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CONTEMPORARY REVIEW

Funding of Studies Supporting IA Guideline Recommendations in Cardiovascular Medicine—A Systematic Review

Emily P. Zeitler, MD, MHS; Alessio Gasperetti, MD; Shayne E. Dodge, BS; Lauren B. Cooper, MD, MHS; Aaron V. Kaplan, MD

ABSTRACT: Each guideline recommendation from the American Heart Association and the American College of Cardiology includes an indication of the level of supporting evidence and the associated strength of recommendation with "IA" recommendations representing those with the highest quality supporting evidence and the least amount of uncertainty for benefit. In this analysis, study type and funding sources were systematically tabulated across these IA guideline recommendations over the past 5 years. Nearly half of studies supporting IA guideline recommendations were randomized controlled trials (45%). Overall, about one third of studies supporting IA recommendations were publicly funded (34.9%) with slightly more funded through industry sources (43.5%). Funding sources varied based on the type of intervention being studied with randomized controlled trials of device, diagnostic, and pharmacological interventions reflecting predominantly industry-funded studies. Over time, studies supporting IA cardiology guideline are funded by industry about twice as often as public sources. Thus, data of adequate quality to support cardiovascular guideline recommendations come from a variety of sources.

Key Words: guideline ■ randomized controlled trial ■ systematic review

American College of Cardiology and American Heart Association (ACC/AHA) guideline recommendations have a profound impact on the practice of cardiovascular medicine. Clinical guideline documents provide a rigorous review of the relevant literature and impart recommendations for clinical practice. As such, guideline documents act as a bridge between clinical research and clinical practice. For each clinical guideline recommendation, 2 related classifications are assigned: a Class of Recommendation and Level of Evidence. The class of each recommendation is reported from I to III. Class I indicates that the treatment or intervention is strongly recommended, and benefit far outweighs risk. Class III indicates that risk outweighs benefit, and the treatment or intervention should be avoided. The Level of Evidence reflects the quality of scientific evidence supporting the recommendation and is based on the type, quantity, and consistency of data from clinical trials and other sources. The highest level, "A," generally reflects evidence from more than one randomized controlled trial (RCT), meta-analyses of high quality RCTs, or one or more RCTs corroborated by high-quality registry studies. The lowest level of evidence, "C," reflects the consensus of expert opinion. Therefore, Class of Recommendation=I/Level of Evidence=A recommendations represent the strongest recommendations based on the highest quality evidence. In shorthand, these types of recommendations are generally referred to as "IA."

Guideline generation is performed under the aegis of professional societies, using a formal process to produce recommendations that are rigorous and free of bias. Guidelines are written by a committee of experts selected by professional societies, based on reputation and domain expertise. Relationships with industry

Correspondence to: Emily P. Zeitler, MD, MHS, Dartmouth-Hitchcock Medical Center, Geisel School of Medicine at Dartmouth, The Dartmouth Institute, 1 Medical Center Drive, Lebanon, NH 03756. E-mail: emily.p.zeitler@hitchcock.org

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Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
AHA	American Heart Association

are considered as one factor in the selection process but generally are not sufficient to disqualify participants, and any existing relationships with industry are reported in the guideline documents. Similarly, funding of clinical research itself is generally accepted as a potential source of bias; therefore, most scientific journals require funding disclosure as a prerequisite for publication. We performed a formal study to characterize funding of research supporting IA recommendations in ACC/AHA cardiovascular guidelines. Awareness of these funding sources is important for comprehensive understanding of the development of guideline recommendations and may have policy implications going forward.

METHODS

Although no review protocol exists for this analysis, the data that support the findings of this study are available from the corresponding author upon reasonable request. See Table S1 for accounting of adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.

Cohort Identification

Current AHA and ACC guidelines were identified as those posted on the ACC website as of April 5, 2019.[1] All clinical guidelines, focused updates, and special reports published over the prior 5 years (2014–2019), were systematically analyzed. Those documents with no IA recommendations were excluded including expert consensus documents, performance measures, historical statements, implementation strategies, and appropriateness criteria documents (Table).

Data Collection

All included ACC/AHA guidelines were reviewed, and IA recommendations were tabulated. Every IA recommendation was classified into 1 of 4 predetermined categories: (1) clinical behavior, (2) pharmacological, (3) device/invasive, and (4) diagnostic. When uncertainty existed about classification, a decision was made by consensus among the investigators.

For every identified IA recommendation, all supporting references listed were collected. Duplicates and those references identified as supporting more than one recommendation were included only once. Review papers were excluded. Prespecified characteristics of each supporting reference were abstracted and recorded in a single database. These characteristics included first author, year of publication, journal of publication, DOI, type of study (eg, RCT, meta-analysis, etc), funding source, type of funding disclosure, and number of patients included in the study. Funding sources were classified as (1) Publicly Funded—the study was supported by the National Institutes of Health or other entirely publicly funded institution (American or otherwise); (2) Funded by a Professional Society—the study was supported by a grant sponsored by a professional society (eg, European Society of Cardiology, ACC, AHA) without any direct industry ties; (3) Company Sponsored—the study was supported by the drug or device company whose product was being studied; (4) No Extramural Funding—investigators and authors reported no external funding; and (5) Funding not disclosed—no disclosure or statement of funding was retrieved. For the subset of RCTs, the number of subjects randomized was also tabulated.

Type of funding disclosure was defined as "Fully Disclosed" if the funding source was clearly reported on the study article, "Partially Disclosed" if the funding source was not reported in the article but was identified after review of additional/supplementary materials (eg, clinicaltrials.gov, online appendices, etc), and as "Not Disclosed" if it was not possible to identify a funding source.

Data collection was performed by a single investigator (A.G.) and later validated by a second investigator (E.P.Z.). Any differences between the investigators during data collection were resolved through negotiated consensus with a contingency that unresolved disagreements would be settled by the senior investigator.

Data Presentation

The distribution of funding sources was calculated by recommendation type in the overall cohort. This was repeated in the RCT subset. Next, based on publication date, the distribution of funding over time was reported in the RCT subset based on number of publications and then number of enrolled patients overall and by recommendation type.

Quality Assessment

In the development of cardiovascular guidelines, the weight given to various studies likely depends on the quality of the evidence presented, which is reflected in study design and presentation among other factors, so it was presumed that articles cited in support of IA recommendations would generally be of high quality. Furthermore, a quality assessment of each study was outside the scope of this analysis, but a subjective overall quality assessment on a sample of studies was

Table 1. Guidelines Characteristics

Guideline	First Author, Year	IA Recommendations (n)					Relevant References (n (%))					
		Total	Behavior	Drug	Device	Diagnostic	Total	Public	Society	Industry	None	NR
AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes	Amsterdam et al, 2014[2]	15	3	2	2	8	51	7 (14%)	0 (0%)	36 (70%)	2 (4%)	6 (12%)
AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation	January et al, 2014[3]	4	2	2	0	0	6	0 (0%)	1 (17%)	2 (33%)	1 (17%)	2 (33%)
AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease	Nishimura et al, 2014[4]	2	0	0	2	0	7	0 (0%)	1 (14%)	2 (29%)	0 (0%)	4 (57%)
ACC/AHA/HRS Guideline for the Management of Adult Patients with Supraventricular Tachycardia	Page et al, 2016[5]	1	0	1	0	0	7	0 (0%)	0 (0%)	5 (71%)	0 (0%)	2 (29%)
ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease	Levine et al, 2016[17]	3	0	3	0	0	4	1 (25%)	0 (0%)	3 (75%)	0 (0%)	0 (0%)
AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease	Gerhard-Herman et al, 2017[6]	11	4	3	4	0	52	18 (35%)	1 (2%)	20 (38%)	8 (15%)	5 (10%)
AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease	Nishimura et al, 2017[7]	4	1	1	2	0	12	2 (17%)	1 (8%)	6 (50%)	0 (0%)	3 (25%)
ACC/AHA/HFSA Focused Update of the 2013 ACC Foundation/AHA Guideline for the Management of Heart Failure	Yancy et al, 2017[8]	6	0	3	0	3	38	14.37 (%)	0 (0%)	20 (52%)	1 (3%)	3 (8%)
AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death	Al-Khatib et al, 2018[9]	7	1	3	3	0	22	7 (32%)	0 (0%)	13 (59%)	2 (9%)	0 (0%)
ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults	Whelton et al, 2018[10]	17	10	6	0	1	44	26 (59%)	0 (0%)	8 (18%)	9 (21%)	1 (2%)
ACC/AHA/HRS Guideline on the Evaluation and Management of Patients with Bradycardia and Cardiac Conduction Delay	Kusumoto et al, 2018[11]	2	0	0	2	0	8	2 (25%)	2 (25%)	2 (25%)	2 (25%)	0 (0%)
AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol	Grundy et al, 2019[12]	10	6	4	0	0	24	7 (29%)	0 (0%)	13 (54%)	3 (13%)	1 (4%)
AHA/ACC Guideline for the Management of Adults with Congenital Heart Disease	Stout et al, 2019[13]	1	0	1	0	0	3	1 (33%)	0 (0%)	2 (67%)	0 (0%)	0 (0%)
ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease	Arnett et al, 2019[14]	11	8	3	0	0	61	34 (56%)	4 (6%)	15 (24%)	7 (12%)	1 (2%)

(*Continued*)

Table 1. Continued

Guideline	First Author, Year	IA Recommendations (n)						Relevant References (n (%))					
		Total	Behavior	Drug	Device	Diagnostic	Total	Public	Society	Industry	None	NR
AHA/ACC/HRS Focused Update of the 2014 AHA/ACC HRS Guideline for the Management of Patients with Atrial Fibrillation	January et al, 2019[15]	3	1	2	0	0	8	2 (25%)	1 (13%)	4 (50%)	1 (13%)	0 (0%)
Total		97	36	34	15	12	347	121 (34.9%)	11 (3.2%)	151 (43.5%)	36 (10.4%)	28 (8.0%)

AAPA indicates American Academy of Physician Assistants; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; ACVPR, American Association of Cardiovascular and Pulmonary Rehabilitation; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASPC, American Society for Preventive Cardiology; HRS, Heart Rhythm Society; NLA, National Lipid Association; NR, not reported; and PCNA, Preventive Cardiovascular Nurses Association.

conducted by 3 investigators (A.G., E.P.Z., and S.D.) that included a random selection of 10% of the RCT cohort and 10% of the non-RCT cohort. These general quality assessments were loosely based on methods of the Cochran Collaboration.[16] Fourteen quality assessment questions were generated (Table S2), and a general overall assessment of quality was assigned based on the answers to these questions and the reviewers' assessment of article quality: high, moderate, low, or very low. When there was disagreement between scores, the lowest score was recorded.

Statistical Analysis

All analyses were performed using the Jamovi project (2019), Jamovi (Version 0.9) (Computer Software). Continuous variables were expressed as mean±SD. Categorical variables were expressed as counts and percentage.

RESULTS

Guidelines and References Cohort

There were 19 AHA/ACC guideline documents published between 2014 and 2019, which included 15 documents with at least one IA recommendation (Table).[2–15,17–21] There were a total of 97 IA recommendations (median number of IA recommendations per guideline was 3 [interquartile range 1–8.5]) classified as follows: 36 (37.1%) clinical behavior, 34 (35.0%) pharmacological, 12 (12.4%) diagnostic, and 15 (15.5%) device/invasive.

Supporting these 97 IA recommendations, 439 references were identified with a median number of references per recommendation of 10 (interquartile range 3.5–43.5). After removing duplicates, data were collected from 347 supporting references of which 89 (25.6%) were observational studies, 19 (5.4%) single arm interventional trials, 162 (46.7%) RCTs, and 76 (22.2%) meta-analysis. Of note, meta-analyses were considered as a single reference rather than evaluating each reference included in the meta-analysis as a separate study.

Funding Source Analysis

Funding sources were assessed for all 347 unique references, and funding sources were fully disclosed in the article for 316 (91.0%) of these. There were no instances of disagreement between reviewers in classification of funding sources. In 3 cases (0.9%), additional funding sources were identified after analyzing supplementary sources; it was not possible to identify a funding source for 28 (8.1%) references.

Approximately one third of IA guideline-supporting references were publicly sponsored (121, 34.9%). Of

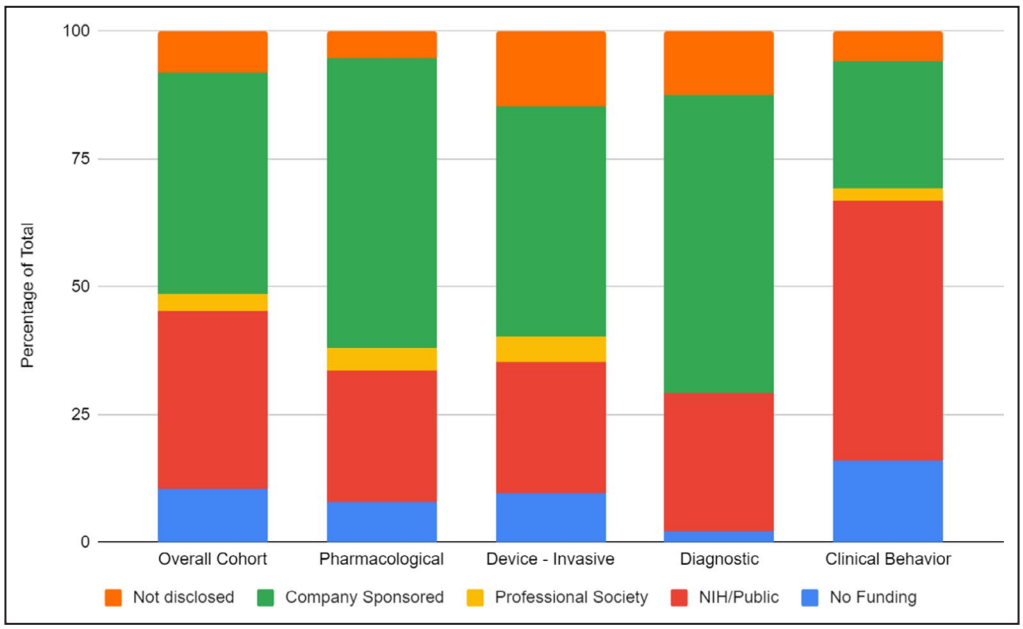

Figure 1. Distribution of funding sources for articles supporting IA recommendations in cardiovascular guideline documents 2014 to 2019 overall and by recommendation type.
NIH indicates National Institutes of Health.

the remaining references, 11 (3.2%) were sponsored by professional societies, 151 (43.5%) were industry sponsored, and 36 (10.4%) did not receive any extramural funding (Figure 1). When examined by recommendation type, the distribution of sponsorship was relatively similar across pharmacologic, device/invasive, and diagnostic studies whereas behavioral studies were disproportionately funded by public sources (25% versus 56.6%, 45.2%, and 58.3%, respectively).

Subgroup Analysis of Meta-Analyses

A total of 76 meta-analyses were cited as supportive evidence for IA guideline recommendations. As

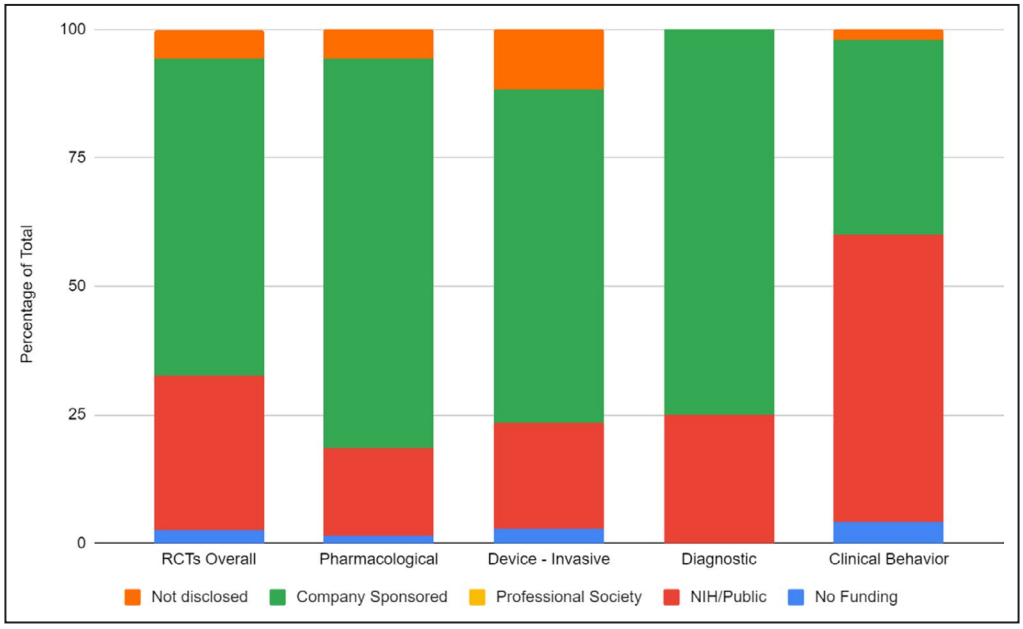

Figure 2. Distribution of funding sources for randomized controlled trial articles supporting IA recommendations in cardiovascular guideline documents 2014 to 2019 overall and by recommendation type.
There were no studies funded by professional societies in this cohort. NIH indicates National Institutes of Health; and RCTs, randomized controlled trials.

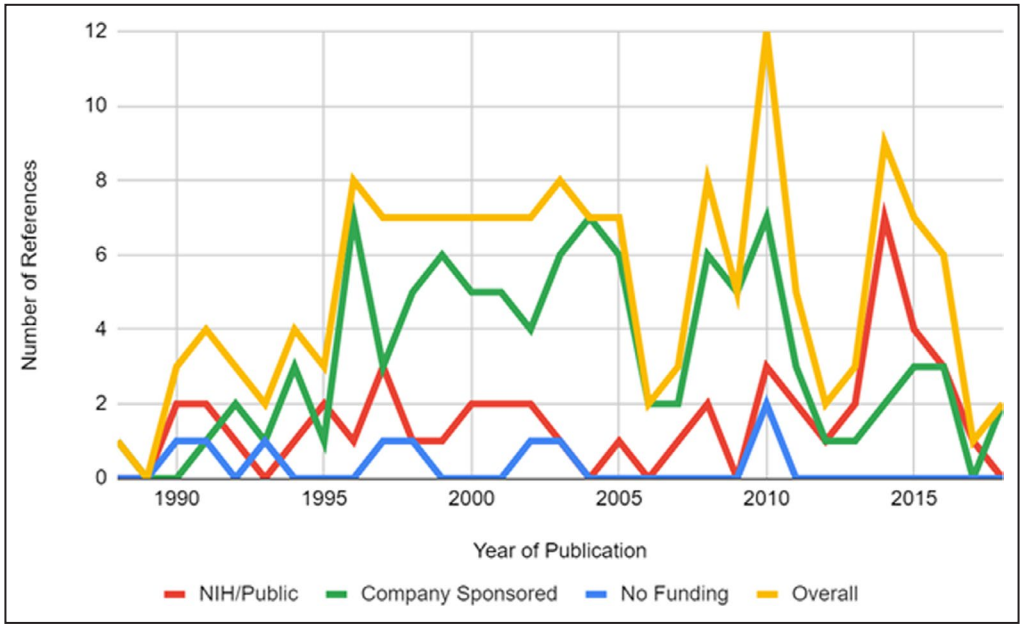

Figure 3. Randomized controlled trials (RCTs) supporting IA recommendations in cardiovascular guideline documents by funding source and year of publication over time.
NIH indicates National Institutes of Health.

noted previously, each of these were considered a single study. In the meta-analysis cohort, 41 supported behavioral recommendations (54%), 24 supported pharmacological recommendations (32%), 8 supported invasive/device recommendations (11%), and 3 supported diagnostic recommendations (4%). Sixty-seven of the 76 meta-analyses supporting IA recommendations came from 4 guideline documents: 2014 Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes (7/76, 9%), 2016 Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease (13/76, 13%), 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (20/76, 20%), and 2019 Guideline on the Primary Prevention of Cardiovascular Disease (27/76, 36%).

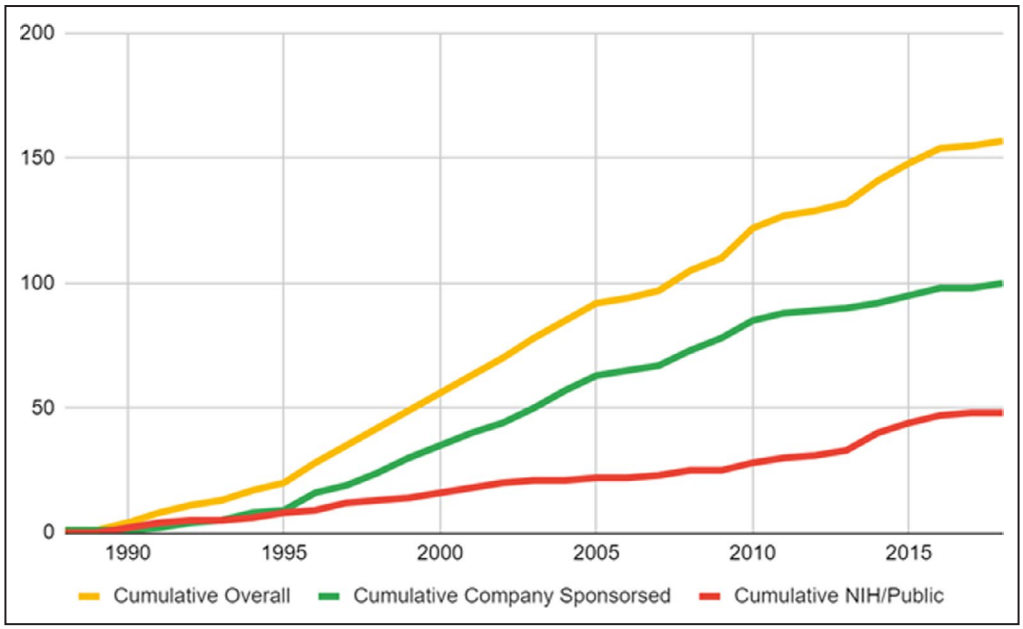

Figure 4. Cumulative randomized controlled trials (RCTs) over time supporting IA guideline recommendations by publication year and funding source.
NIH indicates National Institutes of Health.

The most common source of funding for meta-analyses was National Institutes of Health/public (n=42). Most of the remaining meta-analyses reported no funding (n=24). Few were funded by industry (n=4) or a research foundation (n=1) with the rest not reporting a funding source (n=5).

RCTs Subpopulation Analysis

A funding source analysis was performed in the subset of RCTs: 49 (30.2%) were publicly sponsored, 100 (61.7%) industry sponsored, and 4 (2.5%) reported no funding; in 9 (5.5%) RCTs no funding source was identified (Figure 2). RCTs in the clinical behavior category were more likely to be publicly funded than RCTs in other categories.

In the subgroup of RCTs, industry sponsorship accounted for nearly two thirds of the trials (61.7%). This funding source was more common in pharmacologic and diagnostic trials in which three quarters of RCTs were industry funded (76% and 75%, respectively). However, as with the overall cohort, about half of RCTs of clinical behavior interventions were funded publicly (56%) (Figure 2). Also striking is the difference in the proportion of studies with no extramural funding between the overall and RCT cohorts: 11.7% versus 2.5%, which is likely because of the high cost of an RCT.

Next, clinical trials supporting IA recommendations were organized according to publication date ranging from 1988 to 2018. The overall yearly range of RCT publications supporting IA guideline recommendations was 0 to 12 during this period. Within funding source categories, the range of cited RCT was 0 to 7 (Figure 3). When examined cumulatively, there was a steady accumulation of cited RCTs over time, and the ratio of publicly to industry funded RCTs was relatively constant around 1:2 by the late 1990s (Figure 4). A similar finding was found when the number of enrolled patients was examined (rather than the number of trials).

A notable difference in patient enrollment was observed based on the type of recommendation. RCTs supporting IA recommendations for diagnostic interventions were almost exclusively industry sponsored whereas the number of patients represented by RCTs of device/invasive interventions were more balanced between industry and public sponsorship. By enrollment, clinical behavior studies were predominantly publicly funded, and industry funding accounted for most patient enrollment in drug studies.

Quality Analysis

A random 10% sample of RCTs (n=17) and 10% sample of non-RCT (n=10) studies were generated and assessed for general quality. There were no discrepant quality assessments between reviewers that differed by more than one category. Among all studies, study quality was, on average, "high" based on a general absence of bias sources (Table S3). This was unchanged when examined by study type. When examined by funding source, the majority of studies funded through public and industry sources were assessed to have "high" quality. By chance, 5 studies included in this random sample were funded through other sources (ie, not public or industry sponsored), and quality was less consistent among this smaller group.

DISCUSSION

One of the primary goals in developing guidelines is to distill a body of evidence into recommendations for clinical practice. These recommendations have far-reaching impact on patient care and reimbursement by both government and private payers. Guideline recommendations classified as Class of Recommendation I, Level of Evidence A are those considered to have little uncertainty. We sought to examine the funding sources of the clinical studies used to support these guideline recommendations published over the past 5 years. Within our identified cohort, funding sources were disclosed in most studies (no funding disclosure: 8.1% in the overall cohort; 5.5% in the RCT only cohort) with the majority (78%) of nondisclosing studies having been published more than 10 years ago. This was an encouraging finding as it constitutes a critical component in the assessment of bias in specific investigations or when evaluating a body of evidence.

The funding source for a clinical trial does not a priori determine the quality of the investigation or the level of bias, but there is a heightened concern for potential bias of industry sponsored studies. This is important to recognize because evidence for new drugs and devices understandably largely emerges from industry sources in which commercial success is a driving force behind innovation and investigation. Because the vast majority of industry-sponsored RCTs within the reported cohort are focused on regulatory approval, they are subject to close regulatory oversight meant to compel study rigor and reduce bias.[22,23] Among other functions, this regulatory oversight includes a requirement for the public reporting of results.[24] Despite these safeguards, there remains an implicit hierarchy of evidence favoring publicly sponsored evidence. However, our findings challenge this hierarchy. Indeed, the frequent use of corporate sponsored studies to support IA guideline recommendation offers recognition by guideline committees as to the high quality of some corporate sponsored studies. Furthermore, formal quality assessment on a subset of studies supporting IA recommendations did not suggest differences in quality across funding sources.

In the case of these industry-sponsored investigations designed to answer regulatory questions, once

regulatory threshold has been met, trial infrastructure may be disassembled only to be reassembled when a new application, therapy, or population is investigated. Although this regulatory threshold is primarily relevant in industry-sponsored studies, the disassembly and reassembly problem applies to studies funded by various sources, and this paradigm has contributed to the rising cost of clinical trials. Many multi-stakeholder efforts designed to leverage existing clinical trial infrastructure and other systems-like registries to conduct clinical trials on a recurring basis have not been fully realized with the result being rising trial cost and ongoing evidence gaps.[25–27] In the setting of overall rising costs of clinical trials, the ratio of patients represented in public versus industry-sponsored studies as a surrogate of trial cost has been largely unchanged over time. This suggests that rising costs of clinical trials have affected industry and public funding proportionately.

The proportion of publicly funded studies between the overall cohort and the RCT cohort was similar: 34.9% versus 30%, respectively. However, industry-sponsored studies as a proportion of overall studies differed substantially between the overall and RCT cohorts: 43.5% versus 62%, respectively. Investigations supporting IA recommendations classified as clinical behavior were distinctly less likely to be industry sponsored in both the overall and RCT groups. In contrast, RCTs supporting IA guideline recommendations involving a drug, device, or diagnostic intervention were predominantly industry funded (≥65%). This pattern is also largely reflected in the number of patients randomized in these studies as a surrogate for trial cost. Industry funding was responsible for more than two times the number of randomized patients in publicly funded studies. This difference was more dramatic in diagnostic studies for which industry-funded studies included more than seven times the number of patients of publicly funded studies. Drug, device, and diagnostic interventions make up a substantial part of the practice and business of cardiovascular medicine, so the influence of industry funding is notable and is consistent with corporate goals of evidence generation to develop sustainable and growing markets: high-quality evidence leads to strong recommendations and more rapid clinical adoption leading to greater industry investment, which then leads to more investigation and so on. In the absence of increased public funding or a change in the clinical trial enterprise, the result of this self-perpetuating cycle is that guideline documents may become increasingly focused on areas of clinical practice most amenable to industry-sponsored investigation, that is, studies designed for regulatory or payer evaluation.

Taken together, these findings demonstrate that high-quality evidence as evaluated by content experts can come from a variety of funding sources. These findings highlight the importance of diverse funding to foster clinical research across a broad range of clinical diagnosis and interventions, regardless of commercial interests and potential.

Limitations

There are some important limitations to this analysis. First, as surrogates for impact, we have reported the number of investigations by funding source and, in the case of RCTs, the number of patients enrolled by funding source rather than the total dollar value of investigations. The impact of each investigation varies considerably based on a number of unmeasured factors. Second, and relatedly, the funding sources of evidence supporting class IA guideline recommendations do not represent sponsorship for the totality of evidence in cardiovascular medicine. Third, meta-analyses play an important role in guideline documents especially when representing multiple RCTs; the impact of meta-analyses varies significantly depending on meta-analysis quality, and meta-analysis quality was not assessed. Our analysis did not include the cited studies in meta-analyses in part because these investigations were generally included elsewhere. Fourth, although formal quality assessment on a subset of studies demonstrated high average quality, all supporting references were considered equally regardless of study quality or other factors. Finally, although the proportion of studies with missing funding sources was low (8.1%) the majority of these studies were published more than 10 years ago, which may bias our results toward more contemporary patterns of funding.

CONCLUSIONS

Funding of RCTs supporting IA guideline recommendations comes from a variety of public and private sources. Corporately sponsored studies supporting these recommendations is increasingly common especially regarding drugs, devices, and diagnostic tests. As the costs of running RCTs increase and as public funds available for clinical research stagnate, the role of industry sponsorship is likely to increase. Awareness of these funding sources is important in understanding guideline recommendations and have policy implications for the ongoing evolution of a clinical research system capable of generating high-quality data with diverse funding sources.

ARTICLE INFORMATION

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Affiliations

Heart and Vascular Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH (E.P.Z., S.E.D., A.V.K.); Geisel School of Medicine at Dartmouth, Hanover, NH (E.P.Z., S.E.D., A.V.K.); ; The Dartmouth Institute, Lebanon, NH (E.P.Z.); Centro Cardiologico Monzino, IRCCS, Milan, Italy (A.G.); and Department of Advance Heart Failure & Transplant Cardiology, Inova Heart and Vascular Center, Fairfax, VA (L.B.C.).

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Disclosures

None.

Supplementary Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	n/a
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6-7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7, 20-21
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Table S2. Quality Assessment Rubric.

Quality Question	Yes	No	Unclear	Not applicable
Were participants analyzed within the groups they were originally assigned?				
Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?				
Were cases and controls selected appropriately (e.g., diagnostic criteria or definitions, equal application of exclusion criteria to case and controls, sampling not influenced by exposure status)?				
Was the strategy for recruiting participants into the study the same across study groups?				
Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?				
Did the researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?				
Did the study maintain fidelity to the intervention protocol?				
If attrition was a concern, were missing data handled appropriately (e.g., intention to treat analysis and imputation)				
In prospective studies, was the length of follow-up the same between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls?				
Were the outcome assessors blinded to the intervention or exposure status of participants?				
Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?				
Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?				
Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?				
Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?				

Table S3. Quality assessment in a 10% random sample of RCTs and non-RCTs.

Study Quality by Study Design

	N	Low (n, %)		Moderate (n, %)		High (n, %)	
RCT	17	1	5.9%	2	11.8%	14	82.4%
non-RCT	10	1	10.0%	1	10.0%	8	80.0%

Study Quality by Funding Source

	N	Low (n, %)		Moderate (n, %)		High (n, %)	
Public	7	1	14.3%	1	14.3%	5	71.4%
Sponsored	15	0	0.0%	0	0.0%	15	100%
Other	5	1	20.0%	2	40.0%	2	40.0%