behavior and need to be disclosed. The study also suggested that patients, physicians, and research participants believed that financial transactions weaken the quality of research and evidence (2). Similarly, a review of researcher attitudes illustrated the concern that investigators have about the impact of financial ties on the choice of research topic, research conduct, and publication (3). Further, studies have suggested that trials funded by for-profit organizations are more likely to be associated with favorable outcomes compared with those that are funded by not-for-profit organizations (4–8). These concerns from patients, physicians, researchers, and organizations have led to both external regulation and self-regulation by academic medical centers and the pharmaceutical industry to demonstrate greater transparency and accountability. Regulation measures include the mandatory registration of all clinical trials on ClinicalTrials.gov, requirements for accurate and systematic reporting of authors' conflicts of interest by major journals, declaration of potential FCOI by staff and faculty physicians at university and hospital websites with a recent directive to declare exact dollar amounts received from industry, and development of guidelines by the pharmaceutical industry strictly regulating potential contributions by industry to academic centers and individual physicians (9–12). In their recent comprehensive document, the Institute of Medicine detailed the various FCOI types and suggested clear policy measures—both individual and institutional—to address these issues (1,13).

Broadly stated, FCOI in medicine can be present in research, education, medical practice, and guideline development. Additionally, management of cardiovascular disease represents a substantial component of the U.S. healthcare budget, with significant contributions from expensive novel therapeutic agents including drugs, devices, and strategies. The management of cardiovascular disease and stroke accounts for 16% of the overall healthcare expense in the United States. The 2008 estimate of direct and indirect costs of cardiovascular care in the United States was $297.7 billion (14). In a national survey, cardiologists were twice as likely as family practitioners to receive payments from industry, explained by the fact that cardiologists are viewed by industry as opinion leaders and as being more likely to be involved in research efforts (15). Therefore, potential conflicts of interest in cardiovascular research and publication represent a critically important field that needs investigation.

Recognizing the ability of major randomized cardiovascular disease trials published in high-impact journals to change practice patterns, the primary aim of this study was to examine the impact of authors' self-declared FCOI on the outcomes of major cardiovascular trials. Secondary aims included assessment of trial outcomes by source of funding, conflict of interest subtype (detailed in the following text), and trial endpoints (clinical vs. surrogate).

To perform an even more in-depth analysis of FCOI in major cardiovascular trials, we performed tertiary analyses examining associations between self-reported FCOI and: 1) type of intervention (drug, device, or other); 2) study design (superiority or noninferiority); 3) choice of primary and secondary endpoints (clinical vs. surrogate); 4) statistical analysis (independent vs. nonindependent); and 5) presence or absence of registration on ClinicalTrials.gov. Additionally, trial outcomes, favorable versus unfavorable, were analyzed by independence of statistical analysis.

Methods

Article selection. A MEDLINE search was conducted via PubMed to identify articles for inclusion. We limited our evaluation to major cardiovascular trials published in 3 high-impact general medical journals, namely *The New England Journal of Medicine*, the *Lancet*, or the *Journal of the American Medical Association*. The initial search consisted of articles with the MeSH term *cardiovascular disease* and was limited to randomized controlled trials and clinical trials published from January 1, 2000, through April 15, 2008.

Two independent reviewers (R.E. and K.S.) evaluated the selected publications. They examined in detail the study title, abstract, and methods to ensure that each study represented a randomized trial. Observational studies, cohort studies, commentaries, letters, meta-analyses, and review articles were excluded (Fig. 1). The remaining eligible articles were abstracted systematically via a standardized data collection form as part of the Clinical Trials Reporting Database.

The FCOI were divided into 2 broad categories: FCOI present and FCOI absent. Any author was deemed to have an FCOI if they met the following criteria: stock ownership, employee, consultant, or presence on a speakers' bureau. An FCOI was deemed not present if the author only received research funding or reported no conflict (16). Prior studies have demonstrated that research funding alone did not have an impact on trial results (17). In addition, the National Institutes of Health's recent revision of FCOI standards and directives that describes significant FCOI by the following criteria: salary, consulting honoraria, equity interest, ownership interest, spouses and children's FCOI, intellectual property rights, and travel grants—which does not include research funding (18). Studies not stating any financial disclosures were excluded.

Trial outcomes were deemed positive or favorable if the new intervention (drug, device, combination, or other) was found to be effective with respect to the primary endpoint with statistical significance. Trials were deemed to have clinical endpoints if the primary endpoint was clinical in nature with mortality or morbidity parameters. The endpoint was considered surrogate if it was a radiological or laboratory measure and did not include mortality or morbidity parameters. Trials were considered to be statistically