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Influence of Clinical Trials of Acute Coronary Syndrome Beyond the Primary Hypothesis
A Systematic Review

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IMPORTANCE Conducting a clinical trial involves significant risks, time, and resources. The return on investment for these trials, measured by advancing health care and contributions to the scientific literature, is often uncertain.

OBJECTIVE To assess the long-term effects of major clinical trials of acute coronary syndromes contemporary to the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial, which did not achieve its primary objective.

EVIDENCE REVIEW The Cochrane Central Register of Controlled Trials database was screened for clinical trials of acute coronary syndromes (including unstable angina, ST-elevation myocardial infarction, and non–ST-elevation myocardial infarction) with more than 1000 participants and primary results published between January 1, 2005, and December 31, 2009, in *Circulation*, *European Heart Journal*, *JAMA*, *Journal of the American College of Cardiology*, *The Lancet*, and *The New England Journal of Medicine*. For identified trials, bibliographic information, citations, trial name, registration, inclusion diagnosis, intervention type, sample size, primary outcome result, sponsor information, and academic involvement were extracted. To identify secondary analyses, bibliographic information for citing articles, their citations, and their abstracts were extracted. Clinical practice guideline bibliographies for citations of trial publications were reviewed, and the class and level of evidence of resulting recommendations were extracted.

FINDINGS Of 784 records screened, 30 were primary publications of 25 clinical trials. Through December 31, 2018, these trials were cited a median of 497 times (interquartile range [IQR], 424-931 citations). Trials that did not achieve their primary objective had fewer primary citations (the number of times that each published journal article with the primary [main] results of a trial was cited) (median, 443 [IQR, 396-468] vs 868 [IQR, 645-1774] citations, $P = .006$). The frequency of secondary analyses peaked within 5 years of the primary trial at 643. Trials that did not achieve the primary objective had fewer secondary analyses (median, 15 [IQR, 5-31] vs 18 [IQR, 10-43] analyses, $P = .44$) that were not cited significantly less often (median, 484 [IQR, 191-1299] vs 1124 [IQR, 410-4283] citations, $P = .16$). All trials were cited by at least 1 clinical practice guideline.

CONCLUSIONS AND RELEVANCE This review found that trials that achieved the primary objective were frequently cited. Secondary research activity did not differ by primary result, and the primary trials and secondary analyses contributed to clinical practice recommendations. These data show the long-term importance of clinical trials regardless of primary outcome result.

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Supplemental content

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The conduct of large clinical trials in cardiovascular medicine has led to improved care of patients over the past 4 decades. Paradoxically, the ensuing decrease in mortality and morbidity associated with these advances in acute coronary syndromes (ACS) has correlated with a decrease in the number of new cardiovascular drug development programs compared with other therapeutic areas.[1] This phenomenon has been exacerbated by a parallel increase in the cost and complexity of new drug and device development. Although not all phase 3 trials result in new products or changes in patient management, the emerging lessons often enhance our understanding of disease mechanisms and influence subsequent clinical practice.

A perception exists that trials that fail to confirm their primary hypothesis or objectives are unlikely to merit additional publications after reporting their primary results. Moreover, resources committed to ancillary objectives within a trial before learning the primary result are often seen as unnecessarily high-risk ventures without adequate return on investment. To our knowledge, the longer-term association of clinical trials on cardiovascular medicine irrespective of their primary results has not been systematically evaluated.

The Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial was a large, phase 3, double-blind, placebo-controlled clinical trial of patients with high-risk ST-elevation myocardial infarction (STEMI) intended to receive reperfusion by primary percutaneous coronary intervention (PCI).[2] The early termination of APEX-AMI generated discussion on the advisability of early stopping of clinical trials and the challenge of finding a balance among commercial, ethical, and scientific interests.[3]

Since the 2007 publication of the primary APEX-AMI results,[2] several related studies and 1 meta-analysis have been published using data from the main results and from substudies, many of which were prespecified in the original trial design.[4] The lessons learned from these studies led us to question how a trial that fails to achieve its primary end point, such as APEX-AMI, compares with other large contemporary clinical trials investigating ACS regarding its overall effects.

The objective of our study was to assess the long-term influence of the APEX-AMI trial in the context of other clinical trials of similar type and chronology that enrolled patients with ACS, including unstable angina, STEMI, and non-STEMI, and that had their primary results published between January 1, 2005, and December 31, 2009. We used bibliographic information including publication and citation rates, supplemented with a review of clinical practice guidelines as a proxy of clinical influence. We examined trials that failed to achieve their primary objectives or confirm the primary hypothesis as well as those with statistically significant benefit on their primary outcomes.

Key Points

Question What were the long-term effects of randomized clinical trials of acute coronary syndromes after the primary hypothesis was evaluated?

Findings In this systematic review of 30 primary publications of 25 clinical trials, trials with positive primary outcome results had higher primary study citation rates. Irrespective of the primary outcome result, many trials had secondary analyses and ancillary studies performed using their date a decade after publication and were used as sources for clinical practice guidelines.

Meaning The findings suggest that, regardless of their primary outcome results, clinical trial data may have lasting effects on the academic literature, including clinical practice guidelines.

Methods

Identification of Primary Trials of Interest

For this review, we assessed trials with primary results published 10 to 14 years previously, bracketing the publication of the 2007 primary APEX-AMI results to allow adequate surveillance of the overall influence of a trial. We used citation rates, publications of secondary analyses, and citations in practice guideline documents as a proxy for their influence on clinical practice.

The Cochrane Central Register of Controlled Trials (CENTRAL) was searched for the following terms in the title, abstract, and keywords: *acute coronary syndrome* or *myocardial infarction* or *unstable angina* or *NSTEMI* or *STEMI*; then by the following journals: *The New England Journal of Medicine* or *Journal of the American Medical Association* or *Journal of the American College of Cardiology* or *Circulation* or *European Heart Journal* or *The Lancet* or *NEJM* or *JAMA* or *JACC* or *EHJ*. We limited our search to the calendar years January 1, 2005, to December 31, 2009, to bracket a 2-year window around the APEX-AMI study. Resulting citations were exported to a comma-separated values spreadsheet for manual searching of titles and abstracts in Excel, version 2016 (Microsoft). Studies were screened and data were extracted by a single reviewer (L.M.L.), and when the decision was uncertain, a second reviewer (P.W.A.) was consulted and the final decision was made by consensus.

Records were screened to exclude (1) trials that were not conducted for an intervention for the primary diagnosis of ACS, (2) studies that were not primary results papers, (3) studies with sample sizes of fewer than 1000 patients, (4) pilot studies, (5) studies published in journals not mentioned above, and (6) duplicate records. For records with no abstract in the primary export from the Cochrane Library, abstracts were identified on Scopus using the digital object identifier (DOI). If no abstract could be found on Scopus, the record was included for full-text review. Full text was identified by searching Scopus for the study DOI or article title if no DOI was present. If a study was not identified on Scopus, it was identified through the DOI or the title on Google Scholar. The full text was then screened for the same exclusion criteria as described for the title and abstract review. We then confirmed that the studies assessed patients with ACS and that the article represented the primary outcome result based on references to previous trial publications and on screening the trial registration, if available.

For all articles that met the inclusion criteria, the following Scopus citation data were recorded: authors, title, year of publication, identifiers (including DOI), journal (volume, issue, and page numbers), citation count, and citations per calendar year (2005-2018). The following information was extracted from the full text: (1) trial name, (2) phase, (3) registration number, (4) ACS diagnoses included, (5) fibrinolysis or percutaneous coronary intervention, (6) intervention type, (7) sample size, (8) primary outcome result, (9) sponsors, (10) persons who performed the analysis, and (11) whether a clinical research organization or academic research organization was involved. Trial outcome was coded as *achieved*, also referred to

as *positive*, if the hypothesis or primary objectives under study were confirmed. Trials were coded as *not achieved*, also referred to as *negative*, when the hypothesis or primary objectives were not confirmed or if the trial was terminated early because of futility, safety, or logistical reasons. For trials with a 2 × 2 factorial design, if 1 arm of the trial was positive, the trial overall was coded as achieved. The names of the trial executive committee, steering committee, and authorship or writing committee were also extracted.

Identification of Secondary Studies

With use of Scopus, for each publication of primary trial results, the list of citing articles was searched for those sharing at least 1 author with the main trial to limit the number of records to be screened and was based on the common practice of authorship on secondary analyses to acknowledge the source of the data studied (eMethods in the Supplement). All studies identified through this search were exported as a comma-separated values file, including citation information, identifiers (including DOI), and abstract and citation metrics. The title and abstract of these articles were screened to identify secondary analyses of trial data. For any studies that could not be excluded, the full text was reviewed to determine whether the analysis involved trial data. For the secondary studies, the list of secondary study DOIs was used to identify and export the temporal citation data. For trials with a 2 × 2 factorial design, secondary studies identified as citing both primary results articles were identified by DOI and coded as citing only the primary results article published first. eFigure 1 in the Supplement gives a flow diagram of study identification and inclusion.

Guidelines

We then reviewed clinical practice guidelines in ACS published by the American College of Cardiology, the American Heart Association, and the European Society of Cardiology between January 1, 2005, and December 31, 2018.[5-26] For each trial publication, the top recommendation by class and level of evidence was used as the measure of influence. Top recommendation was ranked as class I higher than class IIa and class IIa higher than class IIb and then by level of evidence in which A is higher than B and B is higher than C. Class III recommendations were included separately, in addition to the other classes in which both exist. Additional details concerning the identification of guidelines and citations of trial analyses and methods for extracting recommendations are given in the eAppendix in the Supplement.

Statistical Analysis

Continuous variables are summarized by median (interquartile range [IQR]) and discrete variables as percentages. Differences among medians were examined by the Mann-Whitney *U* test, and proportions of the discrete variables between positive and negative trials were examined by the χ^2 test. Comparison of trial sample size and number of citations was performed by simple linear regression of log-transformed variables; significance was set at 2-sided $P < .05$. Statistical analysis was performed in SAS, version 9.4 (SAS Institute Inc).

Results

Influence of the Primary Results of the APEX-AMI Trial

The article with the primary results from the APEX-AMI trial has been cited 317 times from the original date of publication in 2017 through to the end of 2018. During that period, 48 related secondary analyses and 1 systematic meta-analysis were published. The 49 secondary studies were cited 1505 times through the end of 2018. Of these studies, 44 secondary analyses and no meta-analyses (89.8% of the 49 secondary studies) were identified by our systematic screen, confirming good sensitivity. Of the 4 secondary analyses that were not identified, the reasons included typographic errors in the citation of the article with the primary results (1 case), citing of substudies (1 case), or the trial protocol publication (2 cases) in lieu of the article with the primary results. The 1 missed meta-analysis did not have a trial author. Trial authors included members of the authorship committee (or authors of the primary results publication), steering committee, or executive committee of the trial. A comparison of APEX-AMI with other trials of similar study type was assessed through screening procedures described below.

Screening for Primary Trials of Interest

From our search of CENTRAL for clinical trials in patients with ACS, 784 abstracts were screened and 30 articles with primary results that met the inclusion criteria were identified.[2,27-55] Five trials used a 2 × 2 factorial design with 2 articles with primary results (1 per arm), resulting in the inclusion of 25 total trials (**Table 1** and eFigure 1 in the Supplement). Of the 25 trials, 11 did not achieve the primary objective, whereas 9 achieved the primary objective. Of the 5 trials with a 2 × 2 factorial design, 1 achieved both primary objectives (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI]) and 4 achieved 1 of 2 objectives (Acute Catherization and Urgent Intervention Triage Strategy [ACUITY], Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation [COMMIT], Clopidogrel and Metoprolol in Myocardial Infarction Trial [CREATE], and Organization for the Assessment of Strategies for Ischemic Syndromes [OASIS-6]).

Overall Characteristics of Articles With Primary Results

Assessment of these trials (including APEX-AMI) during a median follow-up of 143 months (IQR, 115-154 months) revealed a total of 24 852 citations with a median per trial of 497 citations (IQR, 424-931 citations). In **Table 2**, the characteristics of the trials are shown according to whether the primary hypothesis or objectives were achieved. Trials with positive primary outcomes enrolled more patients, were more commonly registered, and involved studies of interventions with drugs or devices. Positive trials had a greater influence as measured by citations of articles with their primary results (median, 868 [IQR, 645-1774] vs 443 [IQR, 396-468] citations, $P = .006$). Among trials with negative primary outcomes, Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction 2 (DIGAMI 2) and Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE) had the highest primary citation rates. In reviewing overall trials and those with negative results, APEX-AMI was positioned within the lowest 25th percentile of primary citations with 317.

Secondary Studies

We then screened all citations for secondary analyses. Among the 24 852 citations of the 30 primary results articles, we identified 3635 articles sharing at least 1 trial author. Based on title, abstract, and full-text review, we found 643 secondary analyses through the end of 2018. Of these, 585 were secondary analyses of trial data (includ-

Table 1. Characteristics of the Included Clinical Trials Ordered by Publication Date

Clinical trial[a]	Publication date	Primary outcome	Registered	Intervention type	Industry sponsored	Inclusion diagnosis	Who performed analysis	Sample size	Citations, No.
CREATE program[27,28]	January 26, 2005	Positive and negative	No	Drug, strategy	Yes	STEMI	Academics	20 201	695
CLARITY-TIMI 28[29]	March 24, 2005	Positive	Yes	Drug	Yes	STEMI	Academics	3491	1552
DIGAMI 2[30]	April 1, 2005	Negative	No	Strategy	Yes	ACS	Academics	1253	822
AMISTAD-II[31]	June 7, 2005	Negative	No	Drug	No	STEMI	Not stated	2118	424
ICTUS[32]	September 15, 2005	Negative	No	Strategy	Yes	Non-STEMI	Academics	1200	407
COMMIT program[33,34]	November 5, 2005	Positive and negative	Yes	Drug, drug	Yes	STEMI	Not stated	45 852	2124
ASSENT-4 PCI[35]	February 18, 2006	Negative	Yes	Strategy	Yes	STEMI	Academics	1667	468
ISAR-REACT 2[36]	April 5, 2006	Positive	Yes	Drug	No	ACS	Academics	2022	645
OASIS-6 program[37,38]	April 5, 2006	Positive and negative	Yes	Drug, strategy	Yes	STEMI	Academics	12 092	805
ExTRACT-TIMI 25[39]	April 6, 2006	Positive	Yes	Drug	Yes	STEMI	Academics	20 506	496
OASIS-5[40]	April 6, 2006	Positive	Yes	Drug	Yes	Non-STEMI/UA	Academics	20 078	931
ACUITY program[41,42]	November 23, 2006	Positive and negative	Yes	Drug, strategy	Yes	ACS	Sponsor, replicated by academics	13 819	1449
APEX-AMI[2]	January 3, 2007	Negative	Yes	Drug	Yes	STEMI	Sponsor, replicated by academics	5745	317
MERLIN-TIMI 36[43]	April 25, 2007	Negative	Yes	Drug	Yes	Non-STEMI/UA	Academics	6560	396
TRITON-TIMI 38[44]	November 15, 2007	Positive	Yes	Drug	Yes	ACS	Academics	13 608	4250
TAPAS[45]	February 7, 2008	Positive	Yes	Strategy	Yes	STEMI	Academics	1071	775
HORIZONS-AMI program[46,47]	May 22, 2008	Positive and positive	Yes	Drug, device	Yes	STEMI	Not stated	3602	1774
FINESSE[48]	May 22, 2008	Negative	Yes	Strategy	Yes	STEMI	Sponsor, replicated by academics	2452	497
EARLY-ACS[49]	May 21, 2009	Negative	Yes	Drug	Yes	ACS	Academics	9492	369
TIMACS[50]	May 21, 2009	Negative	Yes	Strategy	Yes	Non-STEMI/UA	Academics	3031	468
TRANSFER-AMI[51]	June 25, 2009	Positive	Yes	Strategy	Yes	STEMI	Academics	1059	380
SEPIA-ACS1 TIMI 42[52]	September 5, 2009	Positive	Yes	Drug	Yes	Non-STEMI	Academics	3241	127
PLATO[53]	September 10, 2009	Positive	Yes	Drug	Yes	ACS	Academics	18 624	3789
CHAMPION PLATFORM[54]	December 10, 2009	Negative	Yes	Drug	Yes	STEMI	Academics	5362	449
CHAMPION PCI[55]	December 10, 2009	Negative	Yes	Drug	Yes	ACS	Academics	8877	443

Abbreviations: ACS, acute coronary syndromes; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

[a] The eAppendix in the Supplement gives the expansions of the study acronyms.

ing 120 citations by 90 pooled trial data analyses) and 58 citations were in 45 systematic meta-analyses. Overall, these secondary analyses were cited 36 798 times through the end of 2018. **Figure 1**A shows both raw and normalized citation counts per month of follow-up by trial from these secondary studies. There was substantial variation in the number of secondary studies performed using data from each trial; positive trials had a larger number and wider range of secondary analyses published than those with negative primary outcome results. No differences in the rate of publication of secondary analyses were observed among data whether it was normalized by time.

In Figure 1B, the trajectory rate over years for secondary analyses is shown for trials with positive and negative primary outcomes. Publication of secondary analyses for all trials peaked between 3 and 5 years (range, <1 year to 12 years) after publication of the primary results. The peak year for publication of secondary studies of APEX-AMI was 3 years after publication of the primary results. Similar to the results for primary article citations, the number of citations of the secondary analyses was not significantly fewer for negative trials (median, 484 [IQR, 191-1299] vs 1124 [IQR, 410-4283] citations, $P = .16$) (Table 2). Within the cohort of trials with a negative outcome, APEX-AMI had the most secondary analyses performed with the data (followed by Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome [EARLY-ACS], Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombosis in Myocardial Infarction [MERLIN-TIMI 36]) compared with others in this category. Of the positive trials, there were 4 that had substantially more secondary analyses performed (HORIZONS-AMI, Platelet Inhibition and Patient Outcomes

Table 2. Characteristics of Trials by Primary Outcome Result[a]

Variable	Positive result (n = 14)	Negative result (n = 11)	*P* value
Characteristics			
Trial sample size, median (IQR)	12 850 (3241-20 078)	3031 (1667-6560)	.09
Registered	13 (92.9)	8 (72.7)	.17
Pharmaceutical or device intervention	12 (85.7)	6 (54.6)	.09
Industry sponsored, at least partial	13 (92.9)	10 (90.9)	.86
Academics independently perform or validate analysis	12 (85.7)	10 (90.9)	.69
Inclusion criterion			.71
Acute coronary syndrome	4 (28.6)	3 (27.3)	
Unstable angina and/or non-STEMI	2 (14.3)	3 (27.3)	
STEMI	8 (57.1)	5 (45.5)	
Bibliometric measures, median (IQR), No.			
Primary citations	868 (645-1774)	443 (396-468)	.006
Secondary analyses using trial data	16 (10-33)	12 (4-28)	.44
Systematic meta-analyses using trial data	2 (0-4)	1 (0-3)	.26
Total secondary and meta-analyses published	18 (10-43)	15 (5-31)	.44
Citations of secondary analyses	1124 (410-4283)	484 (191-1299)	.16
Guideline citations			
Primary results			
Cited in any guideline	14 (100)	11 (100)	NA
Time to first guideline citation, median (IQR), y	1 (1-2)	2 (0-3)	.78
Total guideline citations, median (IQR)	11 (6-13)	7 (2-9)	.06
Secondary analyses			
Trials with secondary studies cited in guideline	12 (85.7)	8 (72.7)	.42
Secondary studies per trial cited in guideline, median (IQR)	5 (3-10)	3 (2-5)	.08
Follow-up, median (IQR), mo	149 (127-152)	140 (115-159)	.66

Abbreviations: IQR, interquartile range; NA, not applicable; STEMI, ST-elevation myocardial infarction.

[a] Data are presented as number (percentage) of trials unless otherwise indicated.

[PLATO], Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction [TRITON-TIMI 38], and ACUITY) than the remainder of the trials.

Compared with other positive trials (**Figure 2**C) TRITON-TIMI 38 and PLATO had higher rates of citations for both their primary and secondary analyses. Of interest, citations of the secondary analyses substantially exceeded those of the primary trial articles. This pattern was also evident for HORIZONS-AMI and ACUITY. By contrast, despite substantial citations for the primary results of COMMIT, there were no secondary analyses found and few citations to 3 meta-analyses that included the primary results. The primary and secondary analyses of several positive trials continued to be cited later throughout the period of follow-up.

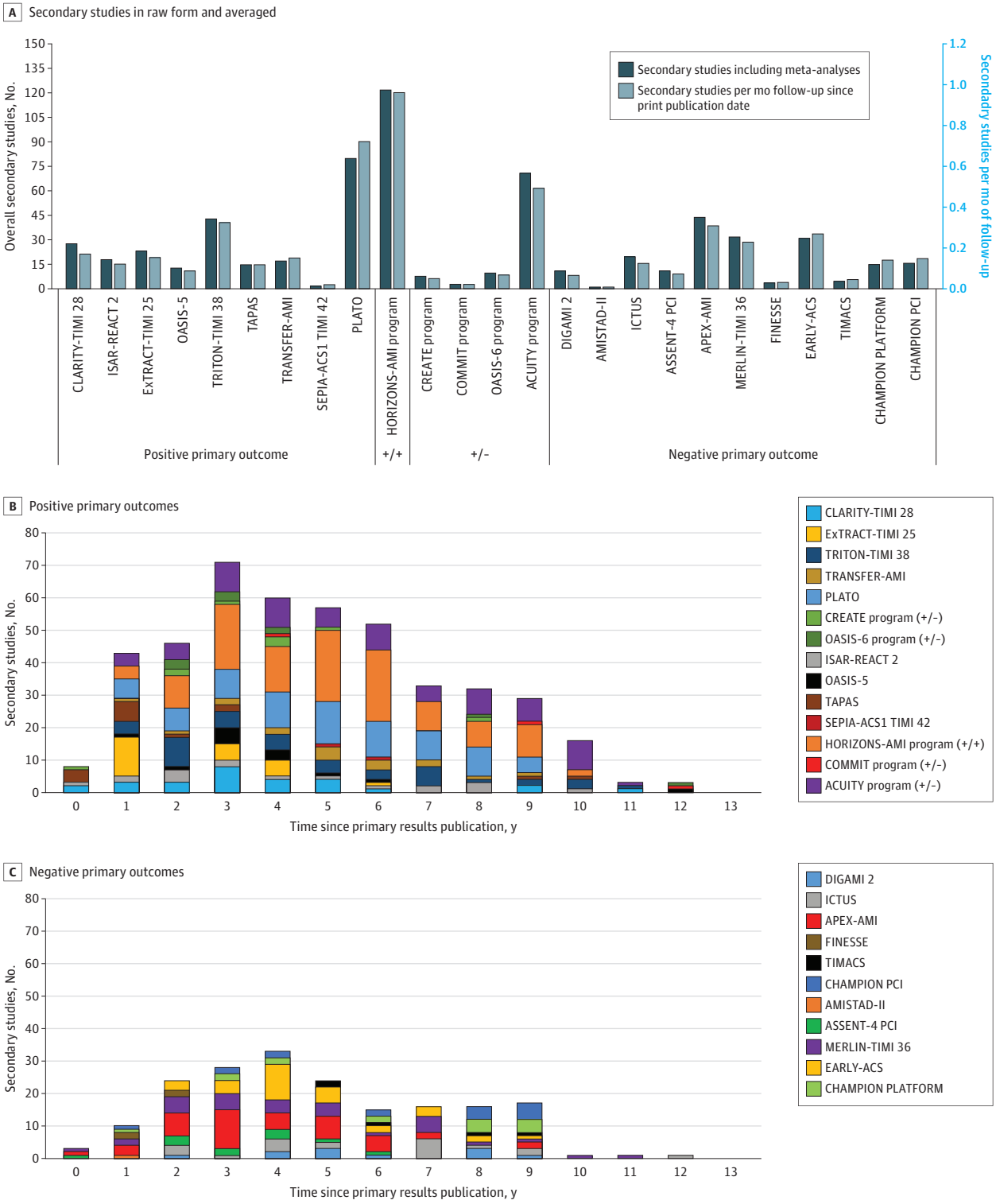
Clinical Influence

In Table 2, citations of primary and secondary analyses given in 22 clinical ACS guidelines published by the American College of Cardiology, the American Heart Association, or European Society of Cardiology from 2005 to 2018 are shown as a proxy for the clinical influence of the analyses. We identified 718 citations of the trials being studied across the 22 guideline documents.

All positive trials were cited in at least 1 guideline document, with a median time of first citation of 1 year (IQR, 1-2 years) after initial publication (Table 2). The median number of guidelines in which any positive trial was cited was 11 (IQR, 6-13). Among the secondary trial studies, at least 1 was cited in any guideline for 12 of 14 studies, with a median of 5 (IQR, 3-10) secondary studies of any trial cited in at least 1 guideline. Of trials that did not confirm the primary hypothesis, all were also cited in at least 1 guideline document, with a median time to citation of 2 years (IQR, 0-3 years) and citation in a median of 7 guidelines (IQR, 2-9 guidelines). At least 1 secondary study was cited in a guideline for 8 of 11 trials, with a median of 3 (IQR, 2-5) secondary studies for each trial cited at least once. The primary results article of APEX-AMI was referenced by 1 guideline as were 6 of 44 secondary studies.

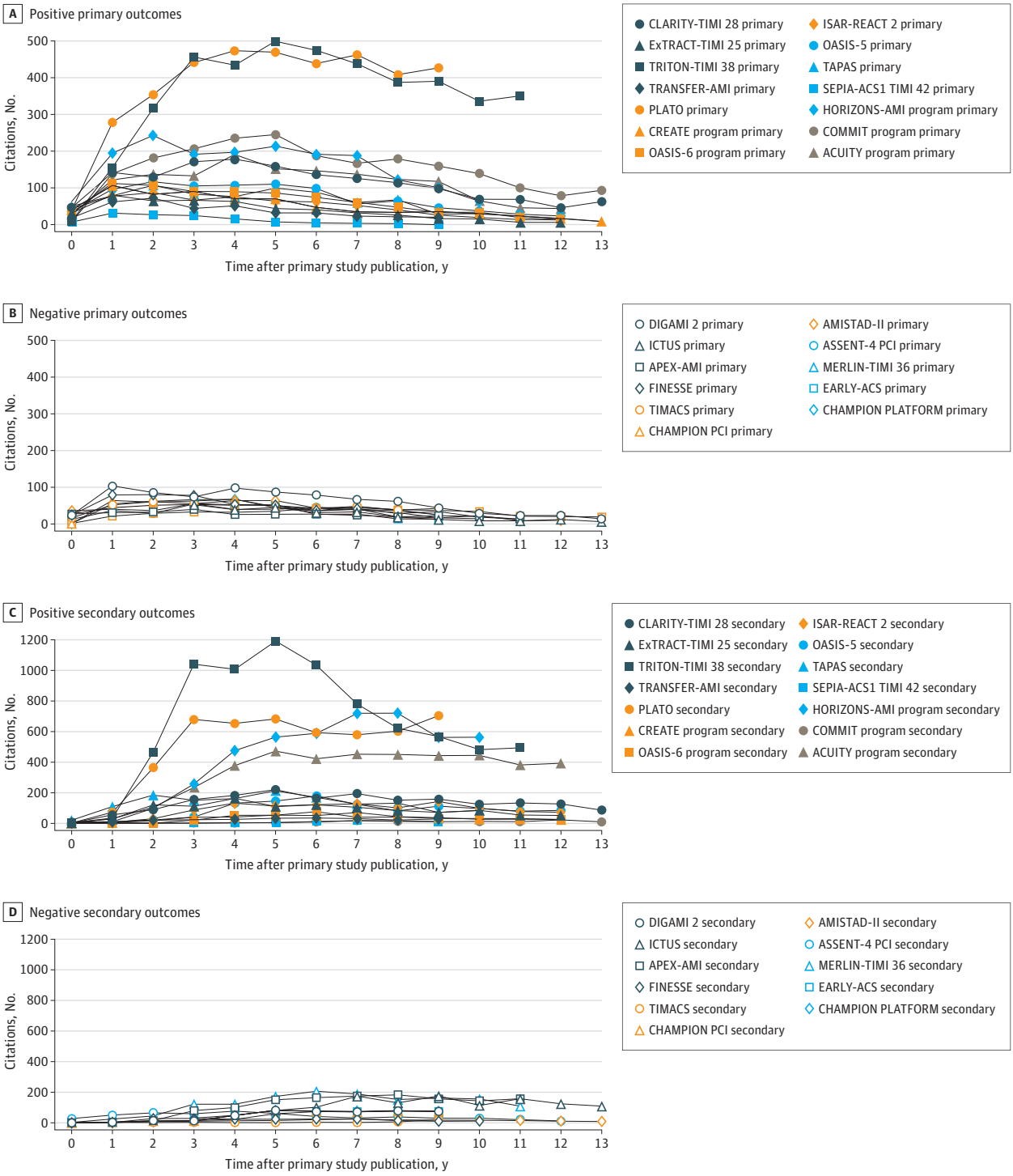
To supplement these bibliometric measures of influence, we turned to the character of recommendations (class of recommendation as well as the level of evidence ascribed to the citations used to support the recommendation) in the guidelines in which trials were cited. Among the 218 citations of the primary results of randomized clinical trials in ACS, we identified 193 top recommendations tied to the trials (**Figure 3** and eTables 1 and 2 in the Supplement). The most common top level of recommendation was I, B (eTable 1 in the Supplement). Positive trials had more recommendations overall and achieved class I recommendations more often than those that did not achieve the primary objective; the latter had more peak class IIb recommendations. On the basis of the level of evidence, the most common peak level attributed to trials was I, B. Positive trials had more recommendations of all 3 levels of evidence (eTable 2 in the Supplement). Guideline recommendations did not significantly persist for multiple issues of guidelines, although the nature of the recommendation and level of evidence may have shifted (eFigures 2 and 3 in the Supplement).

Figure 1. Secondary Study Publication Rate and Citations for Major Clinical Trials in Acute Coronary Syndrome



A, The number of published secondary studies (including secondary analyses and meta-analyses). B and C, The number of secondary study publications is shown for trials that achieved their primary outcomes (B) and those that did not achieve their primary outcomes (C). Trials with 2 × 2 factorial design are presented with both primary study publications summed together. +/+ indicates both arms positive; +/−, 1 arm positive and 1 arm negative. The eAppendix in the Supplement gives the expansions of the study acronyms.

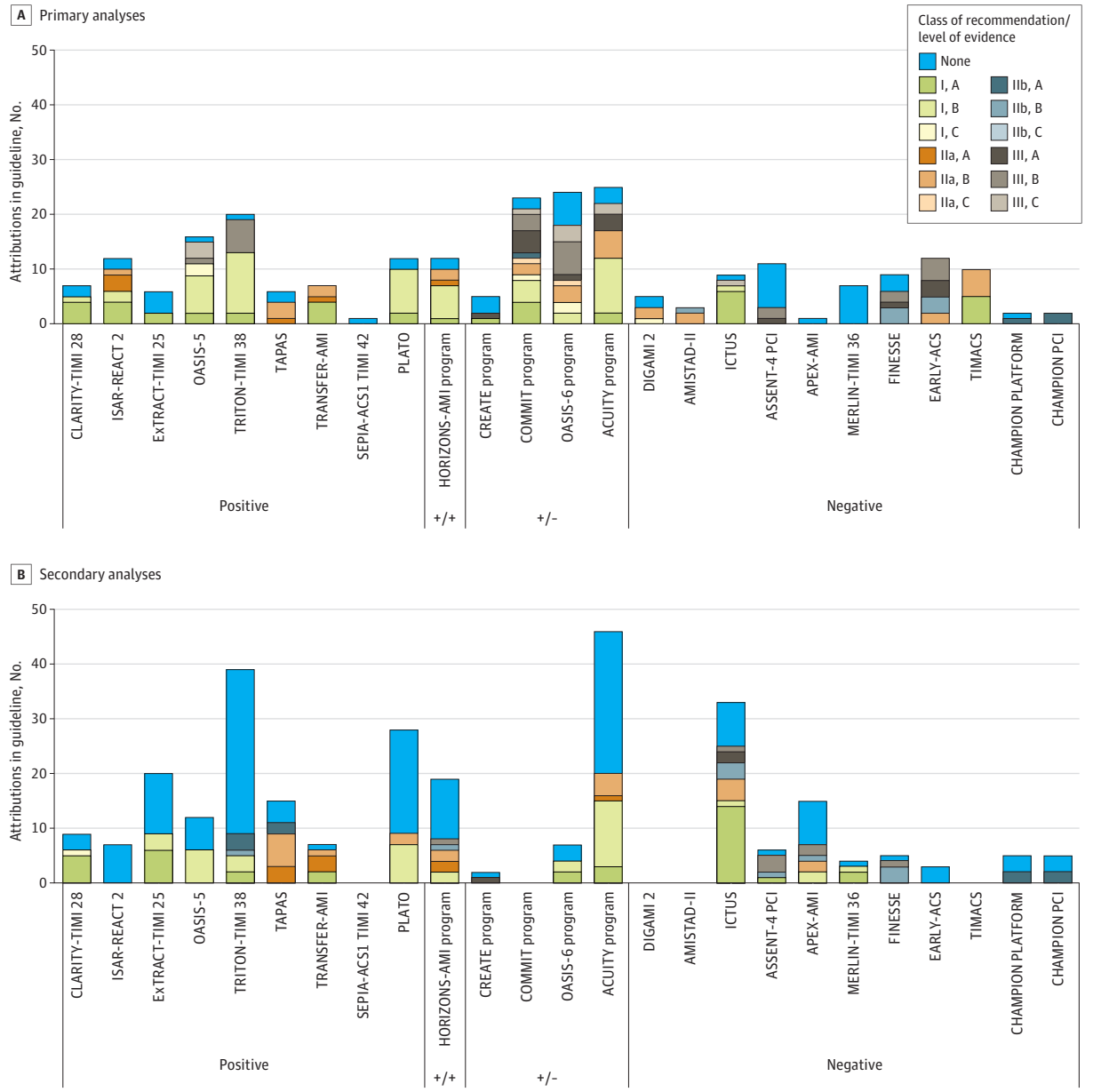
Figure 2. Temporal Citation Rates of Primary and Secondary Analyses of Major Clinical Trials in Acute Coronary Syndrome



Citation rates from the year of primary results publication (year 0) through 2018 (final year of follow-up). Trials with 2 × 2 factorial design are presented with both primary study publications summed together. The eAppendix in the Supplement gives the expansions of the study acronyms.

Of the 643 secondary studies, 269 were cited by the clinical practice guidelines and used to support 137 top recommendations (Figure 3 and eTables 1 and 2 in the Supplement). Similar to the primary studies, the most common top recommendation was I, B. Positive trials had more recommendations overall and had more peak class I and IIa recommendations, whereas trials that did not confirm the primary hypothesis had more peak IIb and III recommendations. Positive trials had more recommendations across all levels

Figure 3. Guideline Recommendations Based on Results of Major Clinical Trials in Acute Coronary Syndrome



Guideline citations of primary and secondary analyses of trials. No level of evidence was associated with citations not linked to recommendations. For secondary studies that were pooled analyses, guideline recommendations and citations were attributed to all trials included. The eAppendix in the Supplement gives the expansions of the study acronyms.

of evidence. The later publication dates of secondary studies limited our ability to assess the longevity of recommendations, although long-standing recommendations were observed for earlier studies (eFigures 4 and 5 in the Supplement).

Discussion

Our study provided several novel findings. We showed that whether the trial achieved its primary objectives, numerous secondary studies may have emerged, resulting in a large number of total citations. Our study was novel in evaluating the primary and secondary citation influence of ACS randomized clinical trials. We found that although positive trials had higher influence at the primary results level, negative trials were similar in the rates of secondary analyses and citations. Furthermore, using clinical guideline citations as a proxy for clinical influence, we found that all major trials were cited in guidelines irrespective of whether the primary hypothesis was supported.

Results in Context

Previous bibliometric analyses (one way of measuring influence, commonly by citation counts) have found that the publication pat-

terns and citations of randomized clinical trials vary by study type, rigor of design, and by clinical specialty.[56-59] Furthermore, although the bibliometric influence varies by trial outcome, trials with negative results are published in influential journals[60] and can be the source of data for secondary analyses.[61,62] However, use of citation counts as the sole measure of influence is inherently flawed because citations are not completely associated with influence and do not capture the association of clinical research with health care practice.[63]

The APEX-AMI study, which stimulated the current report, assessed the C5 complement inhibitor pexelizumab as an adjuvant treatment[2] designed to enhance myocardial perfusion and improve clinical outcomes. However, APEX-AMI was stopped sooner than planned; this decision was based on findings of unexpectedly low event rates without a trend for benefit at the first interim analysis, thereby necessitating an increase in the target sample size. Another influential factor was the contemporaneous release of results from a separate pexelizumab trial demonstrating a lack of effectiveness in patients undergoing coronary bypass surgery.[3,64] Although the APEX-AMI trial did not achieve its primary objective, numerous ancillary analyses and substudies resulted in 48 secondary study publications. Compared with other contemporary ACS trials and irrespective of its primary result, APEX-AMI had a relatively large citation influence. In addition, the data generated through the trial affected evidence-based practice, as measured by incorporation into clinical practice guidelines. Given the substantial personal and financial investment into large cardiovascular trials, this experience supports the important opportunity to analyze the data beyond the primary outcome to share knowledge to improve the care of patients. These results also support the importance of incorporating ancillary studies in the overall trial design to enhance the influence of a trial and fully leverage the comprehensive data collected regardless of the primary outcome.

Broader Implications

Since the era in which the trials in the review were conducted, an impetus has emerged to more readily facilitate data sharing with nontrial investigators.[65] The issues arising from this initiative are both complex and controversial.[66] However, using APEX-AMI as an example, 49 secondary articles engaged a broad cadre of health professionals beyond the original executive and steering committees. After review of these articles, we found 209 nonprimary study personnel consisting of other clinical investigators, trainees, students, and biostatisticians with meaningful coauthor contributions who participated in this ancillary work. Thus, it appears to be feasible to provide extensive analyses with shared involvement of broad groups of investigators to the medical community without formally sharing data with independent groups.

Randomized clinical trials represent the highest standard of evidence for the adoption, use, or discontinuation of use of clinical interventions. Such trials require substantial resources, including economic costs for sponsors and/or funding agencies, the time commitment and effort of study investigators and other personnel, and the risk and personal costs to trial participants. Sharing knowledge from positive and negative trials after the primary results provides information to the public that can inform the optimal care of patients.

Strengths and Limitations

This study has strengths and limitations. We provided a comprehensive long-term assessment of publication experience from large trials in cardiovascular medicine. However, the accuracy of reporting of references and indexing into databases such as Scopus is a limitation, as observed through our capturing 89.9% of all published secondary analyses using APEX-AMI data known to us. Similarly, our annotation of pooled analyses and meta-analyses were manually captured through review of the abstracts and main article texts. Our search for articles on the primary results was limited to top-tier journals with high impact factors. This strategy limited our capture of trials, particularly for those with negative results. For secondary study publications, our use of a shared author with the main trial article authors or steering and executive committee possibly limited our capture of meta-analyses because meta-analyses do not necessarily share authors with the studies they incorporate. Because of the varied nature of secondary analysis reporting, we were unable to assess whether the analyses were prespecified or post hoc. This issue deserves further study. Although heterogeneity exists within many of the subpopulation analyses from many of the trials and their value and insights are open to challenge, some provide confidence in the application of the primary result to high-risk subgroups. To the extent that the data are used for inferring treatment effects based on nonrandomized data, subpopulation analyses contain the usual limitations of any such analysis.[67] This report also underscores that energetic researchers with resources can generate many manuscripts addressing topics beyond the primary hypotheses of large randomized clinical trials that have a substantial influence based on citations.

Conclusions

This review found that trials that achieved the primary objective were frequently cited. Secondary research activity did not differ by primary result, and the primary trial results and secondary analyses contributed to clinical practice recommendations. These data show the long-term importance of randomized clinical trials regardless of primary outcome result.

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