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The Cost of Innovation and Evidence in Cardiac Surgery

[AQ1]**Joanna Chikwe[1], MD, FRCS and Mario Gaudino[2], MD**

Abstract

This review summarizes a meta-analysis of 216 randomized trials of cardiovascular interventions performed during 2008 to 2019, according to the source of trial funding. The meta-analysis showed that on average the results of each trial would change significance if only five patients experienced different outcomes. Industry-sponsored trials were more likely to use composite end-points, non-inferiority designs, and twice as likely as non-industry trials to report results favoring the device arm. Over 80% of industry trials used reporting strategies or "spin" suggesting the device arm was advantageous versus fewer than half of non-industry trials. The review discusses the implications of these findings.

Keywords

transcatheter aortic valve replacement, transcatheter mitral valve repair, percutaneous coronary intervention, randomized clinical trials

[AQ2][AQ3]The adoption of transcatheter aortic valve replacement for aortic stenosis illustrates both the benefits and challenges of device-driven innovation in contemporary cardiovascular care. Four multi-center randomized controlled trials (Partner 1, Partner 2, Partner 3, and the CoreValve pivotal trial), and patient and provider enthusiasm for a non-surgical solution to surgical valve disease, combined to change the face of cardiac surgery in less than a decade. These well-designed and well-executed trials are examples of the highest quality evidence in our specialty. So how relevant is the fact that they, like many other such trials in cardiovascular intervention, were sponsored, designed, and run by manufacturers who had already invested millions of dollars in the development and commercialization of the devices favored by the trial results?

To address this question, we analyzed all randomized trials of cardiovascular interventions published between 2008 and 2019, including coronary, structural heart, and vascular interventions.[1] We compared study design, reporting, and discrepant outcomes between the 53% of trials that reported industry support, and those that did not (Table 1). The most surprizing finding was quite how fragile the outcomes of these important studies were. The findings of a randomized trial can be considered robust if it would take a large number of patients experiencing a different outcome, for example switching from mortality to a survival, to change a statistically significant finding to no longer statistically significant. In four of the trials that we analyzed, it would only have required one patient to experience a different outcome for the trial to switch statistical significance. The median for all cardiovascular interventional trials analyzed was only five patients to change the outcome, which was similar for commercial and non-commercially sponsored trials. The finding that the highest quality evidence in our specialty hinges on such fragile findings is deeply concerning. Three main factors determine whether the results of a trial are robust or not: the number of patients randomized, the event rate, and the difference between event rates in each arm. Importantly, there are no easy fixes in cardiovascular intervention trials since the endpoints of greatest interest (i.e., death and stroke) are relatively infrequent, and in most cases it is not feasible to fund or conduct trials that are able to recruit patients in sufficiently large numbers to address that. Composite endpoints, in which additional outcomes such as repeat hospitalization or reintervention are combined to increase event rates, can increase statistical power and decrease the number of patients needed for randomization, but can also obscure differences in important, rare outcomes such as mortality. Our analysis showed that industry sponsored trials were more likely to use composite endpoints. Irrespective of whether the primary endpoint is composite, reporting the number of patients needed

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Table 1. Characteristics of Randomized Interventional Cardiovascular Trials[1].

Characteristic	Overall	Industry-funded (%)	Independent (%)	P-Value
Total number	216	115 (53.2)	101 (46.8)	NA
Non-inferiority design	45 (20.8)	30 (26.1)	15 (14.9)	0.04
Intention-to-treat	196 (90.7)	104 (90.4)	92 (91.1)	0.45
Composite primary endpoint	128 (59.3)	75 (65.2)	53 (52.5)	0.07
Number of patients, median (IQR)	502 (204, 1702)	800 (353, 2032)	302 (140, 788)	<0.001
Favorable outcome	123 (57.0)	74 (64.3)	49 (48.5)	0.02
Spin[a]	55 (65.5)[a]	29 (80.6)[a]	26 (54.2)[a]	0.02
Fragility index, median (IQR)[b]	62[b]	34 (54.8)[b]	28 (45.2)[b]	NA

[a]82 trials with non-significant difference in primary outcome were evaluated for positive spin in reporting
[b]62 trials with significant difference in primary outcome were evaluated for the number of patients with a different outcome that would change result to non-significant (fragility index)

to change a trial outcome may be as helpful as reporting the number needed to treat, when summarizing the impact of study findings.

We found that cardiovascular industry-sponsored trials were significantly more likely to report findings favoring the device arm than trials without industry funding, and we identified several potential mechanisms. Firstly, industry trials were larger, more likely to use composite endpoints and a non-inferiority design compared to non-industry sponsored trials, and more than twice as likely to show a statistically significant difference favoring the device arm. Secondly, in those trials where no statistically significant difference was shown, more than 80% of industry trials used reporting strategies or "spin" to suggest the device arm was advantageous, compared to fewer than half of non-industry trials. We also observed major discrepancies between published and planned primary endpoints as registered on ClinicalTrials.gov in many trials.

Our findings that the published results of randomized controlled trials in cardiovascular intervention are mostly fragile, often biased towards industry sponsors, and frequently inconsistent with results registered at ClinicalTrials.gov have potential implications for clinical research, guidelines, and practice. There is an urgent need for robust randomized trials designed to answer important clinical questions beyond pre-market approval, in patient populations and practice settings that are underserved by the existing evidence base. This will require strategic direction from major funding bodies and specialty leadership. At the very least this underlines the importance of high-quality, independent clinical registries in providing complementary comparative outcomes data that is adequately powered to detect differences in important clinical endpoints and patient populations, from real-world practice.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Joanna Chikwe MD and Mario Gaudino MD report no relevant disclosures. Joanna Chikwe notes that Cedars-Sinai Medical Center receives honoraria from Edwards-Lifesciences and Medtronic for speaker and consulting activity.

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