Claims-based cardiovascular outcome identification for clinical research: Results from 7 large randomized cardiovascular clinical trials

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Background Medicare insurance claims may provide an efficient means to ascertain follow-up of older participants in clinical research. We sought to determine the accuracy and completeness of claims- versus site-based follow-up with clinical event committee (+CEC) adjudication of cardiovascular outcomes.

Methods We performed a retrospective study using linked Medicare and Duke Database of Clinical Trials data. Medicare claims were linked to clinical data from 7 randomized cardiovascular clinical trials. Of 52,476 trial participants, linking resulted in 5,839 (of 10,497 linkage-eligible) Medicare-linked trial participants with fee-for-service A and B coverage. Death, myocardial infarction (MI), stroke, and revascularization incidences were compared using Medicare inpatient claims only, site-reported events (+CEC) only, or a combination of the 2. Randomized treatment effects were compared as a function of whether claims-based, site-based (+CEC), or a combined system was used for event detection.

Results Among the 5,839 study participants, the annual event rates were similar between claims- and site-based (+CEC) follow-up: death (overall rate 5.2% vs 5.2%; adjusted κ 0.99), MI (2.2% vs 2.3%; adjusted κ 0.96), stroke (0.7% vs 0.7%; adjusted κ 0.99), and any revascularization (7.4% vs 7.9%; adjusted κ 0.95). Of events detected by claims yet not reported by CEC, a minority were reported by sites but negatively adjudicated by CEC (39% of MIs and 18% of strokes). Differences in individual case concordance led to higher event rates when claims- and site-based (+CEC) systems were combined. Randomized treatment effects were similar among the 3 approaches for each outcome of interest.

Conclusions Claims- versus site-based (+CEC) follow-up identified similar overall cardiovascular event rates despite meaningful differences in the events detected. Randomized treatment effects were similar using the 2 methods, suggesting claims data could be used to support clinical research leveraging routinely collected data. This approach may lead to more effective evidence generation, synthesis, and appraisal of medical products and inform the strategic approaches toward the National Evaluation System for Health Technology. (Am Heart J 2019;218:110-22.)

In clinical research, site-based reporting of adverse outcomes with clinical event committee (+CEC) adjudication has become the industry standard[1,2]; however, this system is both resource intensive for sponsors (requiring prolonged site activation and intensive event review) and burdensome to patients and caregivers (requiring additional study-mandated patient visits). The medical drug and device development ecosystem stakeholders have responded to these challenges in a variety of ways. For example, the Medical Device Epidemiology Network spearheaded development and testing of novel methodologies for evidence generation using diverse data

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sources (eg, registries, electronic health records, and claims).[3] Such efforts helped inform Food and Drug Administration national strategies and the development of the National Evaluation System for Health Technology.[4]

Analysis of medical billing records offers an alternative for patient follow-up, with an internationally standardized coding system[5] and an active system of payor-based record auditing. In the United States (US), the Centers for Medicare & Medicaid Services (CMS) provide insurance coverage for nearly all adults 65 years or older and those collecting Medicaid services, aggregating research-identifiable insurance claims for all who are enrolled in fee-for-service programs; private entities provide a similar (although less cohesive) service for younger patients with commercial insurance. Whereas randomized clinical trials using claims-based follow-up have been reported recently from Europe,[6] it remains unknown whether claims-based follow-up is sufficiently accurate to broadly support clinical research in the US.

We linked data from Medicare insurance claims with records from 7 large cardiovascular clinical trials to facilitate a comparison of active, site-based, patient follow-up (+CEC) versus passive follow-up with Medicare insurance claims among older adults (≥65 years) with fee-for-service Medicare coverage in the US.

Methods

Data sources

Seven large cardiovascular clinical trials were selected from the Duke Database of Clinical Trials (Table I). Trials were selected based on (1) initiation of randomization after the year 2000, (2) data available on at least 1 of the outcomes of interest, and (3) more than 500 patients (≥65 years) recruited within the US. Follow-up in these trials varied from 1 month to 2 years. Detailed information on study designs, methods, and primary results was previously published.[7-13] Records included baseline and follow-up data. Both investigator-reported and CEC-adjudicated cardiovascular outcomes were included when available.

Records from clinical trial participants eligible for Medicare insurance participation (≥65 years) at the time of trial randomization and enrolled at US sites (not identifiable by name as Veterans Affairs/military sites or health maintenance organization) were linked to research-identifiable Medicare fee-for-service inpatient claims. Linking was performed using a deterministic linkage process that required an exact match on a series of indirect patient identifiers (Medicare claims data were approved for reuse under Data Use Agreement number: 17758).[14] The identifiers available for linkage differed across the randomized clinical trials and included subsets of sex, admission date, discharge date, surgery date (for MC-1 to Eliminate Necrosis and Damage in Coronary Artery Bypass Graft Surgery Trial [MEND-CABG II]), and full or partial date of birth. Potential end points were not used as a part of the linkage process. Pairings of clinical trial sites and Medicare providers that were generated by these linkages were then evaluated for accuracy using the empirical distribution of indirect identifiers in the Medicare claims database; this process is described in detail in the Supplementary Methods. Only linkages for the verified pairings were retained. Although this process eliminated many potential matches (resulting in a lower linkage rate than is typical), the proportion of false-positive matches was estimated to be <0.01% (eTable II). Using this process, 6,130 (58.4%) of 10,497 "eligible" clinical trial records (from US trial participants ≥65 years) were linked to Medicare insurance claims, including 49.1%-76.5% linkage of records in the individual clinical trials (Table I). This record linkage allowed the creation of longitudinal data files for each trial participant that included both site-based follow-up (investigator-reported and investigator-reported +CEC [site-based +CEC], where available) and claims-based follow-up of prespecified cardiovascular events. Following data linkage, patients without both Medicare A and B fee-for-service coverage at the time of randomization were excluded (n = 291) because it is less likely that Medicare is the primary payor for these patients. Importantly, the Medicare Advantage program was steadily increasing enrollment during the time interval of participant recruitment for these clinical trials. Medicare Advantage claims from this time interval were not available for research purposes, and a substantial portion of the unlinked (but eligible) clinical trial records may have included Medicare Advantage patients. The study was approved by the Duke University School of Medicine Institutional Review Board.

Table I. Linkage rate by trial and overall among trial patients eligible for linkage*

Trial	Total randomized patients†	Linkage rate (total eligible, N = 10,501)
APEX-AMI	5745	359/521 (68.9%)
EARLY ACS	9492	630/1130 (55.8%)
IMPROVE-IT	18,144	1086/2210 (49.1%)
MEND-CABG II	3023	745/1023 (72.8%)
PREVENT IV	3014	1085/1419 (76.5%)
RED-CABG	3080	530/1015 (52.2%)
SYNERGY	9978	1695/3183 (53.3%)
All clinical trials	52,476	6130/10,501 (58.4%)

Summary statistics: n/N (%) for each trial, where n = linked and N = eligible.
EARLY ACS, Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome; *IMPROVE-IT*, Examining Outcomes in Subjects with Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin (P04103); *PREVENT IV*, Project of Ex-vivo Vein Graft Engineering via Transfection; *RED-CABG*, Reduction in Cardiovascular Events by AcaDesine in Subjects Undergoing CABG.
*The study cohort included 5839 patients, following further exclusion of 291 patients who did not have both fee-for-service A and B coverage.
†Total randomized patients include all patients randomized in each clinical trial, including those US participants eligible for Medicare linkage (≥65 years of age) and those not eligible for Medicare linkage due to younger age (<65 years) or international study sites recruitment.

Outcomes of interest followed index (randomization) hospitalization discharge and included death, myocardial infarction (MI), stroke, any coronary revascularization, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG); the date of these cardiovascular events was recorded directly from clinical trial records. Event dates for MI and stroke were set as the date of hospital readmission for Medicare insurance claims, whereas procedure dates used the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) procedure code date. For site-based follow-up, event definitions were established by clinical trial protocols and have been previously published. Both the clinical outcomes and follow-up intervals varied by clinical trial (eTable V). Death and revascularization events were not adjudicated, whereas CEC adjudication of MI and stroke varied by trial and duration of follow-up. Very few recurrent MI, stroke, and revascularization events were captured in the trial databases during follow-up; these events were not included in the data set. For claims-based follow-up, death was identified using the Medicare Beneficiary Summary File. Revascularization events were identified using the following procedure codes: PCI, 00.66, 36.0*x*; CABG, 36.1*x*, and 36.2*x*. MI was identified from Medicare insurance claims using the following standard set of *ICD-9-CM* diagnostic codes: 410.*x*0 and 410.*x*1. Stroke was identified using the following standard set of *ICD-9-CM* diagnostic codes: 430.*xx*, 431.*xx*, 434.*xx*, and 436.*xx*. *ICD-9-CM* coding definitions were similar to those used in other settings and based on preliminary analyses (unpublished) to optimize agreement between claims- and site-based event detection. Following a hospital encounter, hospital centers submit to insurance carriers a billing claim that includes a list of active diagnoses for each hospitalization, including the "primary" diagnosis (generally, the principle reason for hospitalization) and all active "secondary" diagnoses. In this analysis, events were identified based on *ICD-9-CM* primary diagnostic codes (appearing in the primary coding position), unless otherwise specified. Sensitivity analyses further expanded the claims-based event definitions for MI and stroke to include *ICD-9-CM* diagnostic codes in "any (primary or secondary) position" and included an evaluation to "investigator-reported" (but not adjudicated) outcomes (Supplementary Appendix).

To ensure a comparable follow-up period for site- and claims-based outcomes, follow-up was censored at the earlier date corresponding to end of trial participation (whether through end of trial follow-up, death, or early withdrawal) or withdrawal from fee-for-service Medicare coverage.

Statistical analysis

The rate of successful linkage between site- and claims-based patient records was summarized by trial and overall. Within each trial and overall, study records were compared with eligible (but excluded) trial records with respect to baseline characteristics, including patient demographics, medical history risk factors, and in-hospital procedures. Categorical variables were presented as counts (proportions), and continuous variables were presented as medians (interquartile ranges). Comparisons for continuous variables were based on the Wilcoxon test, whereas categorical variables were assessed using the χ^2 test.

Patient-level event indicators from site- and claims-based data sources were cross-tabulated within each trial and pooled across trials without regard to event timing or recurrence. These 2 × 2 tables were accompanied by (1) percent agreement, (2) the simple κ statistic, (3) the prevalence-adjusted bias-adjusted κ statistic (PABAK), and (4) McNemar test for concordance. When event prevalence is low, the κ statistic tends to underestimate agreement. PABAK corrects for low prevalence.[15] A sensitivity analysis was performed at the event level to assess the correspondence of timing between events reported in each data source. Within each individual trial and overall, events were categorized as false matches if the site-based event date occurred more than 14 days outside the window defined by the admission and discharge dates of the claims-based event. Repeat events were very rare, and concordance was very similar after accounting for timing of events, so results are not shown.

Kaplan-Meier plots of time-to-first-event with 95% confidence bands were created for each outcome and were run individually by clinical trial and outcome, as well as pooled across trials. Time origin was defined as randomization, although events occurring between randomization and index hospitalization discharge were discounted because claims data could not distinguish between multiple events occurring during the index hospitalization. No further risk adjustment (beyond initial trial randomization) variables were included in the models. The treatment effect for each trial was reported as hazard ratios (HRs) with 95% CIs estimated from unadjusted Cox models for each outcome by data source.

Results

In the 7 clinical trials, 52,476 participants were randomized. Of these, 10,501 clinical trial records were eligible for linkage to Medicare administrative claims. Fee-for-service A and B claims were successfully linked in 5,839 of the eligible records (55.6%), forming our study cohort (Table I). Compared with clinical trial participants eligible for Medicare linkage who were subsequently excluded from analysis, participants in the study cohort were more likely to be white (92% vs 88%); otherwise, participants reflected linkage-eligible clinical trial enrollment, including mostly men (n = 3,799, 65%) of advanced age (median 72 years, interquartile range 69-77) (Table II). Cardiovascular comorbidities were prevalent, including hypertension (67%), dyslipidemia (62%),

Table II. Correspondence of clinical outcomes (yes/no) data between pooled clinical trial records and claims-based sources (primary dx) among linked records

Outcome	Identified in site-based follow-up	Identified in claims-based follow-up: No	Identified in claims-based follow-up: Yes	Concordance measures: % Agreement	Concordance measures: Simple κ (95% CI)	Concordance measures: Prevalence and bias-adjusted κ (95% CI)	McNemar test *P* value
Death	No	5526 (94.6%)	8 (0.1%)	99.7	0.97 (0.95, 0.98)	0.99 (0.99-1.00)	.503
	Yes	12 (0.2%)	293 (5.0%)				
MI*	No	4835 (96.8%)	48 (1.0%)	98.2	0.59 (0.52, 0.67)	0.96 (0.96-0.97)	.675
	Yes	43 (0.9%)	69 (1.4%)				
Stroke*	No	4417 (99.1%)	11 (0.2%)	99.5	0.64 (0.5, 0.78)	0.99 (0.99-0.99)	1.00
	Yes	10 (0.2%)	19 (0.4%)				
Any revascularization	No	4864 (91.2%)	75 (1.4%)	97.7	0.84 (0.81, 0.86)	0.95 (0.95-0.96)	.019
	Yes	48 (0.9%)	346 (6.5%)				
PCI	No	4929 (92.4%)	71 (1.3%)	97.7	0.81 (0.78, 0.85)	0.95 (0.95-0.96)	.055
	Yes	49 (0.9%)	284 (5.3%)				
CABG	No	5252 (98.5%)	11 (0.2%)	99.8	0.93 (0.88, 0.97)	1.00 (0.99-1.00)	<.001
	Yes	0	70 (1.3%)				

*For MI and stroke, clinical trial data are CEC-adjudicated.

prior MI (37%), PCI (36%), heart failure (26%), and stroke (11%).

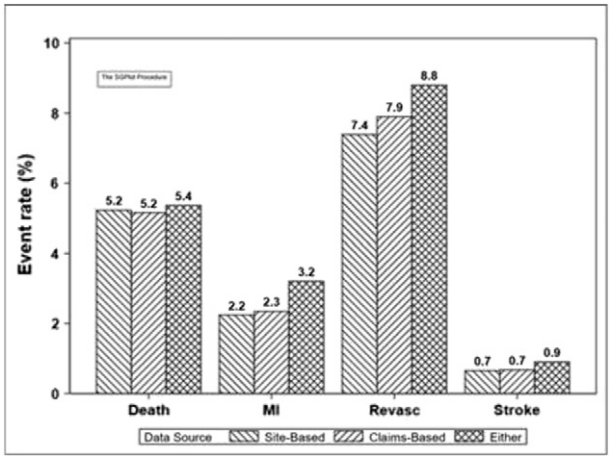
Assessment of event concordance

The % agreement was high between claims- and site-based (+CEC) follow-up methods (driven primarily by patients without clinical events) (Table II), including death (pooled % agreement, 99.7), MI (97.2%), stroke (99.5%), any revascularization (97.7%), PCI (97.7%), and CABG (99.8%). Likewise, adjusted κ estimates were high for each of the outcomes: death (pooled PABAK, 0.99), MI (0.96), stroke (0.99), any revascularization (0.95), PCI (0.95), and CABG (1.00). For both MI and stroke, similar % agreement and adjusted κ were observed whether site-based results were compared with "primary position" or "any position" claims-based results.

Despite high levels of agreement between claims- and site-based (+CEC) follow-up (Figure 1), important differences were observed. Of the 313 total death events, 8 were detected only using claims data, whereas 12 were detected only using site-based trial data (Figure 2). Nine of 12 deaths initially "missed" by claims were identified in claims data after the censoring date. For any revascularization, 75 of 469 patients with a coronary revascularization event were detected only using claims data, whereas 48 were detected only using site-based trial data; 120 of 131 discrepant revascularization events involved PCI, whereas 11 involved CABG. When considering site-based +CEC results versus "primary position" claims-based results for MI or stroke, a similar pattern of patient-level discrepancy was observed; of the 160 patients with MI, 48 were detected only using claims data, whereas 43 were detected only using site-based trial data. Likewise, of the 40 patients with stroke events, 11 were detected only using claims data, whereas 10 were detected only using site-based trial data.

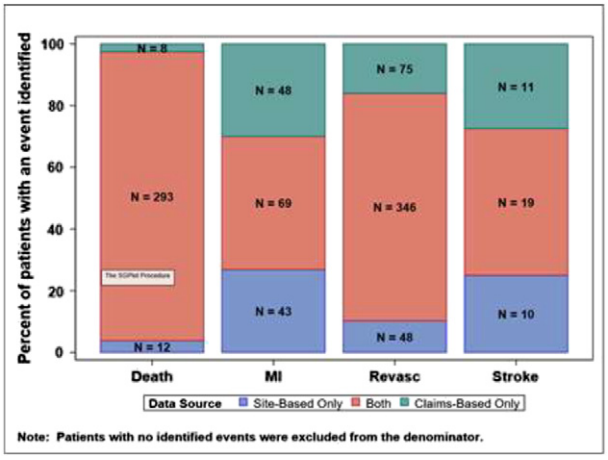
In the 4 clinical trial datasets that included both investigator- and CEC-reported MI events, 31 MI events were detected by claims but not reported by CEC. Of these 31 MI events, 12 (39%) were reported as clinical events by investigators, but available documentation did not fulfill the clinical trial MI definition (and the events were adjudicated as "no event" by CEC). One additional event was detected by CEC through review of records for another event type but not reported by site investigators. In the analogous 5 data sets for stroke, 11 stroke events were detected by claims but not reported by CEC. Of these 11 stroke events, 2 (18%) were reported as clinical events by investigators but adjudicated as "no event" by the CEC. Two additional events were detected by CEC but not reported by site investigators.

Figure 1



Clinical event rates.Clinical event rates using site-based follow-up, claims-based follow-up, or either method of follow-up in the pooled cohort for death, MI, any revascularization, and stroke. This figure demonstrates similar clinical event rates across the 2 follow-up methods but an increased event rate when both methods are used.

Figure 2



Clinical event concordance.Clinical events detected with site-based follow-up, claims-based follow-up, and both methods of follow-up. This figure demonstrates that a substantial number of clinical events are detected exclusively by either site-based follow-up or claims-based follow-up.

Comparison of Kaplan-Meier event rates

When considering time-to-event analysis, site-based (+CEC) follow-up was similar to the "primary position" claims-based follow-up across each of the outcomes of interest (Figure 3, *A-D*). Using combined claims-based plus site-based follow-up to detect events resulted in increased rates of event accrual.

Comparison of randomized treatment effects

Despite event-level discrepancies, randomized treatment effects were similar across each of the 7 individual clinical trials for claims- versus site-based (+CEC) follow-up, as well as the combined follow-up approach (Figure 4, *A-D*). For death and coronary revascularization events, treatment effects were nearly identical using any of the 3 approaches. No treatment-related effect on stroke was observed using claims- or site-based (+CEC) follow-up in the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) and Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trials; however, a lower risk of stroke was observed with ezetimibe plus simvastatin (vs simvastatin only) using claims-based (but not site-based) follow-up in the Examining Outcomes in Subjects with Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin (P04103) study. For MI, modest variation in individual point estimates was observed across follow-up methods, but overall treatment effects were not meaningfully different.

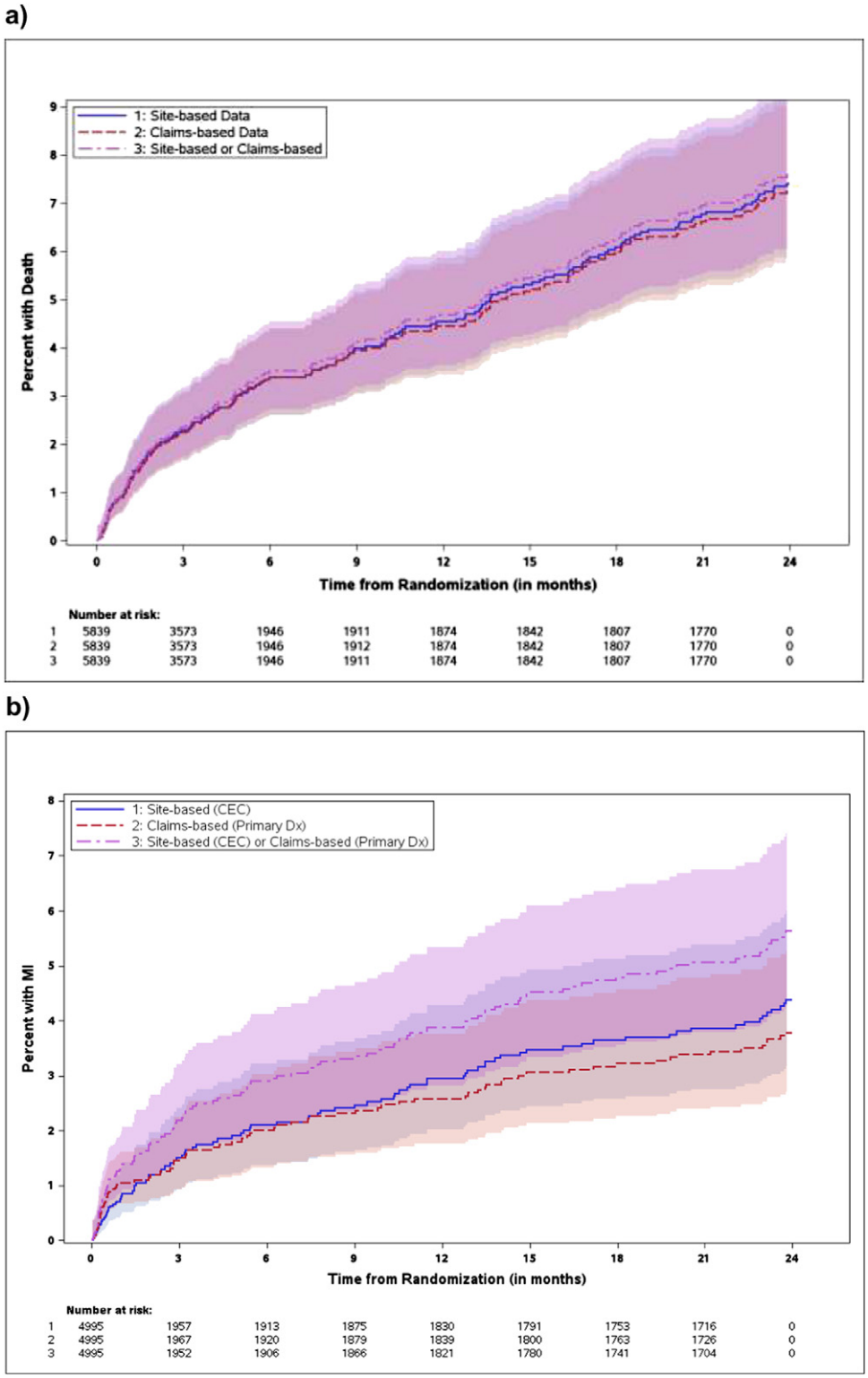
Discussion

In this pooled evaluation of 7 large, randomized, cardiovascular clinical trials, cardiovascular event rates and randomized treatment effects were similar for claims- and site-based (+CEC) methods of patient follow-up. Important event-level discrepancies led to higher rates of event accrual when a combined approach (claims- plus site-based [+CEC] follow-up) was used. This analysis supports the implementation of claims-based patient follow-up in clinical research, including in randomized clinical trials. Nevertheless, widespread implementation will require addressing the delay between event occurrence and the availability of claims data.

Despite event-level discrepancies, randomized treatment comparisons were nearly identical for death and revascularization outcomes. A similar pattern was observed for MI and stroke, with important event-level discrepancies but similar treatment effects. This trend suggests that event-level discrepancies were not influenced by randomized treatment assignment.

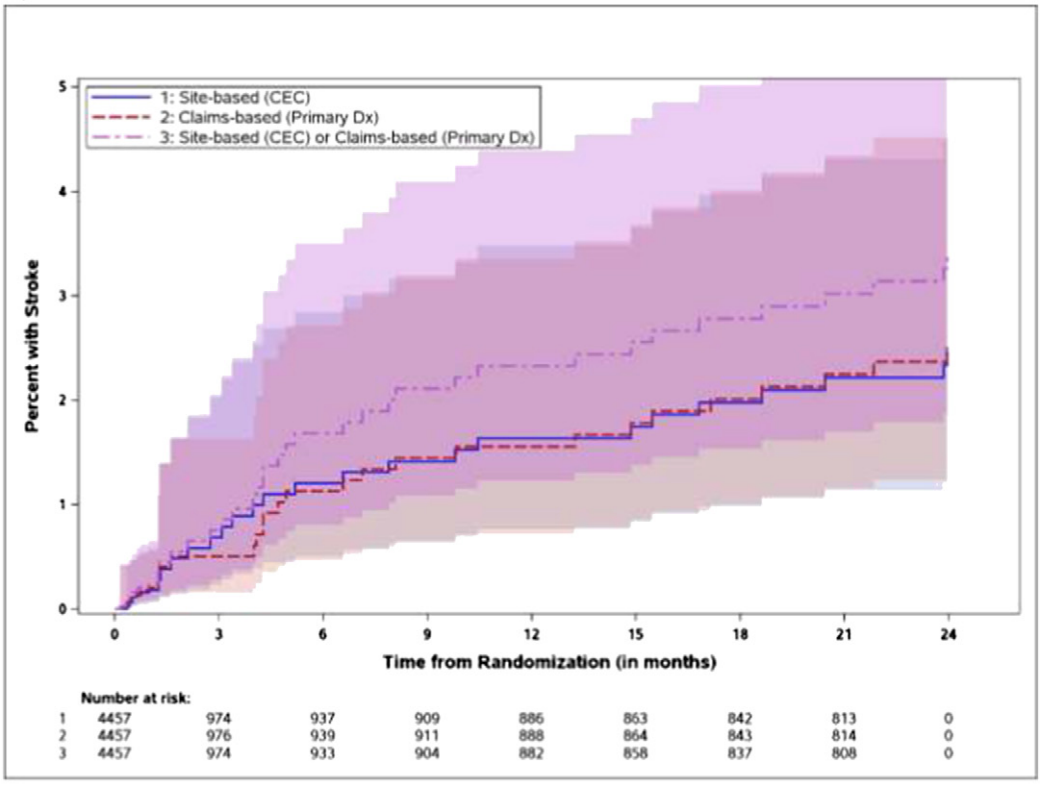
The observation that treatment effects were not meaningfully different regardless of whether claims- or site-based follow-up methods were used (despite event-level discrepancies) is consistent with results of the claims-based follow-up evaluation in the intention-to-treat cohort from the Women's Health Initiative[16] where treatment effects were similar for site- versus claims-based follow-up of MI (HR 1.31 vs 1.29) and revascularization (HR 1.09 vs 1.10) despite event-level discrepancies of 40% and 19% for the 2 respective outcomes. Our analysis has confirmed and extended this finding across

Figure 3



Kaplan-Meier curves.Kaplan-Meier curves for (**A**) death, (**B**) MI, (**C**) stroke, and (**D**) any revascularization. Solid lines indicate Kaplan-Meier curves, whereas shaded bands surrounding those lines indicate 95% confidence bands.*Dx*, diagnosis.

c)



d)

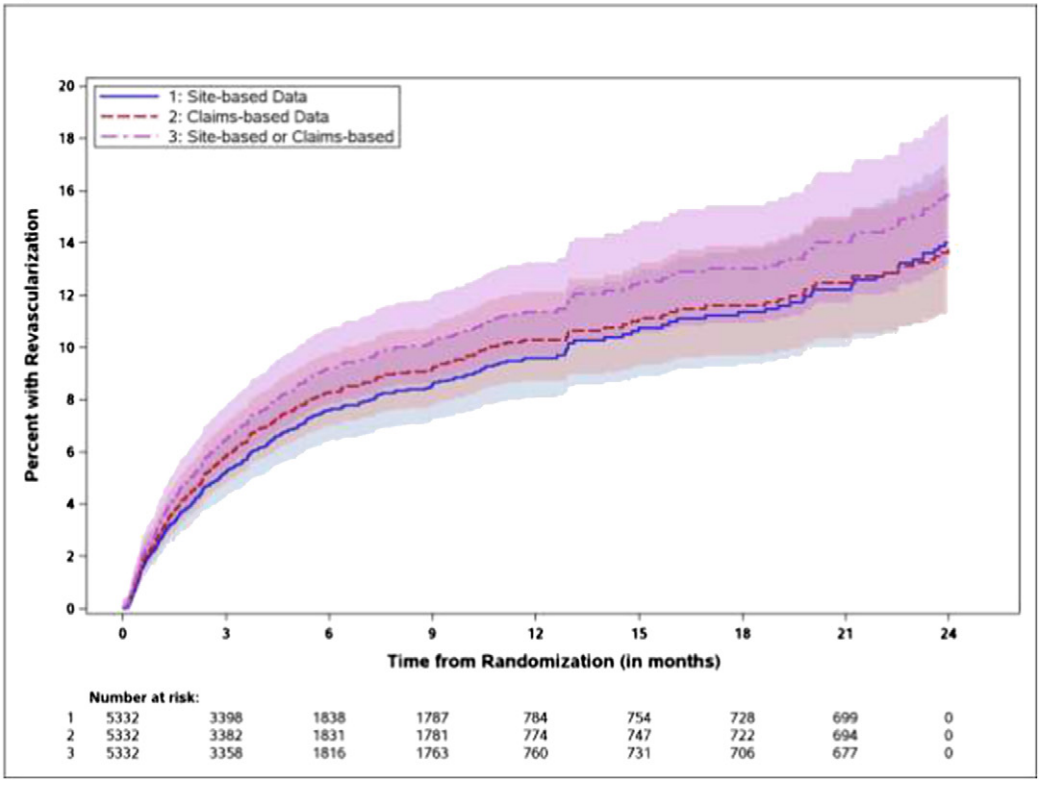
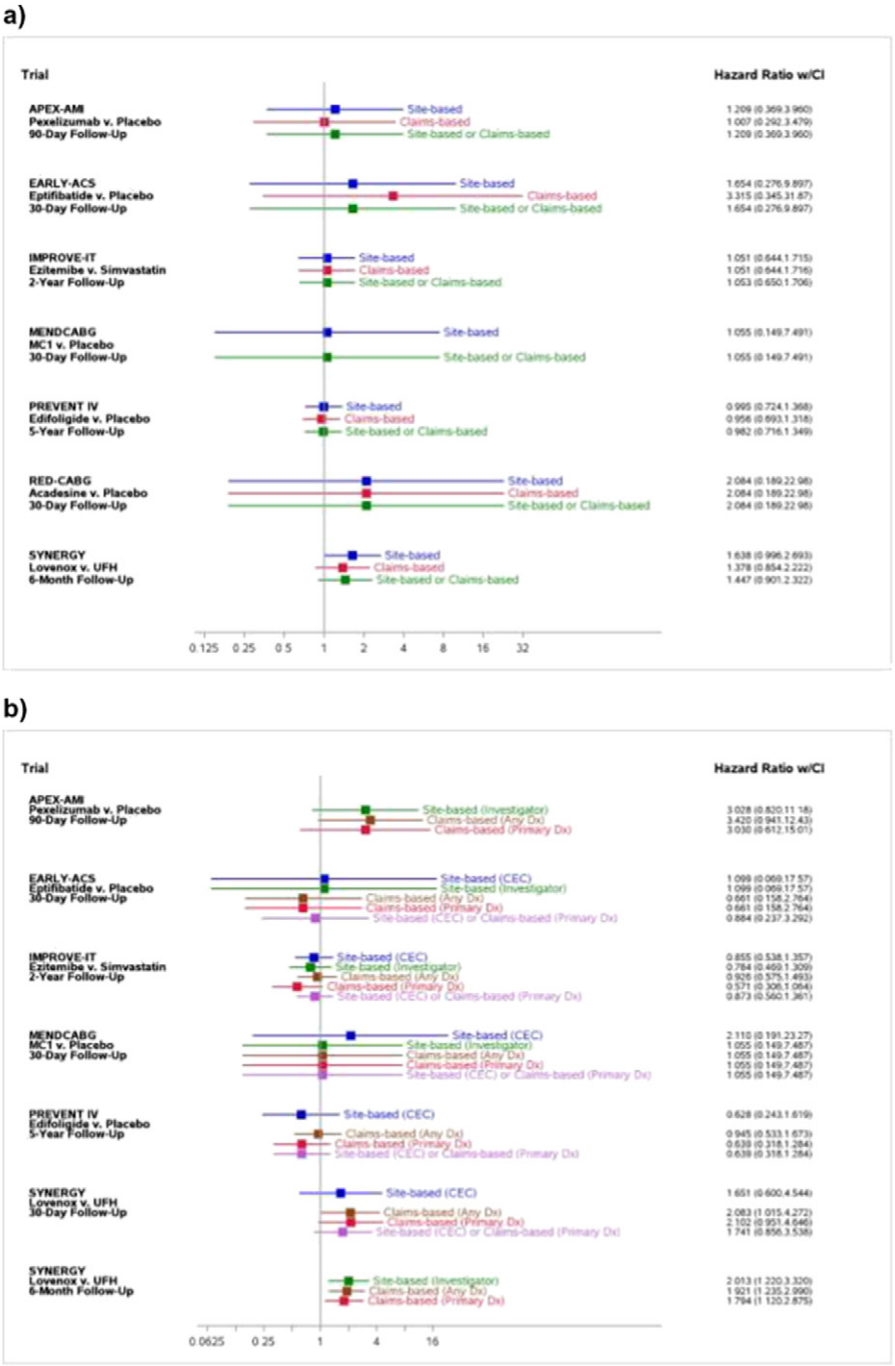
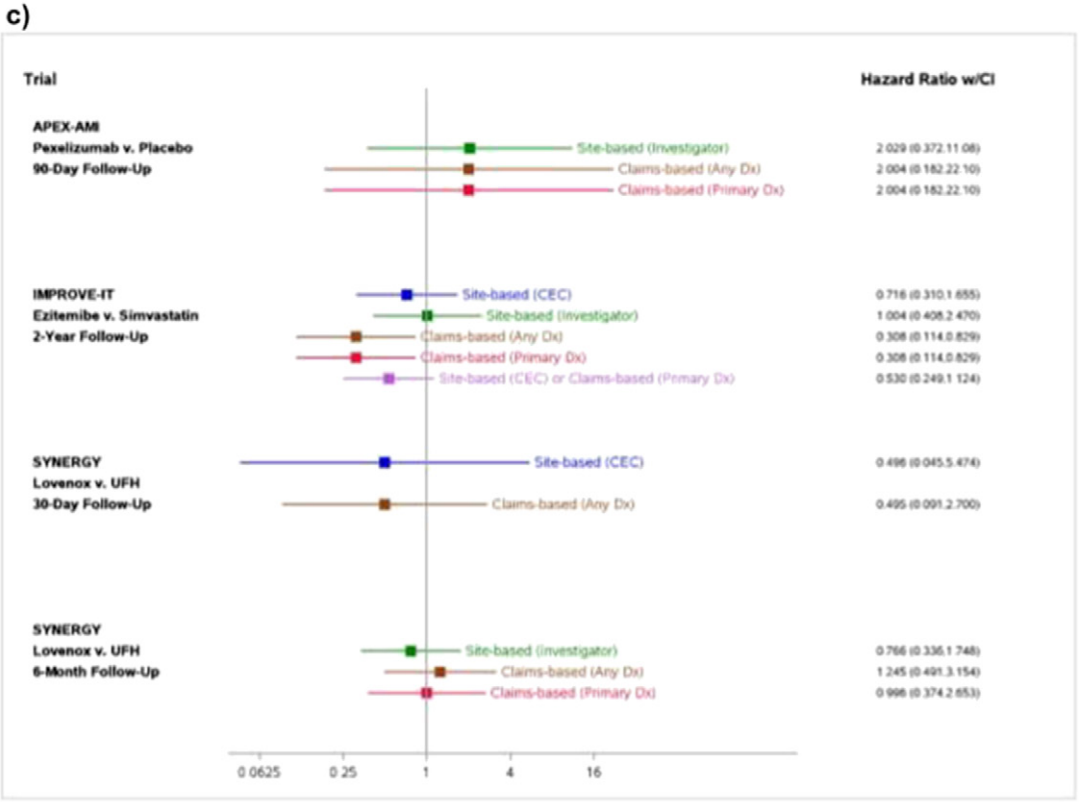


Figure 3 (*continued*).

Figure 4



Randomized treatment effects.Randomized treatment effects for (**A**) death (MEND-CABG II-matched CMS records included only 2 deaths [vs 4 in trial data], insufficient data for calculating HR); (**B**) MI (APEX-AMI did not include CEC adjudication, PREVENT IV investigator data on MI were not recorded consistently, RED-CABG data on MI are not available and the trial is excluded from this graphic, SYNERGY CEC-adjudication of MI data were limited to 30 days [with 6-month follow-up for investigator-reported MI]); (**C**) stroke (APEX-AMI did not include CEC adjudication; PREVENT IV data on stroke are not available and the trial is excluded from this graphic; EARLY-ACS, MEND-CABG II, and RED-CABG stroke data were insufficient for the calculation of HRs and the trials are excluded; SYNERGY CEC-adjudication of stroke data were limited to 30 days [with 6-month follow-up for investigator-reported stroke]); and (**D**) any revascularization (RED-CABG revascularization data are not available and the trial is excluded from this graphic) by clinical trial and follow-up data source. Colored squares indicate point estimates (HRs), whereas horizontal lines indicate 95% CIs.



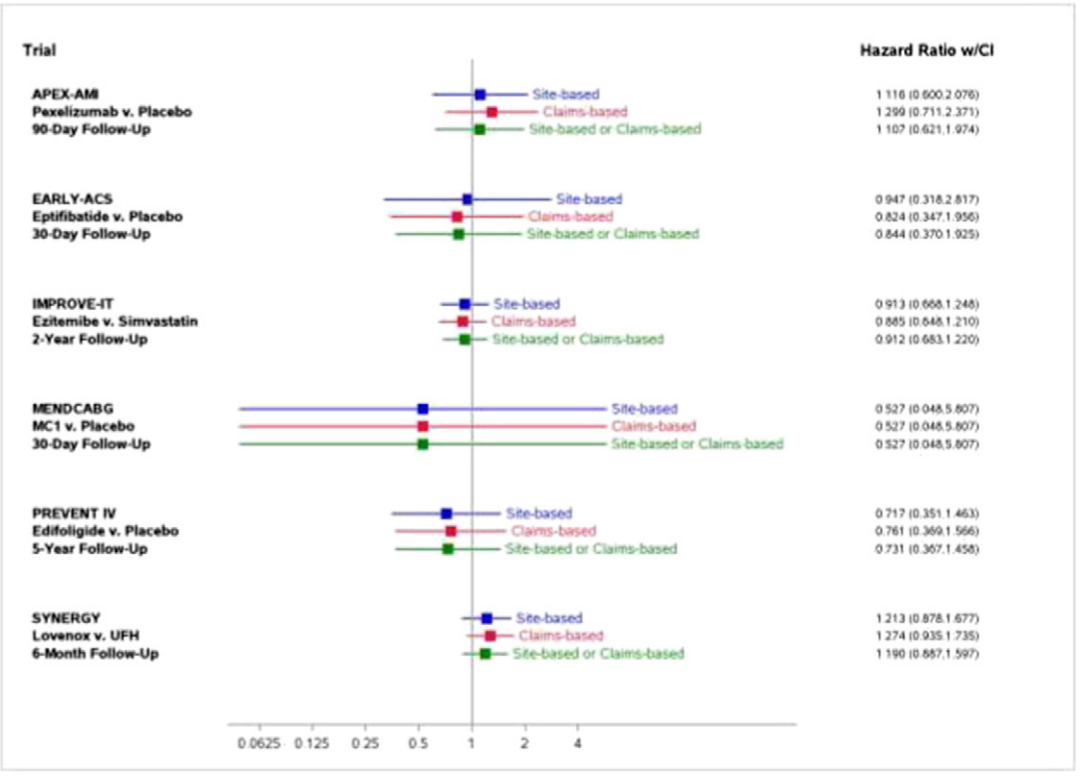


Figure 4 (*continued*).

additional outcomes and across multiple randomized clinical trials.

These data raise an important concern regarding the completeness of outcome ascertainment in pivotal cardiovascular clinical trials. Supplementation of site-based follow-up methods with claims-based follow-up may help to overcome this limitation. Insurance claims are one of many sources of existing electronic healthcare data, and their use is part of a broader effort to leverage existing data to build more efficient clinical research platforms. Insurance claims are routinely generated as a part of nearly every health care encounter in the US. Likewise, the widespread use of the World Health Organization *ICD* administrative codes in 117 countries with translation to 43 different languages offers a means of standardizing outcome definitions for most disease states.[5] These features make insurance claims ideal for a wide range of applications, including long-term follow-up of randomized or observational clinical research cohorts, drug and medical device surveillance systems, and disease outbreak surveillance protocols. In these settings, claims can be used as a primary means of follow-up or as a supplement to more traditional follow-up methods. Finally, claims could also be used as the primary trigger for collection of more detailed patient records for traditional CEC adjudication. With a claims-based "trigger" approach, trial participants would consent to medical records release if insurance claims indicated a diagnosis of the event of interest. The central coordinating center would then reach out to hospital centers for clinical records from these hospitalizations. Using this approach, sites could be closed at the conclusion of patient enrollment. If appropriately applied, each of these approaches could lead to lower costs and resource utilization without compromising the validity of randomized trial results.

Claims-based follow-up has significant strengths but also has important weaknesses and nuances that must be considered when designing clinical protocols. First, insurance claims are not universally accessible. With the recent addition of Medicare Advantage (Part C) plans[17] to the list of available research-accessible files, insurance claims are accessible for most US citizens with disabilities or ≥65 years. However, claims from younger patients (particularly, those with private insurance) remain more difficult to access. Second, although the CMS Virtual Research Data Center has shortened the delay in data availability to 5 months with an estimated claim processing completeness of 93%,[18] it does not currently allow retrieval of patient-level data, limiting subsequent availability for data sharing and results replication. Finally, insurance claims lack a degree of granularity that may be necessary for certain applications (eg, identification of "target lesion" revascularization and patient-reported outcomes). Where this level of specificity is required, insurance claims may serve as a trigger for a targeted, deeper dive into site records for individual patients and hospitalizations.

Limitations

This analysis has many important strengths; however, there are 4 principal limitations to consider. First, there is not a true "gold standard" against which claims-based follow-up can be compared, including for outcomes as seemingly simple as death. In fact, we have provided direct evidence (from trial data) that site-based reporting is incomplete. Consequently, we do not know whether discrepancies are due to over- or underascertainment with one method or the other. Further analysis is needed to understand the cause of differences in event detection between the 2 methods, yet similarities in randomized treatment effects across the follow-up methods provide reassurance that differences are nondifferential. Second, the rigor of our linkage protocol resulted in the inclusion of only 54% of the trials cohort that was eligible for linkage and roughly 10% of the randomized trial participants. In a clinical trial protocol, it is expected that permissions for the use of direct identifiers for linkage to claims data would be obtained from the patient at the time of study enrollment, which would overcome this limitation. Third, our analysis largely included trials with a null treatment effect for our outcomes of interest. Because random noise (ie, incorrectly classified events) would also be expected to yield a null treatment effect, it is possible that this part of our analysis has overestimated the ability of claims to yield a similar treatment effect (vs site-based follow-up). However, given the similar magnitude and directionality of both point estimates and CIs, we do not expect that this had a meaningful effect on our results. Finally, the results included here are only generalizable to the outcomes listed. Additional work will need to be undertaken to address other important outcomes such as bleeding that may be needed to appropriately evaluate both the risks and benefits of an acute coronary syndrome intervention.

Conclusions

Our analysis supports the assertion that insurance claims are a valid source for tracking a variety of cardiovascular outcomes, particularly among older participants in the US. Although important event-level discrepancies were observed, these did not appear to translate into meaningful differences in clinical event rates or randomized treatment effects. If delays in access to claims data are successfully resolved, a hybrid approach (site- plus claims-based follow-up or claims-triggered hospital record queries) may result in a more efficient system of patient follow-up. Future research efforts should target additional outcomes in other disease states, and when possible, research protocols should consider using efficiencies such as claims-based methods

for long-term patient follow-up. The findings from this study will inform strategic priorities within the National Evaluation System for Health Technology and stimulate utilization of claims data in regulatory and other decision making.

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Author contributions

J. M. Brennan: Dr Brennan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Brennan contributed to the conception and design of the study, the data analysis, the data interpretation, the manuscript drafting, and the critical revision of the manuscript.

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Appendix A. Supplementary data

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