Reported Outcomes in Major Cardiovascular Clinical Trials Funded by For-Profit and Not-for-Profit Organizations: 2000-2005

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Surveys of randomized trials published between 1990 and 2000 raised awareness in the medical community that trials funded by for-profit organizations were more likely to report positive findings than those funded by not-for-profit organizations. As a group, these surveys raised questions regarding the design and conduct of industry-funded clinical trials as well as ethical concerns about potential violations of clinical equipoise. Partly in response to these concerns, recommendations have been made to improve academic oversight in industry-sponsored research and to ensure registration and publication of all clinical trials.

Whether this recognition has affected contemporary clinical trials is unknown. To address this question, we surveyed reported outcomes in high-impact cardiovascular clinical trials published between 2000 and 2005 in Jama, The Lancet, and the New England Journal of Medicine, stratifying our analysis according to whether the trial was funded by for-profit or not-for-profit organizations. By focusing on manuscripts published in these 3 journals, we were able to limit our analysis to trials considered to be of high quality on the basis of prior rigorous peer and editorial review. We focused on trials of cardiovascular medicine because they are common, represent an area of considerable public health importance, and are almost equally funded by for-profit and not-for-profit entities. As a substantial number of cardiovascular clinical trials are funded jointly by for-profit and not-for-profit organizations, we were afforded the additional opportunity to address outcomes in the setting of these cost-sharing clinical trials. We also sought to evaluate reported outcomes among trials that used surrogate vs clinical end points.

Context In surveys based on data available prior to 2000, clinical trials funded by for-profit organizations appeared more likely to report positive findings than those funded by not-for-profit organizations. Whether this situation has changed over the past 5 years or whether similar effects are present among jointly funded trials is unknown.

Objective To determine in contemporary randomized cardiovascular trials the association between funding source and the likelihood of reporting positive findings.


Main Outcome Measure The proportion of trials favoring newer treatments over the standard of care was evaluated by funding source.

Results Of the 324 superiority trials, 21 cited no funding source. Of the 104 trials funded solely by not-for-profit organizations, 51 (49%) reported evidence significantly favoring newer treatments over the standard of care, whereas 53 (51%) did not (P=.80). By contrast, 92 (67.2%) of 137 trials funded solely by for-profit organizations favored newer treatments over standard of care (P<.001). Among 62 jointly funded trials, 35 (56.5%), an intermediate proportion, favored newer treatments. For 205 randomized trials evaluating drugs, the proportions favoring newer treatments were 39.5%, not-for-profit; 54.4%, jointly funded; and 65.5%, for-profit trials (P for trend across groups=.002). For the 39 randomized trials evaluating cardiovascular devices, the proportions favoring newer treatments were 50.0%, not-for-profit; 69.2%, jointly funded; and 82.4%, for-profit trials (P for trend across groups=.07). Regardless of funding source, trials using surrogate end points, such as quantitative angiography, intravascular ultrasound, plasma biomarkers, and functional measures were more likely to report positive findings (67%) than trials using clinical end points (54.1%; P=.02).

Conclusions Recent cardiovascular trials funded by for-profit organizations are more likely to report positive findings than trials funded by not-for-profit organizations, as are trials using surrogate rather than clinical end points. Trials jointly funded by not-for-profit and for-profit organizations appear to report positive findings at a rate approximately midway between rates observed in trials supported solely by one or the other of these entities.

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METHODS

We evaluated a consecutive series of 349 randomized trials related to cardiovascular disease prevention and the Divisions of Preventive Medicine and Cardiology, Brigham and Women’s Hospital (Dr Ridker), and the Harvard Medical School (Dr Ridker and Mr Torres), Boston, Mass.

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circular medicine that were published between January 1, 2000, and July 30, 2005, in 3 prominent medical journals, JAMA, The Lancet, and the New England Journal of Medicine. Trials were initially identified using the search term cardiovascular diseases in PubMed/National Library of Medicine, limiting the search to human clinical trials. Trials were included in this analysis if they represented the primary report of the trial itself or were a major secondary report based on additional end points that could be critically evaluated on the basis of the randomization process. Reports were not included if they used the trial apparatus primarily as a prospective cohort or if the reported analyses were not fully dependent on the randomized interventions.

Following a methodology analogous to that used in prior investigations, one of us (P.M.R.) reviewed each clinical trial unaware of the funding source and scored the reported primary study end point on a 7-point ordinal scale designed to address both statistical significance and magnitude of effect: 1 indicated that the standard of care (SOC) was significantly better and highly preferred; 2, the SOC was significantly better and moderately preferred; 3, the SOC was nonsignificantly better; 4, the SOC and newer treatment were equivalent; 5, the newer treatment was nonsignificantly better; 6, the newer treatment was significantly better and moderately preferred; and 7, the newer treatment was significantly better and highly preferred. Trials were further evaluated according to study design (superiority trials vs noninferiority, equivalence, and safety trials), sample size, number of sites (single center vs multicenter), use of clinical or surrogate end points and whether the treatment of interest was a drug, a device, a patient-based behavioral intervention, or a novel medical or surgical procedure.

Simultaneous with this process, one of us (J.T.) reviewed each publication unaware of trial outcome and sought information regarding funding sources, categorizing trials into 1 of 4 groups: those financed exclusively by federal, state, or other not-for-profit foundations (not-for-profit trials); those financed exclusively by for-profit pharmaceutical or device manufacturers (for-profit trials); those financed jointly (not-for-profit and for-profit); and those for which no source of funding was provided. For the purpose of these analyses, trials financed in their entirety by federal, state, or foundation support for which drug or devices were donated without charge were considered not-for-profit trials.

Table 1. Characteristics of the 324 Superiority Trials Included in the Final Analysis, According to Funding Source

<table>
<thead>
<tr>
<th>Intervention, No. (%)</th>
<th>Not-for-Profit (n = 104)</th>
<th>Not-for-Profit and For-Profit (n = 62)</th>
<th>For-Profit (n = 137)</th>
<th>None Cited (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>42 (40.4)</td>
<td>40 (64.5)</td>
<td>112 (81.8)</td>
<td>11 (52.4)</td>
</tr>
<tr>
<td>Device</td>
<td>7 (6.7)</td>
<td>7 (11.3)</td>
<td>16 (11.7)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Drug or device</td>
<td>1 (1.0)</td>
<td>6 (9.7)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other†</td>
<td>54 (51.9)</td>
<td>9 (14.5)</td>
<td>8 (5.8)</td>
<td>9 (42.9)</td>
</tr>
<tr>
<td>End point, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>55 (52.8)</td>
<td>44 (71.0)</td>
<td>96 (70.1)</td>
<td>14 (66.7)</td>
</tr>
<tr>
<td>Surrogate</td>
<td>49 (47.1)</td>
<td>18 (29.0)</td>
<td>41 (29.9)</td>
<td>7 (33.3)</td>
</tr>
</tbody>
</table>


*Percentages may not sum to 100 due to rounding.
†Trials in this category were largely of behavioral, dietary, procedural, or nondevice surgical interventions.

To limit the potential for bias and subjectivity in the scoring of trial outcomes, we compared funding sources after regrouping all trials into 1 of 2 categories, those for which there was clear evidence of a statistical benefit in favor of the newer treatment (scores of 6 or 7) and those for which no statistical evidence of benefit was observed (scores of 1-5). We used the binomial distribution to evaluate whether the number of positive trials observed within a given funding group deviated significantly from a probability of 50%. Tests for trend were used to compare the proportion of trials significantly favoring newer treatments across funding groups (not-for-profit trials, jointly funded trials, and for-profit trials). On an a priori basis, we performed prespecified subgroup analyses among trials using clinical rather than surrogate end points and on the basis of whether the treatment was a drug or device. All analyses were performed using STATA release 8.0 (StataCorp, College Station, Tex). P < .05 was considered statistically significant; all P values were 2 sided.

RESULTS

Of the 349 trials evaluated, 109 (31%) were financed exclusively by for-profit organizations, 153 (44%) were financed exclusively by either for-profit pharmaceutical or device manufacturers, 66 (19%) were funded jointly by for-profit and not-for-profit organizations, and 21 (6%) noted no source of funding. Trials that did not disclose a funding source almost exclusively evaluated behavioral, procedural, dietary, or generic interventions. Three hundred twenty-four trials (93%) were designed to address superiority between the therapies under consideration and form the basis for our primary analyses, whereas 15 trials (4%) were designed to address equivalence or noninferiority and 10 trials (3%) were designed to address safety.

Characteristics of the 324 superiority trials evaluated in the primary analyses are shown in Table 1 according to funding source. Studies funded by for-profit...
organizations tended to have larger median sample size, were less likely
to use surrogate end points, and more likely
to be multicentered than were studies
funded by not-for-profit organizations.

Overall, 190 (58.6%) of the 324 su-
periority trials reported evidence sig-
ificantly favoring newer treatments,
while 112 (34.6%) reported no signifi-
cant difference between therapies, and
22 (6.8%) reported evidence signifi-
cantly favoring SOC. These propor-
tions, however, varied in analyses strat-
ified by funding source.

Among not-for-profit trials, 51 (49%)
of 104 reported evidence significantly
favoring newer treatments, whereas 53
(51%) were either null or significantly
favored SOC (P = .80). By contrast,
among for-profit trials, 92 (67.2%) of
137 reported evidence significantly fa-
vor ing newer treatments with 45
(32.8%) reporting null data or data fa-
vor ing SOC (P < .001). The propor-
tion of trials significantly favoring new
 treatments for studies jointly funded by
for-profit and not-for-profit organi-
sations was approximately midway be-
tween these 2 values (56.5%). In com-
parisons across groups, the difference
in the proportions of positive findings
among not-for-profit trials, jointly
funded trials (not-for-profit and for-
profit), and for-profit trials was statis-
tically significant (Table 2; P = .005).

For randomized trials evaluating
drugs, the proportions favoring newer
agents were 39.5% for not-for-profit,
54.4% for jointly sponsored, and
65.5% for for-profit trials (P for trend
across groups = .002). The greatest dis-
crepancy between not-for-profit and for-
profit trials in terms of the proportion sig-
nificantly favoring newer therapies over
SOC was observed among device trials.

In this setting, 4 (50.0%) of 8 device trials
funded by not-for-profit entities were
positive compared with 9 (69.2%) of 13
funded jointly by not-for-profit and for-
profit entities, and 14 (82.4%) of 17 trials
funded by for-profit entities (P for trend
across groups = .07).

Regardless of funding source, clinical
trials using surrogate end points such as
intravascular ultrasound, quantitative
angiography, plasma biomarkers, and
functional measures were more likely to
report positive findings (67.0%) than
were clinical trials using clinical end
points (54.1%; P = .02). Of interest, and
as shown in Table 1, the use of surro-
gate end points was more prevalent
among not-for-profit trials than among
for-profit trials. To avoid potential con-
 founding on this basis, we also analyzed
separately only those trials using hard
clinical end points. As also shown in
Table 2, among such hard end-point
trials, the proportions favoring newer
treatments were 34.6% for not-for-
profit, 54.6% for jointly funded, and
66.7% for for-profit trials (P for trend
across groups <.001).

Of the original 349 trials evaluated, 15
were specifically designed as noninferi-
 ory trials of which 13 (86.6%) re-
sulted in an outcome consistent with
noninferiority. All but 3 of these trials
were funded in their entirety by for-
profit organizations.

One of us (P.M.R.) was the primary
author or coauthor on 4 of the trials in-
cluded in the current evaluation. Two
of these favored newer treatments, 1
funded by a pharmaceutical company
using a surrogate end point and 1
funded by federal sources using a clin-
ical end point. Two others, funded by
federal sources using clinical end points,
were null.

COMMENT
In this survey of 324 consecutive car-
diovascular clinical trials published in
JAMA, The Lancet, and the New England
Journal of Medicine between 2000 and
2005, we found that those funded by
for-profit organizations were signifi-
cantly more likely to report positive
findings than those funded by not-for-
profit organizations. Furthermore, we
observed that trials jointly sponsored
by for-profit and not-for-profit organi-
sations reported positive findings at a
rate approximately midway between
rates observed in trials supported solely
by 1 or the other of these entities.

As suggested in surveys of random-
ized trials published prior to 2000,1-8
the current data appear to show that
incentives surrounding for-profit
organizations have the potential to in-
fluence clinical trial outcomes. Previous
attempts to explain this phenomenon
have focused largely on design bias,
terpretation bias, data suppression,
and differential data quality.9-11,14

However, with regard to trial design
bias, the direction of effect is not al-
ways predictable. Among studies re-
viewed herein, at least 2 major for-
profit trials25,26 reported significant
evidence of superiority favoring a com-
 peting manufacturer’s innovation. For
example, among 4809 patients ran-
 domized in a noninferiority trial compar-
ing tirofiban to abciximab in the setting of
percutaneous coronary intervention,
abciximab was found to be statistically su-
 perior despite the trial being funded by
the manufacturer of tirofiban.25 Simi-
larly, among 4162 patients with acute
 coronary syndrome randomized in a
noninferiority trial comparing pravasta-
tin to atorvastatin, atorvastatin was
found to be statistically superior de-
spite the trial being funded by the manu-
 facturer of pravastatin.26

With regard to author interpretation
bias and limits on publication, it is pos-
sible that null or even adverse results
from for-profit trials may be marginalized or
suppressed in the clinical literature.8,11
Indeed, suspicion of adverse cardiovas-
cular event suppression has recently
been raised in a major randomized trial
comparing rofecoxib to naproxen among patients with rheumatoid arthritis.32 If pervasive, such effects would be highly problematic for the interpretation of published trials. Although our study design cannot address this issue directly, we believe recently adopted requirements for study registration is an important first step toward full publication of all clinical trial results, regardless of outcome.18

We think it unlikely that systematic differences between trials in terms of quality would have affected our results. By limiting our analysis to manuscripts published in JAMA, The Lancet, and the New England Journal of Medicine, all of the trials reviewed herein can be considered “high quality” based on journal acceptance after a rigorous peer review and editorial review process. It is also uncertain as to what direction any such bias might actually make in terms of reported study outcomes; in our survey of cardiovascular trials published between 2000 and 2005, those funded by for-profit organizations tended to have greater sample size, were more likely to be multicentered, and less likely to use surrogate end points, all characteristics typically associated with high quality.

Beyond these traditional concerns, we believe there are additional issues that help to explain, in part, the observed results. For example, when the first trial report of a truly novel therapy is null or negative, it becomes less likely that any funding source will support subsequent studies. On the other hand, when the first trial of a truly novel therapy is positive, the likelihood of further trials is increased. These subsequent trials understandably and perhaps appropriately are more likely to be funded by for-profit organizations. Furthermore, although both for-profit and not-for-profit organizations are interested in the development of truly novel therapies, for-profit organizations are also commonly interested in evaluating proven therapeutic agents or devices in previously understudied patient populations (such as the elderly or in women) or in settings with different entry criterion than specified in previous trials (for example a lower baseline lipid value, ejection fraction, or arrhythmia hazard).

Although the probability of success for such trials is likely to be greater on an a priori basis compared with trials evaluating entirely novel therapies, such trials can be nevertheless useful for the broader application of medical innovations to clinical practice. By way of example, although the 4S trial of simvastatin in secondary prevention established the clinical efficacy of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors as agents for the treatment of cardiovascular disease in high-risk secondary prevention,28 findings from the subsequent CARE,29 LIPID,30 WOSCOPS,31 AFCAPS/TexCAPS,32 HPS,33 ASCOT,34 PROVE-IT,35 and TNT36 trials extended data for statins into other patient groups.

Similarly, accrual of evidence from multiple trials involving antiplatelet and anticoagulant agents in acute ischemia, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers in congestive heart failure, and drug eluting stents in percutaneous coronary revascularization was required for acceptance of each of these innovations. Moreover, replication is a typical requirement for US Food and Drug Administration approval and for the development of formal evidence-based treatment guidelines. Thus, part of the observed results may reflect the replication that is required in contemporary practice, at least with regard to phase 3 clinical trials. That being said, we also observed in our data instances in which a nonnovel therapeutic agent already in common use did not prove to be effective in rigorous evaluation. Most, but not all, of these latter trials were funded by not-for-profit organizations.

Prior work has suggested that for-profit trials directed and coordinated by recognized academic coordinating centers tend to report positive findings somewhat less often than those for which academic coordination is less evident.7-10 Although not formally evaluated, we noted similar effects in our survey. However, we also observed that despite the relative independence, trials coordinated by recognized academic centers may nevertheless be under pressure to present results in the best possible light, in particular emphasizing favorable subgroup analyses when an overall neutral effect was observed for the primary endpoint. Two such examples of this effect have been reported in the very recent cardiovascular literature suggesting that this is an ongoing issue for investigators.36,37 We also noted that academic direction and oversight of for-profit trials does not always guarantee that the best possible study design available is used. As an example of this issue, a recent academically directed for-profit trial evaluating high-dose statin therapy as a method to achieve atherosclerotic regression was undertaken without an active control group.38

Limitations of our analysis should be considered. First, we limited our evaluation to contemporary cardiovascular trials and thus these data may not generalize to other fields of medical research. We note, however, that evaluations of clinical trials largely published prior to 2000 in several noncardiovascular fields1-9 also suggest that industry-funded research is more likely than not to report favorable results. Second, because we only evaluated trials published in 3 prominent clinical journals, it is possible that publication bias could account for part of our observations. We believe this unlikely for several reasons. First, in prior studies of industry influence that addressed all publications in a given field, almost identical findings have been observed.1,4,7,8 Second, of phase 3 cardiovascular clinical trial reports reviewed as a pilot for this project, those that did not appear in 1 of the 3 journals reviewed herein were very often secondary reports that would not have qualified for study inclusion.

Third, contrary to the often-voiced concern that major journals do not report null studies, we found that a substantial proportion of the cardiovascular trials published in JAMA, The Lancet, and the New England Journal of Medicine between 2000 and 2005 reported either no significant difference between therapies (34.6%) or a significant difference favoring SOC over newer treat-
CARDIOVASCULAR TRIAL OUTCOME BY FUNDING STATUS


diovascular disease and have served as a consultant to several of the above-listed entities. None of these entities played any role whatsoever in the design, interpretation, or drafting of the manuscript. I regret making this omission.

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CORRECTIONS

Incorrect Data and Statement: In the Editorial entitled “The Asymptomatic Hernia: If It’s Not Broken, Don’t Fix It” published in the January 18, 2006, issue of JAMA (2006;295:328-329), there was incorrect reporting of data and an incorrect statement. In the sentence beginning “The risk of hernia incarceration was low....” on page 328, the data point reported as 0.03% should have read 0.3%. Also, in the sentence beginning “In counseling patients with hernias....” on page 329, the statement reading “older, male veterans in Veterans Administration medical centers” should have read “older men in community and academic medical centers.”

Incorrect Value: In the Original Contribution entitled “Watchful Waiting vs Re-pair of Inguinal Hernia in Minimally Symptomatic Men: A Randomized Clinical Trial” published in the January 18, 2006, issue of JAMA (2006;295:285-292), a P value was incorrectly reported. On page 285, in the “Results” section of the Abstract, the value reported as P=0.62 for pain limiting activities should instead have been reported as P=0.06; the corresponding value should also have been reported as P=0.06 in the first paragraph on page 289.

Incomplete Financial Disclosure: In the Original Contribution entitled “Reported Outcomes in Major Cardiovascular Clinical Trials Funded by For-Profit and Not-for-Profit Organizations: 2000-2005” published in the May 17, 2006, issue of JAMA (2006;295:2270-2274), financial disclosures were omitted. Dr Ridker reports that he has received research funding and research support from the National Heart, Lung, and Blood Institute, the Doris Duke Charitable Foundation, the Leucaq Foundation, the Donald W. Reynolds Foundation, the American Heart Association, the James and Polly Amnberg La Vea Charitable Trusts, AstraZeneca, Bayer, Bristol-Myers Squibb, Dade-Behring, Novartis, Pharmacia, Roche, Sanofi-Aventis, and Variofigenics. Dr Ridker reports being listed as a coinventor on patents held by the Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and has served as a consultant to Schering-Plough, Sanofi-Aventis, AstraZeneca, Isis Pharmaceuticals, Dade-Behring, and Interleukin Genetics. Mr Torres reported no financial disclosures.

Errors in Tables: In the Original Contribution entitled “Effect of Blood Pressure Lowering and Antihypertensive Drug Class on Progression of Hypertensive Kidney Disease: Results From the AASK Trial” published in the November 20, 2002, issue of JAMA (2002;288:2421-2431), there were errors in 2 tables. On pages 2424 and 2425, all rows labeled “mean (SE)” in Tables 1 and 2 should have been labeled “mean (SD).” On page 2425, there were small errors in Table 2 (relative % errors from 0%-1.7%); the corrected Table 2 appears below. There are no errors in the text describing the tables or in the interpretation of the results.

Table 2. Antihypertensive Therapy and Blood Pressure During Follow-up

<table>
<thead>
<tr>
<th>Blood Pressure Goal</th>
<th>Interventions</th>
<th>Drug Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pressure, mean (SD), mm Hg†</td>
<td>Lower (8)</td>
<td>Usual (7)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg†</td>
<td>128 (1)</td>
<td>141 (1)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg†</td>
<td>78 (8)</td>
<td>85 (7)</td>
</tr>
<tr>
<td>Visits with mean arterial pressure in goal, %‡</td>
<td>51.6</td>
<td>39.2</td>
</tr>
<tr>
<td>Visits with mean arterial pressure of &lt;107 mm Hg, %‡</td>
<td>81.3</td>
<td>64.1</td>
</tr>
<tr>
<td>Visits with systolic/diastolic blood pressure of &lt;140/90, %‡</td>
<td>68.5</td>
<td>35.3</td>
</tr>
<tr>
<td>Visits with systolic/diastolic blood pressure of &lt;125/75, %‡</td>
<td>24.6</td>
<td>6.1</td>
</tr>
<tr>
<td>Visits with assigned primary drug, %‡</td>
<td>82.7</td>
<td>80.9</td>
</tr>
<tr>
<td>Visits with high dose, %‡</td>
<td>63.6</td>
<td>45.4</td>
</tr>
<tr>
<td>Visits with crossover to 1 of other 2 classes, %‡</td>
<td>3.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Total No. of drug classes, mean (SD)‡</td>
<td>3.07 (1.1)</td>
<td>2.42 (1.17)</td>
</tr>
<tr>
<td>Visits with level 2 (furosemide), %‡</td>
<td>83.2</td>
<td>67.4</td>
</tr>
<tr>
<td>Visits with level 3 (doxazosin), %‡</td>
<td>55.8</td>
<td>35.0</td>
</tr>
<tr>
<td>Visits with level 4 (clonidine), %‡</td>
<td>41.0</td>
<td>27.5</td>
</tr>
<tr>
<td>Visits with level 5 (minoxidil), %‡</td>
<td>35.4</td>
<td>22.9</td>
</tr>
<tr>
<td>Protocol visits held, %</td>
<td>90.3</td>
<td>87.4</td>
</tr>
<tr>
<td>GFRs performed, %</td>
<td>83.2</td>
<td>80.0</td>
</tr>
</tbody>
</table>

*GFR indicates glomerular filtration rate.
†Blood pressure summaries include visits after 3 months and exclude GFR visits.
‡Medication summaries include all visits starting at month 1 and are censored on September 22, 2000, for the calcium channel blocker (amlodipine) group only.

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