

SPECIAL ARTICLE

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

Ashish Aneja, MD,* Ricardo Esquitin, MD,† Kshitij Shah, MD,‡ Rupa Iyengar, MPH,§
Rosane Nisenbaum, PhD,||¶ Magda Melo, MSc,¶ Shiny Matthewkutty, MD,§
Sanjum S. Sethi, MD,§ Muhammad Mamdani, PHARM,¶ Michael E. Farkouh, MD, MSc§¶#
*Cleveland, Ohio; Boston, Massachusetts; Bronx, New York; New York, New York;
and Toronto, Ontario, Canada*

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

From the *Heart and Vascular Center, MetroHealth Campus of Case Western Reserve University, Cleveland, Ohio; †Division of Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; ‡Department of Medicine, James J. Peters VA Medical Center, Bronx, New York; §Zena and Michael A. Weiner Cardiovascular Institute, Mount Sinai School of Medicine, New York, New York; ||Centre for Research on Inner City Health, the Keenan Research Centre in the Li Ka Shing Knowledge Institute of St. Michael's Hospital, and Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada; ¶Applied Health Research Centre, Li Ka Shing Knowledge Institute, University of Toronto, Toronto, Ontario, Canada; and the #Peter Munk Cardiac Centre University of Toronto, Toronto, Ontario, Canada. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 9, 2012; revised manuscript received October 1, 2012, accepted October 8, 2012.

See page 1144

(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).

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.

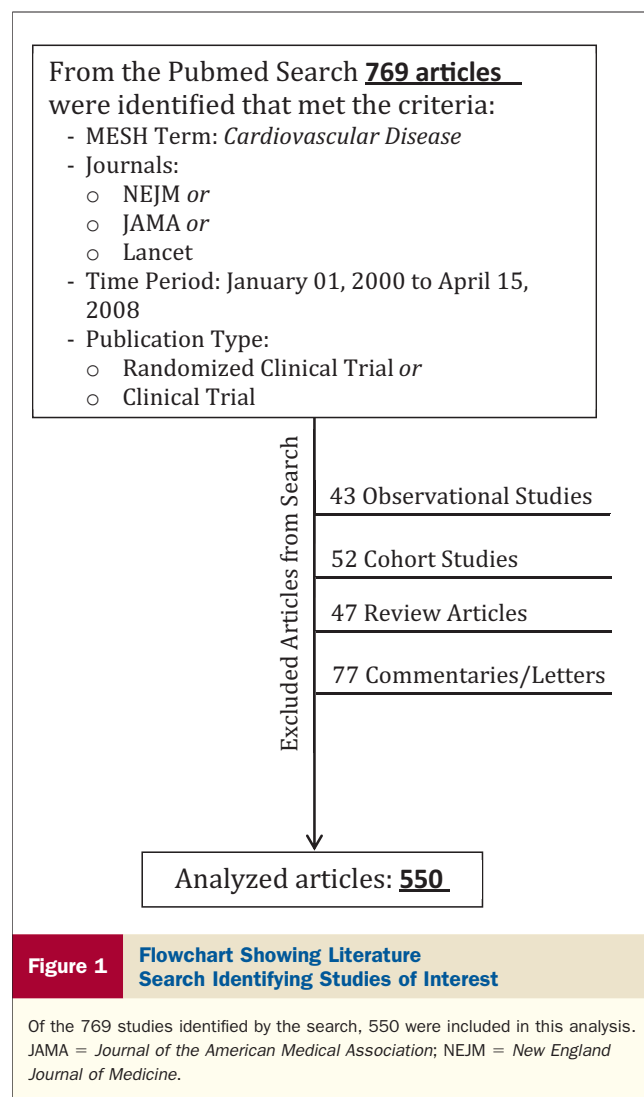
Methods

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



independent if a biostatistician with an academic faculty appointment or who was employed by a government research institute performed the analysis.

Statistical analysis. The associations between FCOI, trial characteristics, and outcomes were evaluated by comparing proportions using the chi-square or Fisher exact tests or logistic regression when more than 2 categories were present and a reference group was defined. We also estimated univariate odds ratios with 95% confidence intervals to quantify the degree of association. A multivariate logistic regression was used to examine further the association between FCOI and a favorable trial result, adjusting for the study characteristics. SAS software version 9.2 (SAS Institute, Cary, North Carolina) was used for all statistical analyses, and 2-sided *p* values <0.05 were considered statistically significant.

Results

Primary analysis: authors' self-declared FCOI and trial outcomes. Of the 769 PubMed citations identified by the initial search, 605 met initial search criteria (Fig. 1). Of

these, 550 articles were selected after screening for articles meeting the prespecified inclusion criteria. In 269 (48.9%) articles, FCOI were absent (39 with no conflict, 230 research funding only), and in 281 (51.1%) articles, FCOI were present (including at least 1 of the following: stock ownership, employee, speaker's bureau, or consultant). Articles were predominantly multicenter trials (89.1%) and reported safety data (71.2%) (Table 1). Financial conflicts of interest were more prevalent in multicenter than in single-center studies (55.5% vs. 15.0%, *p* < 0.0001) and in articles reporting safety data (59.5% vs. 31.0%, *p* < 0.0001). More studies published in *The New England Journal of Medicine* had an FCOI reported than in the *Lancet* (60.1% vs. 39.4%, *p* < 0.0001), but not in the *Journal of the American Medical Association* (60.1% vs. 51.1%, *p* = 0.07). Studies conducted in the United States or Canada alone (33.5%) were less likely to report FCOI than international studies (34.2%) or those conducted both in the United States and Canada (32.4%, *p* = 0.003 and *p* = 0.0005, respectively). When examining the overall impact of FCOI on the likelihood of having a significantly beneficial trial result (Table 2), no differences were noted (60.5% vs. 59.5% in those with and without financial conflict, unadjusted odds ratio: 1.04, 95% confidence interval: 0.74 to 1.47, *p* = 0.81). The effect of FCOI on reporting of favorable outcomes remained not significant even after adjusting for type of study, center location, trial registration, funding source, and intervention type (odds ratio: 1.13, 95% confidence interval: 0.74 to 1.71, *p* = 0.58).

Secondary analysis: financial conflicts of interest and trial results by source of funding, conflict of interest subtype, and trial endpoints. Overall, 34.6% (*n* = 186) were funded solely by not-for-profit organizations, 48.3% (*n* = 260) were funded by industry, and 17.1% (*n* = 92) were funded by a combination. Of the trials sponsored by industry, 75.0% reported FCOI compared with 50.0% for those with combination funding and 21.5% for trials funded by not-for-profit organizations alone (*p* < 0.0001 and *p* < 0.0001, respectively). When separated by type of financial disclosure, favorable versus unfavorable trial results also were distributed similarly: no conflict: 38.2% vs. 39.6%, stock ownership: 15.5% vs. 13.2%, sponsor employee: 14.6% vs. 12.3%, speakers' bureau: 15.8% vs. 16.8%, and consultancy: 5.8% vs. 8.2%, research funding: 6.4% vs. 8.2%, and no mention of financial conflict: 3.9% vs. 1.8% (*p* = 0.57).

When separated by type of financial disclosure, the distribution of favorable trials results was similar (*p* = 0.57): 59.2% (*n* = 213), 63.8% (*n* = 80), 64.0% (*n* = 75), 58.4% (*n* = 89), 51.4% (*n* = 37), 53.9% (*n* = 39), and 76.5% (*n* = 17) for no conflict, stock ownership, sponsor employee, speakers' bureau, consultancy, research funding, and no mention of financial conflict, respectively.

Trials with a surrogate endpoint versus a clinical endpoint were not more likely to have a favorable result (68.7% [*n* = 99] vs. 58.1% [*n* = 451], *p* = 0.051), but were less likely to report a FCOI (38.4% vs. 53.9%, *p* = 0.005). Intervention

Table 1 Journal and Trial Characteristics in Articles Reporting and Not Reporting Authors' Financial Conflict of Interest				
	All (n = 550)	COI Present (n = 281)	COI Absent (n = 269)	p Value
Journal				
NEJM	208 (37.8)	125 (60.1)	83 (39.9)	Reference
Lancet	160 (29.1)	63 (39.4)	97 (60.6)	<0.001
JAMA	182 (33.1)	93 (51.1)	89 (48.9)	0.07
Type of trial				
Single center	60 (10.9)	9 (15.0)	51 (85.0)	<0.001
Multicenter	490 (89.1)	272 (55.5)	218 (44.5)	
Center location				
United States only or Canada only	184 (33.5)	93 (50.5)	91 (49.5)	Reference
International	188 (34.2)	66 (35.1)	122 (64.9)	0.003
United States and Canada	178 (32.4)	122 (68.5)	56 (31.5)	<0.001
Registered on ClinicalTrials.gov				
Yes	120 (21.9)	82 (68.3)	38 (31.7)	<0.001
No	427 (78.1)	198 (46.4)	229 (53.6)	
Funding source				
Industry only	260 (48.3)	195 (75.0)	65 (25.0)	Reference
Nonindustry only	186 (34.6)	40 (21.5)	146 (78.5)	<0.001
Industry and nonindustry	92 (17.1)	46 (50.0)	46 (50.0)	<0.001
Intervention type				
Drug	324 (58.9)	197 (60.8)	127 (39.2)	0.575
Device	54 (9.8)	35 (64.8)	19 (35.2)	Reference
Drug or device	16 (2.9)	7 (43.8)	9 (56.3)	0.136
Other	156 (28.4)	42 (26.9)	114 (73.1)	<0.001
Comparator				
Placebo	209 (64.5)	126 (60.3)	83 (39.7)	0.72
Active	115 (35.5)	67 (58.3)	48 (41.7)	
Safety data reported				
Yes	390 (71.2)	232 (59.5)	158 (40.5)	<0.001
No	158 (28.8)	49 (31.0)	109 (69.0)	

Values are n (%).

COI = conflict of interest; JAMA = *Journal of the American Medical Association*; NEJM = *New England Journal of Medicine*.

types were noted to be 58.9% drug (n = 324), 9.8% device (n = 54), 2.9% drug versus device (n = 16), and 28.3% other (n = 156, i.e., behavioral, dietary, procedural, or

nondevice surgical) forms of intervention. Among drug only trials (n = 324), 64.5% were placebo controlled. Device studies reported a significantly higher proportion of finan-

Table 2 Association Between Authors' Financial Conflict of Interest and Primary Outcome, Hypothesis Type, and Independent Statistical Analysis					
	All	COI Present	COI Absent	OR (95% CI)	p Value
Primary analysis					
Primary outcome					
Significant and beneficial	330	170 (60.5)	160 (59.5)	1.04 (0.74–1.47)	0.81
Nonsignificant	220	111 (39.5)	109 (40.5)		
Secondary analyses					
Hypothesis type					
Noninferiority/equivalence	132	81 (33.2)	51 (22.0)	1.76 (1.17–2.66)	0.006
Superiority	344	163 (66.8)	181 (78.0)		
Primary endpoint type					
Clinical	451	243 (86.5)	208 (77.3)	1.88 (1.20–2.93)	0.005
Surrogate	99	38 (13.5)	61 (22.7)		
Independent statistical analysis					
Yes	271	136 (51.3)	135 (56.5)	0.81 (0.57–1.15)	0.25
No	233	129 (48.7)	104 (43.5)		

Values are n (%).

CI = confidence interval; OR = odds ratio. Other abbreviation as in Table 1.

cial disclosure than other intervention studies (64.8% [$n = 54$] vs. 26.9% [$n = 156$], $p < 0.0001$), but similar rates to drug studies (60.8% [$n = 324$], $p = 0.57$) or drug or device studies (43.8% [$n = 16$], $p = 0.14$). Among drug-only studies, no difference in financial disclosures was observed between placebo-controlled and active controlled trials (60.3% [$n = 209$] vs. 58.3% [$n = 115$], $p = 0.72$).

Tertiary analysis: associations between FCOI and independent statistical analysis, hypothesis type, and registration on ClinicalTrials.gov. Independent statistical analyses were reported in 271 (53.8%) of 504 trials. They did not seem to have a significant association with FCOI (51.3% vs. 56.5%, $p = 0.25$), with 56.7% of statistically independent studies and 69% of nonstatistically independent studies reporting favorable outcomes ($p = 0.008$). Trials registered on ClinicalTrials.gov were more likely to report significant FCOI (68.3%, $n = 120$) versus those not registered at the website (46.4%, $n = 427$, $p < 0.0001$). When classified by hypothesis type, 72.3% ($n = 344$) of trials had a superiority hypothesis and 27.7% ($n = 132$) of trials had an equivalence and noninferiority hypothesis. Equivalence and noninferiority hypothesis trials were more likely than superiority trials to report FCOI (61.4% vs. 47.4%, $p = 0.006$).

Discussion

Our data demonstrate that authors' self-declared FCOI are ubiquitous in major cardiovascular clinical trials and do not seem to have an impact on their outcomes. A subanalysis conducted on the basis of the type of FCOI also does not seem to influence trial outcomes. Furthermore, the selection of surrogate over clinical endpoints does not seem to increase the likelihood of favorable trial results in major cardiovascular clinical trials published in high-impact journals.

On September 27, 2007, the Congress enacted a U.S. law that expanded the types of clinical trials that must be registered on ClinicalTrials.gov (18). Before this date, registration essentially was a voluntary process. As part of the same effort, the International Committee of Medical Journal Editors has required all authors of original research who plan to publish articles in member journals to register their clinical trials into the clinical trials database (19). This mechanism subjects investigators to generalized professional accountability and academic oversight by minimizing the potential for selective reporting, omitting of primary outcomes, and inclusion of post hoc secondary outcomes (20,21). Fines and penalties also are proposed for trials not published within 1 year of closeout. As part of uniform FCOI disclosure, the International Committee of Medical Journal Editors also has developed a standard FCOI declaration form, which has been implemented by high-impact journals (22).

The results of our study are surprising when evaluated in the light of previously published literature, but perhaps represent the most comprehensive and multidimensional

analysis of FCOI in major cardiovascular clinical trials to date. Prior studies examining the impact of study funding sources on outcomes have noted that those funded by for-profit entities have a higher likelihood of reporting favorable results (8,23,24). However, in contrast to prior studies that analyzed trials on the basis of the source of funding of the overall trial, our study evaluated the potential impact of authors' self-declared FCOI on study outcomes from several vantage points.

In our study, trials registered on ClinicalTrials.gov were more likely to have significant reported FCOI. This result is not unexpected because authors registering their studies voluntarily are more likely to have been forthcoming of their potential financial conflicts. The enactment of the registration mandate is likely to improve transparency in clinical trials reporting and to further ameliorate publication bias. The higher likelihood of a significant FCOI in trials originating in the United States and Canada—whether solely North American or international—also is expected because most large pharmaceutical and device corporations are headquartered in this region, increasing the likelihood of collaborative research and potential conflicts. Also, not surprisingly, multicenter trials were more likely to include authors with an FCOI largely because of the large number of collaborators, larger study size, and greater expenditure, usually borne by industry. Similarly, trials funded by not-for-profit entities were less likely to report significant FCOI than trials conducted in collaboration or those sponsored by for-profit organizations. Regardless of these variables, trial outcomes did not seem to have been swayed in one direction.

As previously noted, noninferiority and equivalence design trials were in the minority compared with trials with a superiority hypothesis. These findings lend further support our primary outcomes because noninferiority and equivalence design trials generally require a smaller sample size than superiority trials and are more likely to be adopted as the preferred hypothesis, especially by for-profit entities. We observed a greater proportion of nonstatistically independent studies reporting favorable findings relative to statistically independent studies. Although this finding is interesting and suggests that statistical independence may influence study findings, further research is needed for verification.

The differences between our analysis and prior reports are multifactorial. Apart from the ClinicalTrials.gov mandate, an increasing number of major academic institutions in the United States and Canada have made significant strides toward more transparency and improved regulation, advancing their conflict-of-interest policies. There is some evidence that major academic institutions are implementing steps to limit and reconcile potential FCOI to minimize their impact on trial results, but nationwide data on this important subject are sparse (12,25). Notwithstanding the belief that FCOI declaration is trending in the right direction, a significant proportion of drug and device trials

still are conducted in nonacademic settings, often by stand-alone research organizations with the aid of clinical research organizations, with approval from multi-institutional institutional review boards that potentially can bypass the rigor of an academic institutional review board. This trend is thought to have resulted from the expense and difficulties encountered with conducting clinical research in academic institutes with layers of bureaucracy.

Given the financial imperative for pharmaceutical and device companies to be profitable, it is essential to strengthen systems such as trial registration and reporting of financial disclosures to increase transparency in medical research. Because the cost of developing a single successful drug is nearly \$1.5 billion and the logistics of patient recruitment and follow-up are increasingly challenging, government funding cannot be expected to be a substitute for industry-sponsored trials (26). Thus, it is no surprise that up to 62% of clinical drug trials now are funded by the pharmaceutical industry (27). Although this industry-academia collaboration has produced unprecedented therapeutic and diagnostic tools, efforts to understand the impact of potential biases and addressing them are essential. Although our findings support the notion that FCOI do not affect the reporting of positive outcomes in pivotal cardiovascular trials, further investigation into whether these findings hold true in specific trial designs, including drug trials, device trials, and placebo-controlled trials, is of interest.

Despite the rigorous data extraction, the results of our study are determined on the basis of self-declared FCOI. Although reassuring, this may represent the tip of the iceberg, because a recent study suggests significant underreporting of FCOI by guideline authors (28). We understand that the study's reliance on self-report of FCOI is a limitation. Although imperfect, this method is used widely and is most practical. However, this approach could lead to misclassification, the extent of which is uncertain. We acknowledge that because many FCOI situations may not have been reported, this study has limited applicability to policy making, but further research may provide interesting information at a granular level. In addition, the complete absence of an FCOI in several industry-sponsored trials is surprising, but potentially can be explained by research funding alone not being included as a significant FCOI. The potential impact of publication bias also is difficult to assess and overcome and could have impacted the results of our study. We believe that studies with null findings would have been the most likely to have gone unregistered or unpublished, which would bias our findings toward the null hypothesis, limiting the impact on our conclusions. The true impact of mandatory trial registration on ClinicalTrials.gov on publication bias will become available in the ensuing years. The current trends suggest that compared with 2004 through 2007, the number of trials registered on ClinicalTrials.gov between 2007 and 2010 has increased significantly, with fewer missing data elements. However, most

trials being registered on ClinicalTrials.gov are small, with fewer than 100 patients (29). Additionally, we limited our study to the top 3 general medical journals for practical reasons. The potential impact of casting an even wider net and including articles from other cardiovascular journals is unknown. We believe that this field currently is in a state of active evolution, and further steps are needed to ensure complete declaration of authors' FCOI. In addition, FCOI declaration alone probably does not eliminate potential or perceived problems stemming from FCOI, but represents an important first step in eradicating their impact (30). Recently, there has been recognition of the potential impact of lecturers' and physicians' FCOI on medical students' education and future practice (31).

Conclusions

Our findings suggest no significant influence of reported FCOI on the likelihood of a trial having favorable results. However, current strategies for reporting of FCOI are in a state of evolution and require uniform implementation. An effective but ongoing surveillance and standardization of procedures at the individual and institutional level, as suggested by the Institute of Medicine, is required to address this phenomenon.

Reprints requests and correspondence: Dr. Michael E. Farkouh, The Cardiovascular Institute, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1074, New York, New York 10029. E-mail: Michael.Farkouh@mssm.edu.

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Key Words: cardiovascular ■ clinical trial ■ conflicts of interest ■ financial ■ industry ■ randomized controlled trials.