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ORIGINAL RESEARCH

Prognosis of Claims- Versus Trial-Based Ischemic and Bleeding Events Beyond 1 Year After Coronary Stenting

Neel M. Butala, MD, MBA; Kamil F. Faridi, MD; Eric A. Secemsky, MD, MSc; Yang Song, MS; Jeptha Curtis, MD; Charles Michael Gibson, MD, MS; Dhruv Kazi, MD, MS; Changyu Shen, PhD; Robert W. Yeh, MD, MSc

BACKGROUND: It is unknown whether clinical events identified with administrative claims have similar prognosis compared with trial-adjudicated events in cardiovascular clinical trials. We compared the prognostic significance of claims-based end points in context of trial-adjudicated end points in the DAPT (Dual Antiplatelet Therapy) study.

METHODS AND RESULTS: We matched 1336 patients aged ≥65 years who received percutaneous coronary intervention in the DAPT study with the CathPCI registry linked to Medicare claims. We compared death at 21 months post-randomization using Cox proportional hazards models among patients with ischemic events (myocardial infarction or stroke) and bleeding events identified by: (1) both trial adjudication and claims; (2) trial adjudication only; and (3) claims only. A total of 47 patients (3.5%) had ischemic events identified by both trial adjudication and claims, 24 (1.8%) in trial adjudication only, 15 (1.1%) in claims only, and 1250 (93.6%) had no ischemic events, with annualized unadjusted mortality rates of 12.8, 5.5, 14.9, and 1.26 per 100 person-years, respectively. A total of 44 patients (3.3%) had bleeding events identified with both trial adjudication and claims, 13 (1.0%) in trial adjudication only, 65 (4.9%) in claims only, and 1214 (90.9%) had no bleeding events, with annualized unadjusted mortality rates of 11.0, 16.8, 10.7, and 0.95 per 100 person-years, respectively. Among patients with no trial-adjudicated events, patients with events in claims only had a high subsequent adjusted mortality risk (hazard ratio (HR) ischemic events: 31.5; 95% CI, 8.9–111.9; HR bleeding events 23.9; 95% CI, 10.7–53.2).

CONCLUSIONS: In addition to trial-adjudicated events, claims identified additional clinically meaningful ischemic and bleeding events that were prognostically significant for death.

Key Words: claims ■ clinical trials ■ DAPT ■ end points ■ prognosis

Real-world data are rapidly changing the conduct of cardiovascular clinical trials. Large-scale trials have leveraged real-world data from registries and wearable devices to generate clinical evidence.[1,2] Furthermore, the US Food and Drug Administration evaluates evidence from real-world data to support regulatory decision-making, including the approval of new drugs.[3] The use of administrative claims data to ascertain outcomes in cardiovascular clinical trials offers opportunity to improve clinical trial data collection and reduce trial costs.[4–6] However, it is unknown whether clinical events identified with claims data have similar prognoses compared with traditional, trial-adjudicated clinical events.

Understanding the significance of clinical events is particularly important after percutaneous coronary intervention (PCI), where subtle changes in definitions of trial end points can lead to differences in patient prognosis and trial results.[7–9] Both spontaneous bleeding and myocardial infarction (MI) after PCI are associated

Correspondence to: Robert W. Yeh, MD MSc, Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology, Department of Medicine, Division of Cardiovascular Disease, Beth Israel Deaconess Medical Center, 375 Longwood Ave, Boston, MA 02215, USA. E-mail: ryeh@bidmc.harvard.edu

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CLINICAL PERSPECTIVE

What Is New?

- In addition to trial-adjudicated events in the DAPT (Dual Antiplatelet Therapy) study, administrative claims identified additional clinically meaningful ischemic and bleeding events that were prognostically significant for death.

What Are the Clinical Implications?

- These results demonstrate the incremental value of claims-based end points in identifying additional clinically meaningful events for subsequent adjudication in clinical trials and support the use of claims to augment clinical trial end point ascertainment in future cardiovascular clinical trials.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
NCDR	national cardiovascular data registry

with increased long-term mortality.[10,11] Furthermore, in patients treated with dual antiplatelet therapy for at least 1 year after PCI in the DAPT (Dual Antiplatelet Therapy) study, late ischemic events and bleeding events were both associated with a high risk of mortality.[12] The prognostic significance of claims-based events in comparison with trial-adjudicated events in this clinical context is unknown.

In this study, we compared the prognostic significance of claims-based ischemic and bleeding end points in context of trial-adjudicated ischemic and bleeding end points in the DAPT study. Such results can inform the use of claims-based end points for evaluation of clinical events post-PCI and thereby shed light on the clinical use of claims-based end points in cardiovascular clinical trials more broadly.

METHODS

EXTEND-DAPT Study Overview

This analysis was performed as part of the Extending Trial-Based Evaluations of Medical Therapies Using Novel Sources of Data (EXTEND) Study, which is funded by the National Heart, Lung, and Blood Institute (1R01HL136708). An overview of the aims and methods, including data linkage, has been previously described.[13] The EXTEND-DAPT substudy used data from the DAPT study linked to the American College of Cardiology's NCDR (National Cardiovascular Data Registry) CathPCI Registry and Medicare fee-for-service beneficiary claims.

The DAPT study was a randomized, placebo-controlled clinical trial which enrolled patients who underwent percutaneous coronary intervention and received DAPT consisting of aspirin and a thienopyridine for 1 year.[14] At 12 months following PCI, patients without post-PCI ischemic or bleeding events were randomized to either placebo (12 total months of DAPT) or continued thienopyridine for another 18 months (30 total months of DAPT). The trial was conducted by the Baim Institute for Clinical Research.

Study Population

We included all US patients aged ≥65 years in the DAPT study who could be successfully linked via the NCDR CathPCI registry to the Centers for Medicare and Medicaid Services inpatient claims data for all fee-for-service Medicare-insured patients. Linkage was performed using deterministic algorithms based on age or date of birth, sex, PCI date and stent type, hospital discharge date, and hospital identifiers and has been previously described.[13] These data were also linked to the Medicare Master Beneficiary Summary File to determine dates of death. Patients who could not be linked to the CathPCI registry because of inexact matching characteristics or who were not subsequently found in Centers for Medicare and Medicaid Services fee-for-service claims or the Medicare Master Beneficiary Summary File were excluded. After applying these criteria to 11 648 patients randomized in the DAPT study, a total of 1336 individuals were included in the linked EXTEND-DAPT cohort (Figure S1). Patients were excluded because of age <65 years (5984 patients), patients outside of the United States (1756 patients), lack of corresponding record in the CathPCI registry (1350 patients), lack of corresponding record in Medicare data (530 patients), and insurance coverage with Medicare Advantage (692 patients). Notably, US patients aged ≥65 years who were able to be successfully matched to the Centers for Medicare and Medicaid Services master file were similar to unmatched patients with regard to most measured covariates, apart from being more often women, having a higher rate of peripheral artery disease, and more often presenting initially with stable angina (Table S1).[15]

All baseline characteristics were obtained from information collected in the DAPT study. The study period was from time of randomization (12 months following PCI) to 21 months post-randomization (33 months following PCI), as specified in the DAPT study. This study was approved by the institutional review board at Beth Israel Deaconess Medical Center and the requirement for informed consent

was waived because of retrospective analysis of pre-existing data.

Study Variables

The primary outcome was death at 21 months after randomization (33 months after coronary stenting) as captured in the DAPT study.

The primary exposures were ischemic events (MI and non-hemorrhagic stroke) and bleeding events occurring 12 to 33 months after coronary stenting in trial data and in claims.

Clinical events in trial data were determined based on adjudication by the DAPT study Clinical Events Committee, which was blinded to randomization status. The trial used pre-specified definitions of MI and stroke for adjudication.[16] Major bleeding in this study was defined as any adjudicated event that met criteria for either moderate or severe bleeding according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries classification, or Type 3 or 5 bleeding according to the Bleeding Academic Research Consortium.

Clinical events in administrative claims were defined based on a comprehensive list of previously validated *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9*) diagnosis codes associated with inpatient hospitalizations.[15,17] For each outcome, we identified *ICD-9* codes based on clinical relevance as well as prior literature (Table S2).[18–22] Given that transfusions were included in trial definitions of bleeding, *ICD-9* procedure codes for blood transfusions were also used. An event was counted if the corresponding codes were present in either the primary or secondary billing position during the hospitalization associated with the event. An event in claims data was counted as a match with a Clinical Events Committee-adjudicated event if the hospitalization admission date occurred within 14 days of the event date determined in the trial.

Statistical Analysis

We compared characteristics and outcomes among 4 groups: (1) those with clinical events identified in both the trial and claims; (2) those with clinical events identified in the trial only; (3) those with clinical events identified in claims only; and (4) those with no clinical events. Categorical variables were reported as counts and percentages, and continuous variables were reported as means (SDs). Between-group differences were assessed using an ANOVA test for continuous variables or a Pearson $\chi 2$ test for categorical variables.

Among the randomized study population, we examined (1) the number of patients with ischemic and bleeding events after randomization in both the trial and in claims-based measures and (2) the annualized mortality rate per 100 person-years after each event. Patients experiencing both ischemic and bleeding events contributed data to both the ischemic events groups and the bleeding events groups; however, for patients with >1 of the same type of event in the trial or in claims, only the earliest event was included.

Cox proportional hazards regression models with exposure status as a time-dependent variable were created to evaluate the independent association of ischemic events or bleeding events with mortality. The time-updated models allowed for patients to contribute both unexposed (ie, before event) and exposed (ie, after event) person-time. Given the limited sample size, ischemic events and bleeding events models were adjusted for a single variable indicating the predicted probability of having ischemic events or bleeding events, respectively, at 21 months using previously developed risk adjustment models that formed the basis of the DAPT score.[23] Hazard ratios (HRs) among different pairs of groups were compared using a Wald test as well as a global Chi-squared statistic and Wald test.

In a supplemental post-hoc analysis, we examined the percentage of patients with claims-only events who had Bleeding Academic Research Consortium Type 2 bleeding events. We additionally compared the annualized mortality rates among any patients with ischemic or bleeding events in trials and all patients with ischemic or bleeding events in claims, including patients with bleeding events in both trials and claims in both groups. Statistical analyses were performed using a software program (SAS, version 9.4; SAS Institute Inc).

RESULTS

Of the 1336 patients in the EXTEND-DAPT cohort, 47 patients (3.5%) had ischemic events identified with both trial adjudication and claims, 24 (1.8%) had trial-adjudicated ischemic events only, 15 (1.1%) had ischemic events in claims only, and 1250 (93.6%) had no ischemic events (Figure 1A). These 4 groups of patients had similar baseline characteristics with the exception of treated vessel and drug-eluting stent type (Table 1). A total of 44 patients (3.3%) had bleeding events identified with both trial adjudication and claims, 13 (1.0%) had trial-adjudicated bleeding events only, 65 (4.9%) had bleeding events in claims only, and 1214 (90.9%) had no bleeding events (Figure 1B). Notably, of the 65 patients with bleeding events in claims alone, 18 (28%) had Bleeding Academic Research Consortium Type 2 bleeding events in the trial data. These 4 groups of patients also had similar baseline characteristics with the exception of presentation with stable angina and treated vessel (Table 2).

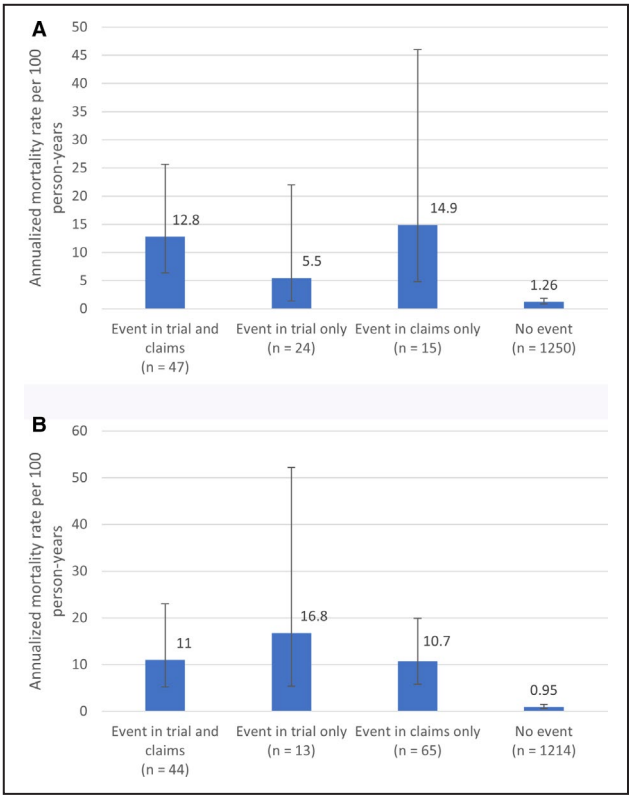

Figure 1. Frequency of ischemic and bleeding events in trial vs claims and subsequent annualized mortality rate during the 21-month post-randomization period.
(**A**) Ischemic events; (**B**) Bleeding events. The annualized rate was calculated as: (number of subjects who died after a clinical event)/(total follow-up years for each of the 3 cohorts after a clinical event). For the 'no event' group, the annualized mortality rate is calculated as: (number of subjects who died/total follow-up years). Error bars indicate 95% CIs.

The unadjusted annualized mortality rate after an ischemic event identified with both trial adjudication and claims, an ischemic event identified with trial adjudication only, an ischemic event identified with claims only, and among those without an ischemic event was 12.8, 5.5, 14.9, and 1.26 per 100 person-years, respectively (Figure 1A). The unadjusted annualized mortality rate after a bleeding event identified with both trial adjudication and claims, a bleeding event identified with trial adjudication only, a bleeding event identified with claims only, and among those without a bleeding event was 11.0, 16.8, 10.7, and 0.95 per 100 person-years, respectively (Figure 1B).

The adjusted HRs for mortality following an ischemic event were 21.5 (95% CI, 9.1–50.4) when identified with both trial adjudication and claims, 9.5 (95% CI, 2.2–40.9) when identified with trial adjudication only, and 31.5 (95% CI, 8.9–111.9) when identified with claims only, relative to those who did not have an event (Figure 2A). Although CIs for point estimates were wide, the lower bound of the CIs in each group did not cross 1. There was no significant difference in the mortality HR in pair-wise comparisons across these 3 groups.

The adjusted HRs for mortality following a bleeding event were 17.7 (95% CI, 7.0–44.8) when identified with trial adjudication and claims, 48.7 (95% CI, 13.6–73.6) when identified with trial adjudication only, and 23.9 (95% CI, 10.7–53.2) when identified with claims only, relative to those who did not have an event (Figure 2B). Once again, although CIs for point estimates were wide, the lower bound of the CIs in each group did not cross 1. Again, there was no significant difference in the mortality HR in pair-wise comparisons across these 3 groups.

In supplemental analysis, the unadjusted annualized mortality rate after any ischemic event identified via trial adjudication (n=71) was 10.1 person-years (95% CI, 5.4–18.8) and the unadjusted annualized mortality rate after any ischemic event identified via claims (n=62) was 5.5 person-years (95% CI, 1.4–22.0; Table S3). Additionally, the unadjusted annualized mortality rate after any bleeding event identified via trial adjudication (n=57) was 12.3 person-years (95% CI, 6.6–22.8) and the unadjusted annualized mortality rate after any ischemic event identified via claims (n=109) was 10.8 person-years (95% CI, 6.7–71.4).

DISCUSSION

This study examined the prognosis of claims-based versus trial-based clinical events in the DAPT study. We found that, in addition to trial-adjudicated events, ischemic and bleeding events ascertained using claims were prognostically significant for death. These results demonstrate the incremental value of claims in identifying additional clinically meaningful outcomes in future cardiovascular clinical trials.

This study extends prior knowledge on prognosis of ischemic and bleeding events post-PCI. Previous studies have evaluated the relationship between post-PCI clinical events and mortality with differing definitions of end points and duration of follow-up. In the CHAMPION-PHEONIX trial, both centrally Clinical Events Committee-adjudicated MI and site investigator-identified MI had independent prognostic significance for higher 30-day death.[24] Ischemic and bleeding events ascertained from electronic health records have also previously been demonstrated to identify patients with poor prognosis in the first year after PCI.[10] Additionally, trial-adjudicated bleeding events have been associated with worse outcomes up to 1 year,[25] and registry-based ascertainment of bleeding events was associated with increased risk of death up to 2 years post-PCI.[11,26] A sub-analysis of the DAPT study found that both trial-adjudicated

Table 1. Baseline Characteristics of Patients With Ischemic Events in Trials and Claims Data

Characteristics	Event in Both Trial and Claims (n=47)	Event in Trial Only (n=24)	Event in Claims Only (n=15)	No Event (n=1250)	*P* Value*
Clinical characteristics					
Age, y					
Mean±SD, n	72.3±6.3 (47)	71.0±4.2 (24)	73.9±5.4 (15)	71.8±5.5 (1250)	0.312
Median (Q1, Q3)	71.0 (67.1, 74.0)	70.3 (68.0, 74.5)	73.0 (69.0, 76.0)	71.0 (67.0, 75.0)	
Range (min, max)	(65.0, 89.0)	(65.0, 80.0)	(65.0, 84.0)	(65.0, 91.0)	
Women	38.3% (18/47)	33.3% (8/24)	33.3% (5/15)	32.5% (406/1250)	0.954
Race					
American Indian or Alaska Native	0.0% (0/47)	0.0% (0/24)	0.0% (0/15)	0.2% (3/1244)	0.691
Asian	0.0% (0/47)	0.0% (0/24)	0.0% (0/15)	0.6% (8/1244)	
Black	4.3% (2/47)	4.2% (1/24)	0.0% (0/15)	3.9% (48/1244)	
Native Hawaiian or Other Pacific Islander	0.0% (0/47)	0.0% (0/24)	0.0% (0/15)	0.2% (2/1244)	
White	93.6% (44/47)	87.5% (21/24)	100.0% (15/15)	93.4% (1162/1244)	
Other	2.1% (1/47)	8.3% (2/24)	0.0% (0/15)	1.7% (21/1244)	
Hispanic or Latino	2.2% (1/46)	12.5% (3/24)	0.0% (0/14)	2.3% (29/1246)	0.095
Body mass index, Kg/m^2					
Mean±SD, n	29.3±.2 (47)	29.3±6.0 (24)	27.9±3.7 (15)	29.7±5.3 (1250)	0.650
Median (Q1, Q3)	28.6 (25.6, 31.3)	28.3 (25.8, 32.3)	26.9 (24.8, 31.2)	29.0 (26.0, 32.5)	
Range (min, max)	(22.0, 46.3)	(20.8, 43.0)	(22.0, 35.0)	(15.7, 52.2)	
Diabetes mellitus	46.8% (22/47)	52.2% (12/23)	26.7% (4/15)	32.4% (405/1249)	0.290
Insulin	21.3% (10/47)	13.0% (3/23)	0.0% (0/15)	8.1% (101/1249)	0.144
Oral medications	21.3% (10/47)	34.8% (8/23)	20.0% (3/15)	20.7% (258/1249)	0.428
Diet controlled or no treatment	4.3% (2/47)	4.3% (1/23)	6.7% (1/15)	3.7% (46/1249)	1.000
Hypertension	89.4% (42/47)	83.3% (20/24)	100.0% (15/15)	84.8% (1057/1246)	0.244
Peripheral artery disease	17.0% (8/47)	18.2% (4/22)	6.7% (1/15)	10.1% (124/1233)	0.714
Congestive heart failure	19.1% (9/47)	8.3% (2/24)	13.3% (2/15)	5.8% (72/1241)	0.510
Previous myocardial infarction	22.2% (10/45)	34.8% (8/23)	33.3% (5/15)	20.5% (250/1217)	0.481
Stroke/transient ischemic event	6.4% (3/47)	0.0% (0/22)	6.7% (1/15)	5.4% (68/1249)	0.501
Prior procedures					
Previous percutaneous coronary intervention	46.8% (22/47)	58.3% (14/24)	53.3% (8/15)	34.1% (424/1242)	0.673
Coronary artery bypass graft	23.4% (11/47)	20.8% (5/24)	20.0% (3/15)	16.2% (202/1248)	1.000
Indication for index procedure					
Acute coronary syndrome	25.5% (12/47)	16.7% (4/24)	13.3% (2/15)	14.7% (184/1250)	0.625
STEMI	0.0% (0/47)	0.0% (0/24)	6.7% (1/15)	4.2% (52/1250)	0.174
NSTEMI	25.5% (12/47)	16.7% (4/24)	6.7% (1/15)	10.6% (132/1250)	0.306
Unstable angina[3]	12.8% (6/47)	16.7% (4/24)	6.7% (1/15)	15.2% (190/1250)	0.754
Stable angina	31.9% (15/47)	37.5% (9/24)	66.7% (10/15)	45.4% (568/1250)	0.060
Other	29.8% (14/47)	29.2% (7/24)	13.3% (2/15)	24.6% (308/1250)	0.534
Procedural characteristics					
Treated vessel					
Left main	0.0% (0/60)	0.0% (0/30)	5.0% (1/20)	1.3% (21/1658)	0.030
LAD	38.3% (23/60)	20.0% (6/30)	40.0% (8/20)	37.7% (625/1658)	
RCA	28.3% (17/60)	53.3% (16/30)	45.0% (9/20)	33.2% (550/1658)	
Circumflex	23.3% (14/60)	26.7% (8/30)	10.0% (2/20)	23.4% (388/1658)	
Venous graft	10.0% (6/60)	0.0% (0/30)	0.0% (0/20)	4.0% (66/1658)	
Arterial graft	0.0% (0/60)	0.0% (0/30)	0.0% (0/20)	0.5% (8/1658)	

(*Continued*)

Table 1. Continued

Characteristics	Event in Both Trial and Claims (n=47)	Event in Trial Only (n=24)	Event in Claims Only (n=15)	No Event (n=1250)	*P* Value*
DES types, identified at index (per patient)					
Cypher	19.5% (8/41)	10.0% (2/20)	21.4% (3/14)	12.8% (149/1160)	0.038
Endeavor	14.6% (6/41)	5.0% (1/20)	14.3% (2/14)	14.4% (167/1160)	
TAXUS	24.4% (10/41)	0.0% (0/20)	21.4% (3/14)	20.3% (236/1160)	
Xience/PROMUS	41.5% (17/41)	85.0% (17/20)	42.9% (6/14)	50.2% (582/1160)	
>1 DES type	0.0% (0/41)	0.0% (0/20)	0.0% (0/14)	2.2% (26/1160)	
Minimum stent diameter (per patient)					
<3	48.9% (23/47)	70.8% (17/24)	40.0% (6/15)	48.1% (601/1250)	0.113
≥3	51.1% (24/47)	29.2% (7/24)	60.0% (9/15)	51.9% (649/1250)	
Total stent lengths, mm (sum per patient)					
Mean±SD, n	27.1±16.0 (47)	27.1±15.2 (24)	25.3±16.6 (15)	26.2±16.2 (1250)	0.917
Median (Q1, Q3)	20.0 (16.0, 32.0)	25.0 (15.0, 39.0)	24.0 (12.0, 32.0)	23.0 (15.0, 30.0)	
Range (min, max)	(8.0, 85.0)	(8.0, 56.0)	(8.0, 74.0)	(8.0, 140.0)	
Randomization group					
Placebo	61.7% (29/47)	54.2% (13/24)	53.3% (8/15)	50.2% (628/1250)	0.762
Continued thienopyridine	38.3% (18/47)	45.8% (11/24)	46.7% (7/15)	49.8% (622/1250)	

STEMI indicates ST-segment–elevation myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; LAD, left anterior descending; RCA, right coronary artery; and DES, drug-eluting stent.

*Between-group differences were assessed using an ANOVA test for continuous variables or a Fisher exact test for categorical variables comparing first 3 columns only (no event column not included).

ischemic and bleeding events beyond 1 year and up to 30 months post-PCI were associated with worse mortality.[12] However, there are limited data on the prognostic impact of clinical events that may not meet strict criteria for trial adjudication at this interval. We found that ischemic and bleeding events identified only via administrative claims have a similar prognosis for death as trial-adjudicated events beyond 1 year after PCI, despite controlling for baseline ischemic or bleeding risk. These results suggest that ischemic and bleeding events continue to have poor prognostic impact beyond 1 year after PCI, irrespective of clinical event definition or ascertainment mechanism.

The results from this study demonstrate the potential value of claims-based approaches to ascertain additional clinically meaningful events in clinical trials. Some have suggested that using claims to augment outcome ascertainment in clinical trials can improve the efficiency of clinical trial data collection.[4–6] However, studies evaluating the accuracy of claims in ascertaining clinically adjudicated outcomes in large observational studies have found discordant results.[20,27,28] An analysis of the DAPT study found that claims data had moderate agreement with trial-adjudicated MI, but poor agreement for trial-adjudicated bleeding and stroke.[15,17] Nevertheless, treatment effects of extended-duration DAPT after PCI using claims-derived events were numerically similar to those using adjudicated events.[17] Discrepancies between trial- and claims-based events may stem from differences between the stringent trial end point definitions and the broad inclusion criteria in claims-based approaches, particular for softer end points. However, these additional claims-based events were not simply mild events not meeting the adjudication threshold, as the vast majority of claims-only bleeding events were also not captured as lesser severity Bleeding Academic Research Consortium Type 2 events in the trial. We find that instances in which claims and trials are discordant in identifying a clinical event are still clinically meaningful for patient mortality after PCI. Thus, claims may help identify additional patients with ischemic and bleeding events with important prognostic implications post-PCI that would have otherwise not been captured in traditional trial adjudication. Future trials can incorporate authorization for linkage to insurance data prospectively using direct identifiers to identify such events in claims, and this can serve as an adjunct to existing trial adjudication processes. Future studies are needed to determine the prognosis of other claims-based end points for their potential to augment cardiovascular clinical trials in other contexts.

This study has implications for use of real-world data to ascertain outcomes in future cardiovascular clinical trial design. As has been seen with the additional events captured with centralized adjudication in

Table 2. Baseline Characteristics of Patients With Bleeding Events in Trials and Claims Data

Characteristics	Event in Both Trial and Claims (n=44)	Event in Trial Only (n=13)	Event in Claims Only (n=65)	No Event (n=1214)	*P* Value*
Clinical characteristics					
Age, y					
Mean±SD, n	74.4±6.4 (44)	74.4±6.4 (13)	73.5±5.4 (65)	71.6±5.4 (1214)	0.728
Median (Q1, Q3)	73.0 (70.0, 80.5)	74.0 (70.0, 80.0)	72.0 (70.0, 76.0)	70.0 (67.0, 75.0)	
Range (min, max)	(65.0, 87.0)	(66.0, 85.0)	(65.0, 89.0)	(65.0, 91.0)	
Women	38.6% (17/44)	30.8% (4/13)	43.1% (28/65)	32.0% (388/1214)	0.717
Race					
American Indian or Alaska Native	0.0% (0/44)	0.0% (0/13)	0.0% (0/65)	0.2% (3/1208)	0.210
Asian	0.0% (0/44)	7.7% (1/13)	0.0% (0/65)	0.6% (7/1208)	
Black	4.5% (2/44)	7.7% (1/13)	3.1% (2/65)	3.8% (46/1208)	
Native Hawaiian or Other Pacific Islander	2.3% (1/44)	0.0% (0/13)	0.0% (0/65)	0.1% (1/1208)	
White	88.6% (39/44)	84.6% (11/13)	95.4% (62/65)	93.5% (1130/1208)	
Other	4.5% (2/44)	0.0% (0/13)	1.5% (1/65)	1.7% (21/1208)	
Hispanic or Latino	4.7% (2/43)	0.0% (0/13)	1.5% (1/65)	2.5% (30/1209)	0.689
Body mass index, Kg/m^2					
Mean±SD, n	28.5±5.3 (44)	29.2±4.6 (13)	29.6±5.5 (65)	29.7±5.3 (1214)	0.538
Median (Q1, Q3)	27.3 (24.6, 31.1)	29.0 (27.0, 31.7)	29.0 (26.1, 31.6)	29.0 (26.0, 32.5)	
Range (min, max)	(19.3, 44.7)	(21.1, 36.1)	(19.0, 47.0)	(15.7, 52.2)	
Diabetes mellitus	32.6% (14/43)	38.5% (5/13)	46.2% (30/65)	32.5% (394/1213)	0.366
Insulin	4.7% (2/43)	7.7% (1/13)	12.3% (8/65)	8.5% (103/1213)	0.425
Oral medications	25.6% (11/43)	30.8% (4/13)	30.8% (20/65)	20.1% (244/1213)	0.840
Diet controlled or no treatment	2.3% (1/43)	0.0% (0/13)	3.1% (2/65)	3.9% (47/1213)	1.000
Hypertension	81.8% (36/44)	92.3% (12/13)	86.2% (56/65)	85.1% (1030/1210)	0.705
Peripheral artery disease	18.6% (8/43)	15.4% (2/13)	15.6% (10/64)	9.8% (117/1197)	0.937
Congestive heart failure	9.1% (4/44)	7.7% (1/13)	10.9% (7/64)	6.1% (73/1206)	1.000
Previous myocardial infarction	19.0% (8/42)	23.1% (3/13)	19.7% (12/61)	21.1% (250/1184)	0.893
Stroke/Transient ischemic attack	7.0% (3/43)	7.7% (1/13)	6.2% (4/65)	5.3% (64/1212)	1.000
Prior procedures					
Previous percutaneous coronary intervention	40.9% (18/44)	30.8% (4/13)	43.8% (28/64)	34.6% (418/1207)	0.745
Coronary artery bypass graft	18.2% (8/44)	23.1% (3/13)	18.5% (12/65)	16.3% (198/1212)	0.890
Indication for index procedure					
Acute coronary syndrome	15.9% (7/44)	23.1% (3/13)	9.2% (6/65)	15.3% (186/1214)	0.263
STEMI	6.8% (3/44)	0.0% (0/13)	4.6% (3/65)	3.9% (47/1214)	0.842
NSTEMI	9.1% (4/44)	23.1% (3/13)	4.6% (3/65)	11.4% (139/1214)	0.090
Unstable angina[3]	13.6% (6/44)	7.7% (1/13)	7.7% (5/65)	15.6% (189/1214)	0.681
Stable angina	43.2% (19/44)	15.4% (2/13)	52.3% (34/65)	45.1% (547/1214)	0.046
Other	27.3% (12/44)	53.8% (7/13)	30.8% (20/65)	24.1% (292/1214)	0.206
Procedural characteristics					
Treated vessel					
Left main	0.0% (0/63)	0.0% (0/21)	1.3% (1/80)	1.3% (21/1604)	0.032
LAD	33.3% (21/63)	23.8% (5/21)	52.5% (42/80)	37.0% (594/1604)	
RCA	23.8% (15/63)	52.4% (11/21)	26.3% (21/80)	34.0% (545/1604)	
Circumflex	33.3% (21/63)	19.0% (4/21)	15.0% (12/80)	23.4% (375/1604)	
Venous graft	7.9% (5/63)	0.0% (0/21)	3.8% (3/80)	4.0% (64/1604)	
Arterial graft	1.6% (1/63)	4.8% (1/21)	1.3% (1/80)	0.3% (5/1604)	

(*Continued*)

Table 2. Continued

Characteristics	Event in Both Trial and Claims (n=44)	Event in Trial Only (n=13)	Event in Claims Only (n=65)	No Event (n=1214)	*P* Value*
DES types, identified at index (per patient)					
Cypher	12.2% (5/41)	23.1% (3/13)	15.3% (9/59)	12.9% (145/1122)	0.613
Endeavor	12.2% (5/41)	7.7% (1/13)	10.2% (6/59)	14.6% (164/1122)	
TAXUS	22.0% (9/41)	7.7% (1/13)	25.4% (15/59)	20.0% (224/1122)	
Xience/PROMUS	51.2% (21/41)	53.8% (7/13)	49.2% (29/59)	50.4% (565/1122)	
>1 DES type	2.4% (1/41)	7.7% (1/13)	0.0% (0/59)	2.1% (24/1122)	
Minimum stent diameter (per patient)					
<3	40.9% (18/44)	46.2% (6/13)	52.3% (34/65)	48.5% (589/1214)	0.509
≥3	59.1% (26/44)	53.8% (7/13)	47.7% (31/65)	51.5% (625/1214)	
Total stent lengths, mm (sum per patient)					
Mean±SD, n	28.9±20.4 (44)	28.8±16.4 (13)	22.8±12.0 (65)	26.3±16.2 (1214)	0.113
Median (Q1, Q3)	22.5 (16.5, 29.0)	28.0 (15.0, 41.0)	18.0 (15.0, 28.0)	23.0 (15.0, 31.0)	
Range (min, max)	(8.0, 99.0)	(8.0, 61.0)	(8.0, 80.0)	(8.0, 140.0)	
Randomization group					
Placebo	45.5% (20/44)	30.8% (4/13)	41.5% (27/65)	51.6% (627/1214)	0.695
Continued thienopyridine	54.5% (24/44)	69.2% (9/13)	58.5% (38/65)	48.4% (587/1214)	

STEMI indicates ST-segment–elevation myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; LAD, left anterior descending; RCA, right coronary artery; and DES, drug-eluting stent.

*Between-group differences were assessed using an ANOVA test for continuous variables or a Fisher exact test for categorical variables comparing first 3 columns only (no event column not included).

clinical trials,[24] claims-based end points can identify additional meaningful events beyond trial adjudication as well as patients with poor prognosis, both of which can inform the understanding of an intervention's broader long-term effects. Thus, predetermined definitions in clinical trials may be missing key events that have important prognostic value. However, given that claims-based end point ascertainment may not be as precise in identifying specific clinical events, it may be best suited to operate in parallel with traditional trial adjudication processes. A hybrid model in which claims-based events can trigger further trial adjudication and review may enhance the efficiency of clinical trial event ascertainment. It is important to note that, while both trial-adjudicated and claims-based clinical events are clinically meaningful, events of both types may not be in the causal pathway of a particular intervention being studied. Subtle differences in definitions of clinical events can have different prognostic implications and trial results,[7–9] as in the case of the EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial in which variations in definition of periprocedural MI can lead to differing conclusions.[29,30] As such, incorporation of claims into the case definition of any trial must align with the intended construct of the outcome meant to be tested in the trial hypothesis. Although no statistically significant differences were found between claims versus trial-based definitions of events, this study was underpowered to detect some clinically meaningful differences. Future studies will be important to determine if claims capture clinically distinct phenotypes that may have different long-term clinical prognoses for a given intervention.

This study's findings must be interpreted in context of its limitations. First, our cohort included only a subset of the full DAPT study that could be linked to Medicare claims data, as a large number of DAPT study patients were aged <65 years or enrolled outside of the United States. The results thus may not be generalizable to other claims data sets or populations. Second, the number of events in our study is small, leading to wide CIs for HR estimates. Finally, this study only used *ICD-9* codes, and results may differ with *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10*) codes, although sensitivity of *ICD-9* versus *ICD-10* codes in ascertaining cardiovascular end points is generally similar,[31] and most of the specific codes for MI and bleeding diagnoses across classification schemes are the same. Future research should investigate the prognostic significance of *ICD-10* codes for ascertaining events.

In examining patients in the DAPT study linked to administrative claims data, we found that clinical events identified with claims data had a prognostic impact similar to clinical events identified via trial adjudication. These results demonstrate the incremental value of claims-based end points in identifying additional clinically meaningful events for subsequent adjudication and support the use of claims to augment clinical trial

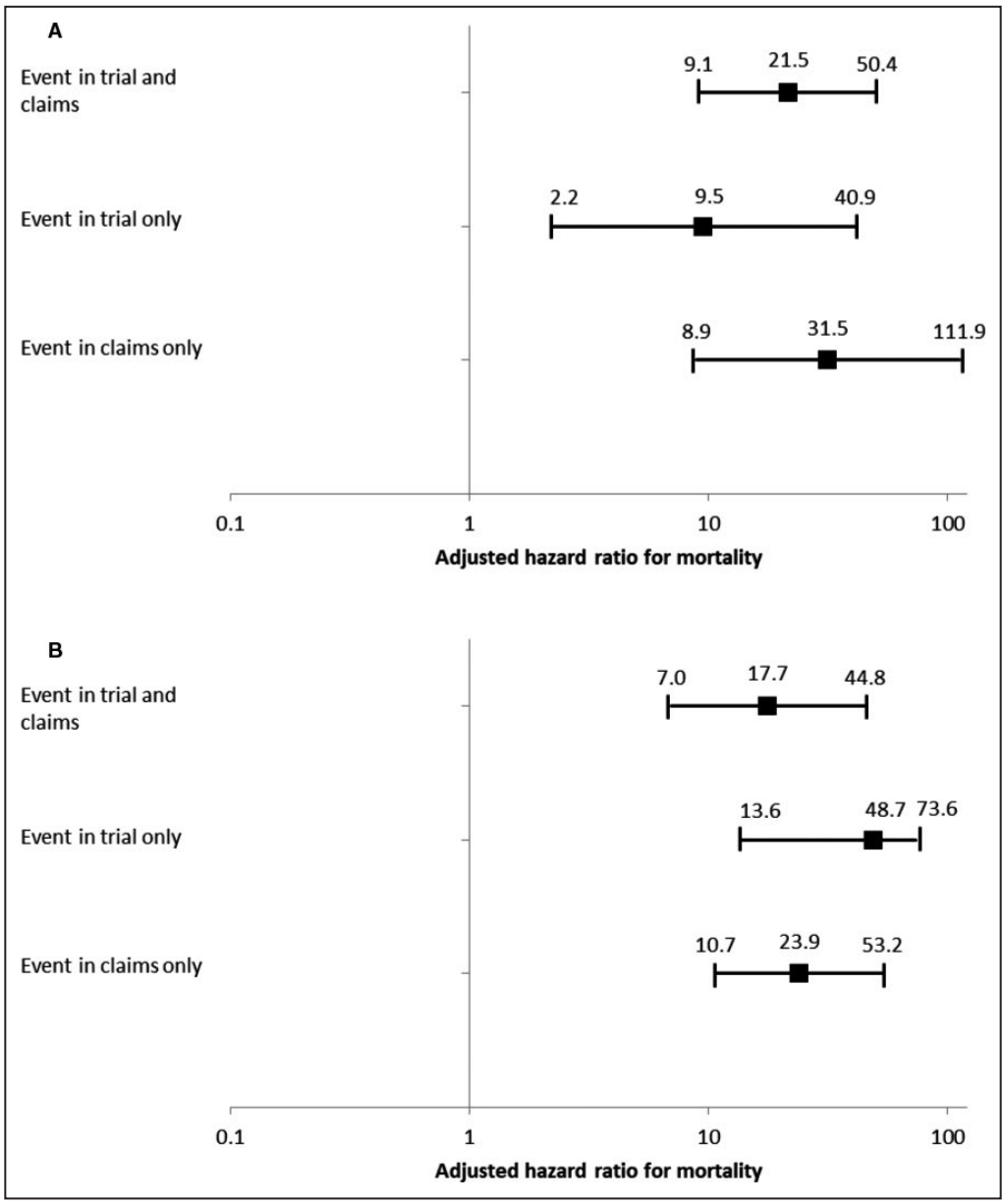

Figure 2. Adjusted risk of mortality after trial vs claims-based ischemic or bleeding events during the 21-month post-randomization period.
(**A**) Ischemic events; **(B)** Bleeding events. Hazard ratios compare risk of death of patients with clinical events relative to those without such events. Models are adjusted for predicted probability of having ischemic or bleeding events at 21 months based on models from the DAPT (Dual Antiplatelet Therapy) study. The DAPT study ischemic risk model includes whether a patient had a myocardial infarction at presentation, prior percutaneous coronary intervention or MI, history of heart failure or left ventricular ejection fraction <30%, vein graft percutaneous coronary intervention, stent diameter <3 mm, use of a paclitaxel-eluting stent, smoking status, diabetes mellitus, peripheral artery disease, hypertension, and renal insufficiency. The DAPT study bleeding risk model includes age, peripheral artery disease, hypertension, and renal insufficiency. For ischemic events, pairwise *P* value comparing both trial and claims vs trial only, 0.304; pairwise *P* value comparing both trial and claims vs claims only, 0.576; and pairwise *P* value comparing trial only vs claims only, 0.193, based on the Wald test. Global Chi-squared statistic comparing all ischemic event 3 groups, 2.861; and *P* value from Wald test comparing all 3 groups, 0.239. For bleeding events, pairwise *P* value comparing both trial and claims vs trial only, 0.145; pairwise *P* value comparing both trial and claims vs claims only, 0.545; and pairwise *P* value comparing trial only vs claims only, 0.283 based on the Wald test. Global Chi-squared statistic comparing all 3 bleeding event groups, 2.878; and *P* value from Wald test comparing all 3 groups, 0.237.

end point ascertainment in future cardiovascular clinical trials. Future studies will be important to determine the prognosis of other claims-based end points and whether claims capture clinically distinct phenotypes that may have different implications for a given intervention in other contexts.

ARTICLE INFORMATION

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Affiliations

From the Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology, Division of Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Boston, MA (N.M.B., E.A.S., D.K., C.S., R.W.Y.); Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA (N.M.B.); Section of Cardiovascular Medicine, Department of Medicine, Yale School of Medicine, New Haven, CT (K.F.F., J.C.); and Baim Institute for Clinical Research, Boston, MA (Y.S., C.M.G., R.W.Y.).

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Supplementary Material

Tables S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics and Outcomes of Matched and Unmatched Patients ≥65 Years Old in the EXTEND-DAPT Study.

Measure	Matched FFS Patients (N=1336 Patients)	UnMatched Patients (N=2572 Patients)	P-value
Demographics			
Age (years)			
Age Mean±SD (N)	71.8±5.5 (1336)	71.5±5.3 (2572)	0.094
Female	32.7% (437/1336)	29.5% (759/2572)	0.041
Race-Non-White	6.6% (88/1330)	7.5% (190/2544)	0.359
Hispanic or Latino	2.5% (33/1330)	3.6% (91/2534)	0.068
BMI (Kg/m^2) Mean±SD (N)	29.6±5.3 (1336)	29.7±5.3 (2550)	0.761
Medical History			
Diabetes mellitus	33.2% (443/1334)	34.4% (883/2569)	0.476
Hypertension	85.1% (1134/1332)	83.1% (2134/2569)	0.099
Current cigarette smoker or within past year[1]	11.3% (149/1322)	10.8% (276/2546)	0.704
Stroke/TIA	5.4% (72/1333)	4.8% (123/2564)	0.439
History of major bleeding	1.0% (13/1330)	1.1% (29/2559)	0.745
Congestive heart failure	6.4% (85/1327)	6.8% (173/2562)	0.734
Peripheral arterial disease	10.4% (137/1317)	8.2% (207/2525)	0.027
Previous percutaneous coronary intervention	35.2% (468/1328)	37.0% (947/2562)	0.292
Coronary artery bypass graft	16.6% (221/1334)	18.0% (462/2567)	0.267
Atrial fibrillation	4.8% (63/1326)	4.8% (124/2560)	0.937
Indication for Index Procedure			
ACS	15.1% (202/1336)	19.1% (490/2572)	0.002
STEMI	4.0% (53/1336)	6.6% (170/2572)	<.001
NSTEMI	11.2% (149/1336)	12.4% (320/2572)	0.254
Unstable Angina[3]	15.0% (201/1336)	16.1% (414/2572)	0.405
Stable Angina	45.1% (602/1336)	40.9% (1053/2572)	0.014
Other	24.8% (331/1336)	23.9% (615/2572)	0.555

BMI = body mass index, NSTEMI = non-STE elevation myocardial infarction, SD = standard deviation, STEMI = ST-elevation myocardial infarction, TIA = transient ischemic attack

Table S2. ICD-9 Codes Used to Assess Clinical Events.

Outcome	ICD-9 code	Description
Myocardial Infarction	410.xx (excluding 410.x2)	Acute myocardial infarction (excluding subsequent episode of care)
Stroke	433.11	Occlusion and stenosis of carotid artery with cerebral infarction
	434.01	Cerebral thrombosis with cerebral infarction
	434.11	Cerebral embolism with cerebral infarction
	434.91	Cerebral artery occlusion, unspecified with cerebral infarction
	435.9	Unspecified transient cerebral ischemia
	997.02	Iatrogenic cerebrovascular infarction or hemorrhage
Major Bleeding	285.1	Acute posthemorrhagic anemia
	362.81	Retinal hemorrhage
	379.23	Vitreous hemorrhage
	423.0	Hemopericardium
	430.x	Subarachnoid hemorrhage
	431.x	Intracerebral hemorrhage
	432.x	Other and unspecified intracranial hemorrhage
	432.9	Intracranial hemorrhage not otherwise specified
	455.2	Internal hemorrhoids with complication including bleeding
	455.5	External hemorrhoids with complication including bleeding
	455.8	Unspecified hemorrhoids with complication
	456.0	Esophageal varices with bleeding
	456.20	Esophageal varices in diseases classified elsewhere, with bleeding
	459.0	Hemorrhage, unspecified
	530.21	Ulcer of esophagus with bleeding
	530.70	Gastroesophageal laceration-hemorrhage syndrome
	530.82	Esophageal hemorrhage
	531.0	Acute gastric ulcer with hemorrhage
	531.01	Acute gastric ulcer with hemorrhage, with obstruction
	531.20	Acute gastric ulcer with hemorrhage and perforation
	531.21	Acute gastric ulcer with hemorrhage and perforation, with obstruction
	531.40	Chronic or unspecified gastric ulcer with hemorrhage
	531.41	Chronic or unspecified gastric ulcer with hemorrhage, with obstruction
	531.60	Chronic or unspecified gastric ulcer with hemorrhage and perforation
	531.61	Chronic or unspecified gastric ulcer with hemorrhage and perforation with obstruction
	532.0	Acute duodenal ulcer with hemorrhage
	532.01	Acute duodenal ulcer with hemorrhage, with obstruction

	532.20	Acute duodenal ulcer with hemorrhage and perforation
	532.21	Acute duodenal ulcer with hemorrhage and perforation with obstruction
	532.40	Chronic duodenal ulcer with hemorrhage
	532.41	Chronic duodenal ulcer with hemorrhage, with obstruction
	532.60	Chronic duodenal ulcer with hemorrhage and perforation
	532.61	Chronic duodenal ulcer with hemorrhage and perforation with obstruction
	533.0	Acute peptic ulcer with hemorrhage
	533.01	Acute peptic ulcer with hemorrhage, with obstruction
	533.20	Acute peptic ulcer with hemorrhage and perforation
	533.21	Acute peptic ulcer with hemorrhage and perforation, with obstruction
	533.40	Chronic peptic ulcer with hemorrhage
	533.41	Chronic peptic ulcer with hemorrhage, with obstruction
	533.60	Chronic peptic ulcer with hemorrhage and perforation
	533.61	Chronic peptic ulcer with hemorrhage and perforation, with obstruction
	534.0	Acute gastrojejunal ulcer with hemorrhage
	534.01	Acute gastrojejunal ulcer with hemorrhage, with obstruction
	534.20	Acute gastrojejunal ulcer with hemorrhage and perforation
	534.21	Acute gastrojejunal ulcer with hemorrhage and perforation, with obstruction
	534.40	Chronic gastrojejunal ulcer with hemorrhage
	534.41	Chronic gastrojejunal ulcer with hemorrhage, with obstruction
	534.60	Chronic gastrojejunal ulcer with hemorrhage and perforation
	534.61	Chronic gastrojejunal ulcer with hemorrhage and perforation, with obstruction
	535.01	Acute gastritis with hemorrhage
	535.21	Gastric mucosal hypertrophy with hemorrhage
	535.31	Alcoholic gastritis with hemorrhage
	535.41	Other gastritis with hemorrhage
	535.51	Unspecified gastritis and gastroduodenitis with hemorrhage
	535.61	Duodenitis with hemorrhage
	536.71	Eosinophilic gastritis with hemorrhage
	537.83	Angiodysplasia of stomach and duodenum with hemorrhage
	537.84	Hemorrhagic Dieulafoy lesion of stomach and duodenum
	562.02	Diverticulosis of small intestine with hemorrhage
	562.03	Diverticulitis of small intestine with hemorrhage
	562.12	Diverticulosis of colon with hemorrhage
	562.13	Diverticulitis of colon with hemorrhage
	568.81	Hemoperitoneum

	569.3	Hemorrhage of rectum and anus
	569.85	Angiodysplasia of intestine with hemorrhage
	569.86	Hemorrhagic Dieulafoy lesion of intestine
	578.0	Hematemesis
	578.1	Blood in stool
	578.9	Hemorrhage of gastrointestinal tract, unspecified
	596.7	Hemorrhage into bladder wall
	599.70	Hematuria
	599.71	Gross hematuria
	623.8	Noninflammatory disorders of vagina including hemorrhage
	626.2	Excessive menstruation
	626.6	Metrorrhagia
	626.8	Other disorders of menstruation and other abnormal bleeding from female genital tract
	627.0	Premenopausal menorrhagia
	627.1	Postmenopausal menorrhagia
	719.10-19	Hemarthrosis
	729.92	Nontraumatic hematoma of soft tissue
	770.3	Pulmonary Hemorrhage
	784.7	Epistaxis
	784.8	Hemorrhage from throat
	786.30	Hemoptysis, unspecified
	786.39	Other hemoptysis
	852.0x	Traumatic subarachnoid hemorrhage
	852.1x	Subarachnoid hemorrhage following injury with open intracranial wound
	852.2x	Subdural hemorrhage following injury
	852.3x	Subdural hemorrhage following injury with open intracranial wound
	852.4x	Extradural hemorrhage following injury
	852.5x	Extradural hemorrhage following injury with open wound
	853.x	Other and unspecified intracranial hemorrhage following injury
	997.02	Iatrogenic cerebrovascular infarction or hemorrhage
	998.11	Hemorrhage complicating a procedure
	998.12	Hematoma complicating a procedure
	9900.00-04 (Procedure codes)	Blood transfusion

Table S3. Annualized mortality rate after clinical event in trial versus claims during the 21-month post-randomization period.

	Ischemic events		Bleeding events	
	Event in trial (N = 71)	**Event in claims (N = 62)**	**Event in trial (N = 57)**	**Event in claims (N = 109)**
n per 100 person-years annualized mortality rate after an event	10.1 (5.4, 18.8)	5.5 (1.4, 22.0)	12.3 (6.6, 22.8)	10.8 (6.7, 17.4)

Figure S1. Study cohort and exclusion criteria in the EXTEND-DAPT study.