HHS Public Access

Author manuscript

Am Heart J Plus. Author manuscript; available in PMC 2024 March 14.

Published in final edited form as:

Am Heart J Plus. 2023 December ; 36: . doi:10.1016/j.ahjo.2023.100339.

Optimal $P2Y_{12}$ inhibitor durations in older men and older women following an acute myocardial infarction: A nationwide cohort study using Medicare data

Ryan P. Hickson[a,b,c,d,e,*], **Anna M. Kucharska-Newton**[b,f], **Jo E. Rodgers**[g], **Betsy L. Sleath**[a], **Gang Fang**[a]

[a]Division of Pharmaceutical Outcomes and Policy, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, United States of America

[b]Department of Epidemiology, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, United States of America

[c]Geriatric Research, Education, and Clinical Center, Veterans Affairs Pittsburgh Healthcare System, United States of America

[d]Center for Health Equity Research and Promotion, Veterans Affairs Pittsburgh Healthcare System, United States of America

[e]Office of New Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, United States of America

[f]Department of Epidemiology, College of Public Health, University of Kentucky, United States of America

[g]Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, United States of America

Abstract

Study objective: Identify optimal $P2Y_{12}$ inhibitor durations balancing ischemic-benefit and bleeding-risk outcomes after acute myocardial infarction (AMI) in older men and women.

[*]Corresponding author at: Division of Pharmaceutical Outcomes and Policy, UNC Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill, CB# 7573, Chapel Hill, NC 27599-7573, United States of America. rphickson.rph@gmail.com (R.P. Hickson).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Submission declaration

This manuscript is not under review at any other journal. An earlier version of the results from this work were included as part of Ryan Hickson's PhD dissertation at UNC completed in 2020.

CRediT authorship contribution statement

Ryan P. Hickson: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Anna M. Kucharska-Newton:** Conceptualization, Methodology, Writing – review & editing. **Jo E. Rodgers:** Conceptualization, Methodology, Writing – review & editing. **Betsy L. Sleath:** Conceptualization, Methodology, Writing – review & editing. **Gang Fang:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2023.100339.

Design: Observational retrospective cohort with 2 years of follow-up, using clone-censor-weight marginal structural models to emulate randomization.

Setting: 20 % sample of US Medicare administrative claims data.

Participants: $P2Y_{12}$ inhibitor new users ≥66 years old following 2008–2013 AMI hospitalization.

Exposures: 12- to 24-month $P2Y_{12}$ inhibitor durations in 1-month intervals.

Main outcome measures: Effectiveness outcome (composite of all-cause mortality, recurrent AMI, ischemic stroke), safety outcome (hospitalized bleed), and negative control outcome (heart failure hospitalization).

Results: Of 28,488 $P2Y_{12}$ inhibitor new users, 51 % were female, 50 % were > 75 years old, 88 % were White/non-Hispanic, and 93 % initiated clopidogrel. Negative control outcome results for 16- through 24-month durations appeared most likely to meet assumptions of no unmeasured confounding. Compared to men taking 24-month therapy, men taking 16-month therapy had higher 2-year risks of the composite effectiveness outcome (relative risk [RR] = 1.08; 95 % confidence interval [95%CI]:1.00–1.15) with similar bleeding risks (RR = 0.98; 95%CI:0.85–1.13). Compared to women taking 24-month therapy, women taking 16-month therapy had similar 2-year risks of the composite effectiveness outcome (RR = 0.98; 95%CI:0.92–1.04) and lower bleeding risks (RR = 0.88; 95%CI:0.80–0.96).

Conclusions: Older men taking 24-month $P2Y_{12}$ inhibitor therapy had the lowest composite effectiveness outcome risk with no increased bleeding risk compared to shorter durations. Women taking 16-month versus 24-month $P2Y_{12}$ inhibitor therapy had similar composite effectiveness outcome risks but a substantially lower hospitalized bleeding risk, suggesting durations beyond 15–17 months lacked benefit while increasing bleeding risk.

Keywords

Acute coronary syndrome; Dual anti-platelet therapy; Gender disparities; Geriatrics; Risk assessment; Secondary prevention

1. Introduction

Dual antiplatelet therapy (DAPT)—low-dose aspirin plus a $P2Y_{12}$ inhibitor—has demonstrated benefit in preventing major adverse cardiovascular and cerebrovascular events in randomized controlled trials (RCTs) and is often part of guideline-recommended secondary prevention for acute myocardial infarction (AMI) [1]. When post-AMI DAPT is indicated, 2016 American College of Cardiology/American Heart Association guidelines recommend continuing aspirin indefinitely, but in most scenarios, $P2Y_{12}$ inhibitor therapy may be discontinued after “at least” 12 months to reduce the risk of bleeding [1]. The ischemic-benefit/bleeding-risk tradeoff has led to considerable debate regarding the optimal therapy duration, with 12 RCTs published since 2010 directly comparing anywhere from 3- up to 48-month $P2Y_{12}$ inhibitor durations [2–13].

Differences between women and men exist in AMI pathophysiology and symptom presentation [14,15]. Therefore, women and men may respond differently to secondary prevention medications. When comparing longer to shorter $P2Y_{12}$ inhibitor durations for composite major adverse cardiovascular and cerebrovascular events, 7 RCTs reported subgroup results by sex: 1 found statistically significant results favoring longer vs. shorter durations in men [12], 5 others also had non-significant estimates favoring longer durations in men [6–10], and 6 RCTs reported either non-significant estimates favoring shorter durations or found no difference in women [6–11].

While statistical tests to detect subgroups interactions within each of these trials may not individually identify a difference in results between men and women (comparisons for which they were not powered to detect), the overall pattern of findings across these 7 RCTs suggest men may be more likely than women to benefit from longer $P2Y_{12}$ inhibitor durations for the prevention of composite major adverse cardiovascular and cerebrovascular events. Some composite outcomes in these RCTs included bleeding and one study found that men and women experienced a similar increase in the rate of bleeding when comparing 30- vs. 12-month $P2Y_{12}$ inhibitor therapy [12], but most RCTs did not report bleeding safety outcomes separately for men and women. A meta-analysis of 6 RCTs comparing longer DAPT durations (12 months) vs. shorter DAPT durations (3 or 6 months) found that the comparative 1-year rate of bleeding was similar in men and women (P-interaction = 0.25), but men could potentially be more likely than women to benefit from longer durations for the comparative 1-year rate of major adverse cardiac events (P-interaction = 0.08) [16].

A major limitation of the existing evidence comparing the effectiveness of $P2Y_{12}$ inhibitor durations is that much of the US Medicare population is underrepresented, with an average age < 65 in 9 of 12 RCTs [2–5,8–12]. Additionally, of 36,221 participants in these 12 RCTs, only 27 % were women. Of note, women often have their first AMI later in life and account for ~50 % of Medicare AMI hospitalizations [17–20]. The optimal duration of $P2Y_{12}$ inhibitor therapy is largely unknown among older adults in real-world settings, especially among older women given their bleeding risk may be higher [1,21,22]. Therefore, we aimed to identify the optimal $P2Y_{12}$ inhibitor duration following an AMI hospitalization among men and women 66 years of age and older using a novel clone-censor-weight marginal structural modeling approach, emulating a trial that randomized patients to different therapy durations.

2. Materials and methods

The University of North Carolina at Chapel Hill institutional review board approved and waived informed consent requirements for this secondary analysis of administrative claims data. A 20 % sample of 2007–2015 fee-for-service Medicare claims (enrollment summary, medical service claims, and Part D prescription claims) was the primary data source [23]. Our data use agreement with the Centers for Medicare and Medicaid Services (CMS) prohibits sharing research data; access to Medicare administrative claims data for research can be requested through application with CMS. Prescriber and contextual characteristics were identified by linking to previously described data sources [19].

Patients with 2008–2013 AMI hospitalizations (primary/secondary position *International Classification of Diseases, Ninth Revision* [ICD-9] code 410.x1) [24] were eligible if they (1) were ≥ 66 years old; (2) had no recent $P2Y_{12}$ inhibitor use/indication in 12 months pre-AMI; (3) filled a $P2Y_{12}$ inhibitor prescription between hospital admission and 30 days post-discharge; and (4) did not discontinue $P2Y_{12}$ inhibitor therapy before a second prescription fill (Fig. 1). Restricting our sample to only patients who filled a $P2Y_{12}$ inhibitor (i.e., had an indication without major contraindications) helps mitigate unmeasured confounding in observational research [25]. This study's sample is a subset of our previously described $P2Y_{12}$ inhibitor new-user cohort, where the only missing baseline variable was age of the index $P2Y_{12}$ inhibitor prescriber (1.3 % missing and stochastically imputed) [19,26,27].

A retrospective cohort design was used (Fig. 2). Follow-up occurred in 30-day intervals (i.e., person-months) beginning in month 2 (days 31–60 post-AMI), and continued until experiencing an outcome, censoring, or end of follow-up after 24 months (2 years).

2.1. Exposure

$P2Y_{12}$ inhibitor therapy duration in months was the exposure. We compared results for 13 different regimens (in 1-month intervals) of 12 to 24 continuous months of $P2Y_{12}$ inhibitor therapy without discontinuation. Medication stop dates are typically unavailable in administrative prescription claims data. To differentiate medication discontinuation from continuous use with suboptimal adherence (e.g., nonadherence from missed doses every other day), a "gap days" approach was used [19,28]. Medication availability is assessed during each day in the measurement period, and once a period of consecutive days (e.g., 30 days) have passed where the patient had no medication available and did not fill a prescription to replenish their supply, they are classified as discontinuing their medication. If a patient filled a 30-day supply prescription and a "gap days" measure of 30 was used to determine the discontinuation date, that patient would have a proportion of days covered (PDC) medication adherence of 50 % on the discontinuation date if they were actually continuing to use the medication with suboptimal adherence but were misclassified as discontinuing the medication [30d prescription/(30d prescription + 30d gap day) = 50 %].

To operationalize this in our study, $P2Y_{12}$ inhibitor availability was assessed each day of follow-up using prescription fill dates and days supply from Part D prescription claims, accounting for oversupply (e.g., filling prescriptions a few days early so a patient's supply of medication does not run out) and hospitalizations (medications normally taken at home are provided by the hospital, so a patient's home supply would not be used during this period) [19,20,29]. The last day of a 30-day drug-free interval was the stop date (i.e., 30 consecutive days without therapy) [19]. The month of discontinuation was determined from this stop date (e.g., month 14 if discontinued between 391 and 420 days). The robustness of estimates when using our 30-day "gap days" measure to determine the discontinuation date was evaluated in sensitivity analyses (see Section 2.4.3 below).

2.2. Outcomes

The effectiveness outcome was a composite of (1) all-cause mortality, (2) recurrent AMI [24], and (3) ischemic stroke (Table 1) [30–37]. In previously studied Medicare populations,

this AMI algorithm had a positive predictive value (PPV) of 94.1 % [24], and this ischemic stroke algorithm had a PPV of 88.6 % and specificity of 99.8 % [36].

The safety outcome was a hospitalized bleed, including intracranial hemorrhages [30–35,38–41], gastrointestinal hemorrhages [32,33,38–40,42], and other bleeding events (Table 1) [32,33,38–40]. Our hospitalized bleed outcome measure was primarily developed from an algorithm with PPV 89 % to identify clinically confirmed definite or probable bleeding at any anatomical site as the primary reason for hospitalization among anticoagulant users [38]. Similar algorithms had a PPV of 92 % with diagnosis codes in the primary position only to identify hospitalization for bleeding of any severity level in patients treated with $P2Y_{12}$ inhibitors after receiving PCI for an AMI [43].

Additionally, a negative control outcome was used to assess the potential impact of unmeasured confounding (Table 1) [44]. Heart failure hospitalizations [45–48] were chosen as the negative control outcome because (1) in the absence of residual confounding, no association was expected between $P2Y_{12}$ inhibitor duration and risk of heart failure hospitalizations, and (2) potential unmeasured confounders in our data source (e.g. healthy-user/sick-stopper characteristics and cardiovascular disease severity) between $P2Y_{12}$ inhibitor duration and clinical effectiveness/safety outcomes are also potential unmeasured confounders between $P2Y_{12}$ inhibitor duration and heart failure hospitalizations [44,49,50]. The ICD-9 codes for our negative control outcome had a PPV of 97 % to identify incident heart failure hospitalizations when used in the primary diagnosis field [45], but we expanded our search to these ICD-9 codes in any position to maximize our sensitivity to identify acute decompensated or chronic stable heart failure hospitalizations [47], as neither were expected to be associated with duration of $P2Y_{12}$ inhibitor therapy in the absence of unmeasured confounding.

2.3. Covariates

Our research framework and baseline covariates (V in equations)—including pre-AMI and index AMI characteristics as well as contextual characteristics—were previously described [19,51]; however, in this study, variables measured 30 days post-AMI were included in time-varying covariates, not baseline covariates. Patient baseline characteristics included sociodemographics, healthcare/medication utilization measures, comorbidity burden, specific comorbidities/medications that could impact ischemic/bleeding risks, and medications with $P2Y_{12}$ inhibitor drug-drug interactions.

The following time-varying covariates (L in equations) were measured: $P2Y_{12}$ inhibitor out-of-pocket cost, deductible/coverage-gap Part D benefit phase, proton-pump inhibitor use, and hospice admission. Time-varying covariates attributed to time t were measured in time period $t\text{-}1$ to maintain correct confounder-exposure-outcome temporal ordering [52–55] in our clone-censor-weight analysis described below (e.g., when estimating probability of remaining uncensored during month 14 of follow-up, time-varying covariates were measured at the end of month 13).

Time-dependent effects (E in equations) attributed to time t were similarly measured at time $t\text{-}1$. Time-dependent effects were interacted with time when calculating inverse

probability weights in our clone-censor-weight analysis described below; the probability of remaining uncensored and event-free was hypothesized to depend upon when these events occurred within the timeframe of post-AMI care (e.g., first few months vs. >1 year after index AMI hospitalization) [20,56–58]. Time-dependent effects were inpatient and emergency room admissions; outpatient primary care/cardiologist visits; use of other AMI secondary prevention medications; $P2Y_{12}$ inhibitor product (brand-name clopidogrel, generic clopidogrel, brand-name prasugrel, brand-name ticagrelor); coronary revascularization; and $P2Y_{12}$ inhibitor prescriber characteristics (sex, age, specialty). For each non-$P2Y_{12}$ inhibitor AMI secondary prevention medication (statin, angiotensin-converting enzyme [ACE] inhibitor/angiotensin II receptor blocker [ARB], beta-blocker), use during each period was classified as either not taking, taking but nonadherent (PDC <0.80), or taking and adherent (PDC ≥0.80). Additionally, AMI/ischemic stroke and bleeding hospitalizations were time-dependent effects when they were not the outcome.

See Supplemental Tables S1–S2 for a full list of all covariates. Additional details can be found in the footnotes of these tables regarding how covariates were measured; Part D benefit phase, $P2Y_{12}$ inhibitor prescription fill characteristics, and $P2Y_{12}$ inhibitor prescriber characteristics used the last value carried forward if no information was available within the 30-day *t-1* time period of measure.

2.4. Statistical analysis

Covariate distributions were described separately for men and women. To overcome immortal-time bias and selection bias when estimating clinical effectiveness and safety of treatment durations in real-world observational data, we used a 3-step marginal structural modeling approach: cloning, censoring, and weighting [59,60]. This approach was applied separately for all 3 outcomes and estimates are interpreted similarly to an RCT per-protocol analysis that adjusts for time-varying confounding. When clone-censor-weight marginal structural models are successfully implemented to emulate an RCT, (1) there should be little to no difference in the risk of hospitalized heart failure (negative control outcome) among assigned $P2Y_{12}$ inhibitor durations, and (2) longer $P2Y_{12}$ inhibitor durations should have similar or higher risk of hospitalized bleed (positive control outcome) than shorter durations [44,61]. We decided a priori that when cumulative incidence curves aligned with these expected findings for negative and positive control outcomes, $P2Y_{12}$ inhibitor durations would be identified as comparable in our study, being more likely to meet the causal inference exchangeability assumption [62]. Estimates for $P2Y_{12}$ inhibitor durations that did not align with these expected findings for negative and positive control outcomes were interpreted cautiously because there may be unmeasured confounding or even a lack of clinical equipoise for patients receiving these $P2Y_{12}$ inhibitor durations in real-world clinical practice, thereby violating the exchangeability assumption [44,63].

All analyses were conducted using SAS 9.4 (SAS Institute Inc).

2.4.1. Marginal structural modeling using cloning, censoring, and weighting

—To emulate randomization, each patient's data was copied 13 times, and each of these 13 "clones" was assigned to remain on $P2Y_{12}$ inhibitor therapy continuously from 12 to

24 months in 1-month intervals (i.e., 12-, 13-, 14-, …, 24-month durations). Assignment to these 13 therapy durations was analogous to randomization at AMI discharge [59,64].

Once a patient's actual $P2Y_{12}$ inhibitor duration deviated from their clone's "randomly" assigned duration, the clone was censored [59]. Clones were given a 1-month grace period to discontinue therapy (e.g., clones assigned 14-month therapy were not censored if patient actually discontinued in months 13–15, but they must remain off therapy for all months after discontinuation had occurred) [65,66]. Deviations from assigned therapy durations were measured using 3 censoring mechanisms [52]: stopping therapy early (C^{stop} in equations), stopping therapy appropriately but later restarting ($C^{restart}$ in equations), and continuing therapy too long (C^{cont} in equations). Clones were also censored from loss to follow-up (C^{abd} in equations) if they (1) lost Medicare fee-for-service continuous enrollment, or (2) had 2 consecutive months with no $P2Y_{12}$ inhibitor available but had not yet discontinued (immeasurable inpatient time for adherence-related prescription claim measures) [29]. Finally, clones were censored when death was a competing risk in safety and negative control outcome analyses (C^{death} in equations).

Inverse probability weights (IPWs) were calculated for the probability of remaining uncensored through month t to eliminate time-varying selection bias introduced from informative censoring, constructing a hypothetical pseudo-population where all patients follow their assigned treatment regimen with no censoring [59,67]. Unstabilized IPWs were calculated using person-month pooled logistic regression [54,55,65] (Supplemental Eq. S1) and truncated at 1st and 99th percentiles [66,68].

2.4.2. Cumulative incidence curves—After calculating IPWs, pooled logistic regression was used to calculate event-free survival probabilities through month *t*; cumulative incidence curves were calculated—separately for men and women-—using weighted survival probabilities and the product-limit method (Supplemental Eq. S2) [52,65,69]. Then, 2-year risks, relative risks (RRs), and risk differences (RDs) were calculated, comparing shorter $P2Y_{12}$ inhibitor durations to the 24-month reference duration. The goal of our analyses was not to determine statistical significance for the different $P2Y_{12}$ inhibitor durations and outcomes under study; instead, we used confidence intervals (CIs) to represent the precision and uncertainty of our estimated effect sizes for scientific inference [70,71]. The 95 % CIs were calculated with 500-iteration nonparametric boot-strapping with replacement from the original cohort, followed by cloning, censoring, and weighting within each iteration [53,65,69].

2.4.3. Sensitivity analyses—Two sets of sensitivity analyses were conducted. First, the 30-day drug-free interval to measure $P2Y_{12}$ inhibitor discontinuation was varied to shorter (15-day) and longer (45-day) intervals [19,28]. Second, analyses were stratified by calendar date of the index AMI discharge based on availability of $P2Y_{12}$ inhibitor products in the US market [19]. Point estimates from sensitivity analyses that fell within primary analyses' 95 % CIs were identified as consistent with primary findings.

3. Results

Overall, 28,488 $P2Y_{12}$ inhibitor new users (51 % women) were eligible for effectiveness and safety analyses. Among all 341,079 $P2Y_{12}$ inhibitor prescription fills from index AMI admission through 2 years post-AMI discharge in these 28,488 patients, 82 % and 15 % of prescription fills were for 30-day and 90-day supply, respectively. In negative control outcome analyses, 1581 patients with heart failure hospitalizations within 30 days post-AMI were excluded. See Online Supplemental Materials for these results: person-month distribution of all covariates in original, cloned, and weighted samples (Supplemental Tables S1–S2); crude outcome event rates (Supplemental Table S3); details on analytic samples after cloning and censoring (Supplemental Tables S4–S6); distribution of IPWs before truncating (Supplemental Table S7); and unadjusted and baseline-covariate-adjusted clone-censor-weight marginal structural model results (Supplemental Figs. S1–S2 and Supplemental Tables S8–S13).

3.1. Results for men

Of 13,920 men in effectiveness and safety analyses, 41 % were ≥76 years old, 90 % were White/non-Hispanic, 16 % had history of bleeding, 75 % had index AMI managed with PCI and stent(s), and 92 % initiated clopidogrel (Table 2; see Supplemental Table S14 for all baseline characteristics).

Men taking 24-month therapy had the lowest 2-year risk of death, recurrent AMI, or ischemic stroke (18.5 %; 95 % CI: 17.5, 19.5; Fig. 3A). Men taking the shortest duration of 12 months had the lowest 2-year bleed risk (4.4 %; 95 % CI: 3.8, 5.2; Fig. 3B). However, hospitalized bleed cumulative incidence curves sometimes did not separate until 9+ months after therapy discontinuation, and estimates were imprecise with wide confidence intervals. Men taking between 16- and 24-month $P2Y_{12}$ inhibitor durations had similar 2-year heart failure hospitalization risks (19.0–19.7 %; Fig. 3C); these durations were identified as most comparable for causal inference in men.

3.2. Results for women

Of 14,568 women in effectiveness and safety analyses, 58 % were ≥76 years old, 87 % were White/non-Hispanic, 14 % had history of bleeding, 68 % had index AMI managed with PCI and stent(s), and 95 % initiated clopidogrel (Table 2; see Supplemental Table S14 for all baseline characteristics).

Women taking 14-month $P2Y_{12}$ inhibitor therapy had the lowest 2-year risk of death, recurrent AMI, or ischemic stroke (20.1 %; 95 % CI: 18.9, 21.1; Fig. 4A). Women taking the shortest duration of 12 months had the lowest 2-year bleed risk (5.4 %; 95 % CI: 4.6, 6.4; Fig. 4B). Compared to women who continued therapy for longer durations and had higher bleed risks, the risk of bleeding began to decrease within the month following $P2Y_{12}$ inhibitor discontinuation. Women taking between 16- and 24-month $P2Y_{12}$ inhibitor durations had similar 2-year heart failure hospitalization risks (23.7–25.2 %; Fig. 4C); these durations were identified as most comparable for causal inference in women.

3.3. Summary of effectiveness and safety results in men and women

Magnified cumulative incidence curves for 16- to 24-month $P2Y_{12}$ inhibitor durations show shorter vs. longer durations were less effective at preventing the composite effectiveness outcome in men (Fig. 5A), but no difference was observed in women (Fig. 5B). The 2-year composite effectiveness estimates comparing 16-month vs. 24-month durations in men were RR = 1.08 (95 % CI: 1.00, 1.15) and RD = +1.4 % (95 % CI: +0.0, +2.6); in women the 16-month vs. 24-month RR = 0.98 (95 % CI: 0.92, 1.04) and RD −0.4 % (95 % CI: −1.7, +0.8).

There were no differences in the risk of the bleeding safety outcome in men attributable to $P2Y_{12}$ inhibitor therapy durations (Fig. 5C), but shorter durations were substantially safer than longer durations in women (Fig. 5D). The 2-year hospitalized bleeding estimates comparing 16-month vs. 24-month durations in men were RR = 0.98 (95 % CI: 0.85, 1.13) and RD = −0.1 % (95 % CI: −0.8, +0.6); in women the 16-month vs. 24-month RR = 0.88 (95 % CI: 0.80, 0.96) and RD = −0.7 % (95 % CI: −1.3, −0.2).

3.4. Sensitivity analyses

When varying the $P2Y_{12}$ inhibitor discontinuation measure to 15- and 45-day drug-free intervals, all estimates among patients taking between 16- and 24-month $P2Y_{12}$ inhibitor durations were consistent with estimates from primary analyses. When analyses were stratified by index AMI discharge date, several estimates were inconsistent with primary analyses; however, these inconsistent estimates were mostly (1) for $P2Y_{12}$ inhibitor durations <16 months and/or (2) among patients discharged before July 1, 2011. Therefore, these inconsistent estimates did not impact our interpretation of primary analyses and were less concerning when applying findings to current clinical practice. See Supplemental Tables S8–S13 for sensitivity analyses results.

4. Discussion

In this real-world observational retrospective cohort study, clone-censor-weight marginal structural models emulated a stratified RCT to assess clinical outcomes of 12- to 24-month $P2Y_{12}$ inhibitor durations following an AMI hospitalization among men and women ≥66 years old. Durations between 16 and 24 months were identified as most likely to meet assumptions for no residual confounding and to therefore be comparable for causal inference in both men and women. Men taking 24-month therapy had the lowest 2-year risk of the composite effectiveness outcome without evidence of increased bleeding risk compared to men taking shorter durations. Women taking 16-month compared to 24-month $P2Y_{12}$ inhibitor therapy had similar 2-year risks for the composite effectiveness outcome but a 0.7 % lower absolute risk (12 % lower relative risk) of hospitalized bleeds.

The directionality of our composite effectiveness findings was consistent with most of the 7 RCTs that reported results separately in men and women: longer vs. shorter durations appeared beneficial in men while longer vs. shorter durations lacked benefit in women [6–12]. Beyond that, comparisons of our findings to these RCTs are difficult. Our study population was older and had more women, only 71 % underwent PCI with stent placement

(100 % in RCTs), and 100 % had an index AMI (0–56 % across RCTs). Additionally, 16- to 24-month $P2Y_{12}$ inhibitor durations were identified as comparable in our study, but RCTs often compared shorter durations (3- or 6-month vs. 12-month) [6,9,10] or included durations longer than 24 months [8,11,12]. Like our study, composite major adverse cardiovascular and cerebrovascular events in RCTs included death, AMI, and stroke, but differed slightly across trials (e.g. cardiovascular mortality only or composite outcome included bleeding). Finally, cloned patients' data in our study were "assigned" $P2Y_{12}$ inhibitor durations after surviving 30 days post-AMI, and then 2-year outcomes were assessed; in RCTs, 12- to 24-month outcomes were often assessed following a 6- to 12-month event-free landmark period for study eligibility.

Our results differed substantially from the only other observational study evaluating effectiveness and safety for DAPT durations separately in men and women [21]. While differences in eligibility criteria, measures, design, and analyses explain many differences [19], we believe deficiencies exist in their time-varying Cox proportional hazard models that led to conflicting findings: e.g., bleeding rates doubled with physician-recommended DAPT discontinuation (compared to continuing DAPT) [21]. This is the complete opposite of the expected association: the rate of a known adverse drug reaction should remain stable or decrease if that medication was discontinued. Reverse causality from incorrect temporal ordering of confounders, exposure, and outcome may explain this unexpected finding in their study. Our approach using clone-censor-weight marginal structural models not only encourages diligent consideration for correct temporal ordering of measures [53–55,65], but our estimates—analogous to per-protocol RCT estimates—may be easier to interpret than hazard ratios from Cox models with time-varying exposures [59,72].

In our study, >90 % of patients were taking clopidogrel, but current guidelines recommend prasugrel or ticagrelor over clopidogrel after acute coronary syndromes (ACSs) [1,73,74]; however, this recommendation is not without controversy, especially in older patients and patients with higher bleeding risks [75]. Prasugrel is often not recommended in patients >75 years old [1,74,75], and meta-analysis of RCTs in older adults found 1-year ticagrelor versus clopidogrel after ACS had no effect on composite cardiovascular death, AMI, and stroke (RR 1.04; 95 % CI: 0.69, 1.65) but was associated with an increased risk of major or minor bleeding (RR 1.40; 95 % CI: 1.11, 1.76) [76]. Among patients discharged after July 1, 2011 in our study—once all $P2Y_{12}$ inhibitors were available on the market—4.2 % took ticagrelor, 8.5 % took prasugrel, and 87.3 % took clopidogrel. Our findings are therefore most applicable to patients taking clopidogrel for 12+ months post-AMI, and clopidogrel use remains common in the U.S. Medicare population with data through 2017 [77].

A nationwide registry study in Denmark of patients undergoing PCI for ACS from 2013 to 2016 found that continuing DAPT beyond 12 months versus continuing only aspirin had no benefit in preventing death or major adverse cardiovascular events, but DAPT beyond 12 months came with a 4 % increased absolute risk of hospitalized bleeds over the next 2 years [78]. Comparison to our study is difficult though, as patients in the Danish study were more likely to be younger, male, taking ticagrelor, and to discontinue their $P2Y_{12}$ inhibitor between 12 and 15 months [19], and analyses were not stratified by sex. However, underpowered sensitivity analyses from the Danish study suggested continuing clopidogrel

plus aspirin versus only aspirin beyond 12 months may lower the risk of death and major adverse cardiovascular events [78]. Future research should investigate the effectiveness and safety of durations for specific $P2Y_{12}$ inhibitor agents in older adults, including strategies of switching from more potent $P2Y_{12}$ inhibitors to clopidogrel [56].

While we adjusted for baseline diagnosis of atrial fibrillation and baseline use of anticoagulant therapy, we do not recommend using these analyses to guide decisions of using triple versus double therapy [79]. Our analyses did not directly make these comparisons, and patients with an atrial fibrillation diagnosis (~7 %) or using anticoagulant therapy (~7 %) at baseline only made up a small portion of our study sample.

The older men in our study had the greatest benefit in reducing the 2-year risk of death and ischemic outcomes while remaining on $P2Y_{12}$ inhibitor therapy for 23 months post-AMI, and this longer $P2Y_{12}$ inhibitor therapy did not come with a substantial increase in bleeding risk. We hypothesized that we did not observe a clear pattern of increased hospitalized bleeding risk in men attributed to longer $P2Y_{12}$ inhibitor durations because (1) the effect size was small for this type of bleeding outcome among men primarily taking clopidogrel, or (2) there were heterogeneous treatment effects in men. In exploratory analyses, we stratified patients by the presence/absence of high-bleeding-risk characteristics at the time of index AMI (results not shown). The absolute risk of ischemic and bleeding outcomes both differed greatly between these low- and high-bleed-risk strata, but our findings were consistent when comparing $P2Y_{12}$ inhibitor durations within the strata separately: longer $P2Y_{12}$ inhibitors appeared to benefit men by lowering the risk of the composite ischemic outcome without increasing the risk of hospitalized bleeds substantially. Among men primarily taking clopidogrel, the effect size for hospitalized bleeds attributed to longer $P2Y_{12}$ inhibitor durations investigated within our study may have been too small to precisely detect, but unmeasured confounding and outcome measurement error cannot be completely ruled out.

U.S. clinical guidelines have previously made similar recommendations for $P2Y_{12}$ inhibitor durations for both men and women following an AMI, including recommendations of treatment for “up to” 12 months for patients managed medically or with fibrinolysis [80,81]; durations of “at least” 12 months for AMI patients managed with PCI and stents, with “up to” 15 months being reasonable with drug-eluting stents [82,83]; or durations of “at least” 12 months for all AMI patients regardless of the intervention strategy [1]. We adjusted for type of AMI and AMI intervention strategy at baseline, but future studies should directly investigate how the type of AMI and the type of AMI intervention strategy (e.g., PCI with drug-eluting stent, medical management, etc.) may modify the effect of $P2Y_{12}$ inhibitor duration on ischemic and bleeding outcomes, separately in men and women.

Our literature review of the RCTs that compared different $P2Y_{12}$ inhibitors in men and women separately found a fairly consistent pattern across studies where longer durations tended to benefit men for the reduction of major adverse cardiovascular and cerebrovascular events while women received little to no benefit from longer durations in most of these trials [6–12]. We would argue the clinical guidelines should consider in greater detail how men and women may respond differentially to longer vs. shorter $P2Y_{12}$ inhibitor durations.

Additionally, the guidelines are largely based on evidence from RCTs, but these trials have underrepresented older patients, especially older women [84,85].

In the current study, men taking 23+ months of $P2Y_{12}$ inhibitor therapy had the lowest 2-year risk of the composite ischemic effectiveness outcome on average, with little to no increased bleeding risk. However, women who continued $P2Y_{12}$ inhibitor therapy beyond 15–17 months post-AMI had an increased bleeding risk with no benefit in risk reduction of the effectiveness outcome. Our previous findings suggested women should not receive shorter $P2Y_{12}$ inhibitor durations than comparable men simply because they are female [19], but that final matched sample included only 69 % of the cohort, with the female matched sample becoming more similar to the full male sample.

In this study, given that women continuing $P2Y_{12}$ inhibitor therapy beyond 15–17 months post-AMI received no benefit from a reduction in the risk of the composite effectiveness outcome but were at a greater risk of harm from hospitalized bleeds, on average, continuing $P2Y_{12}$ inhibitor therapy beyond 15–17 months post-AMI may be more harmful than beneficial. However, when an older woman's clinical presentation is more similar to that of the male post-AMI Medicare population (e.g., <76 years old and explicit clinical factors suggesting ischemic benefits outweigh bleeding risks), then $P2Y_{12}$ inhibitor durations longer than 15–17 months post-AMI may be considered.

4.1. Limitations

Unmeasured confounding is a major concern when using observational research for causal inference, and the validity of our estimates assumes no residual time-varying confounding. We adjusted for clinical factors that may impact prescriber recommendations to continue/stop $P2Y_{12}$ inhibitor therapy (e.g., prescriber-perceived need characteristics in Supplemental Tables S1–S2) and factors that may impact patient adherence to preventive therapy (e.g., enabling, and patient-perceived need characteristics in Supplemental Tables S1–S2). However, residual confounding is still possible from unmeasured variables that may affect both outcomes and decisions regarding duration of $P2Y_{12}$ inhibitor therapy (e.g., laboratory measures for kidney function). Using negative and positive control outcomes allowed us to identify therapy duration comparisons where this assumption of no residual time-varying confounding most likely held. We focused our interpretation on findings for 16- to 24-month $P2Y_{12}$ inhibitor durations where we were most confident that this assumption held. However, if readers disagree with our determination of which groups were most comparable for causal inference, we included results for all 12- to 24-month durations for their interpretation.

Second, the validity of our estimates assumes correct model specification. The parameterization of our IPW models were informed from the literature [20,52,56–58], but model misspecification could lead to extreme weights, near violations of positivity, and bias. Our IPWs were truncated to mitigate this bias [65,68]. Additionally, our cumulative incidence model was parametric, encoding when and how discrete time hazards were allowed to vary over time and between comparison groups. A nonparametric model that does not make any assumptions about the functional form of these cumulative incidence curves would have been preferred, but we were not able to use a "saturated" marginal

structural model due to the sparsity of outcome events in some follow-up periods (especially hospitalized bleeds in the months following $P2Y_{12}$ inhibitor discontinuation) [86]. A restricted cubic spline for the assigned months of $P2Y_{12}$ inhibitor therapy, categorization of follow-up time into the smallest intervals feasible with our data, and an interaction term between these variables (Supplemental Eq. S2) allowed the discrete time hazards some flexibility to vary over time and between comparison groups [65].

Third, we used existing standards for health services research using secondary claims data, but variable misclassification is possible given administrative claims are designed for billing, not research. Our ischemic effectiveness and bleeding safety outcomes were based on ICD-9 diagnoses in the primary position, which typically have higher PPV but lower sensitivity compared to ICD-9 codes in any position [87]. In RCTs and prospective cohorts/registries, bleeding outcomes are often categorized by type and/or severity of the bleed, and comparative safety bleeding outcomes assessed based on the type/severity of bleeding may be preferred to facilitate clinical decision-making regarding the optimal duration of $P2Y_{12}$ inhibitor therapy in this population [12,88]. However, our data using ICD-9 diagnoses to assess bleeding outcomes does not capture data on hemoglobin drop or hemodynamic instability and cannot classify bleeding outcomes based on these scales [43]. Despite this, ICD-9 code algorithms using the primary diagnosis position have shown high PPV in identifying hospitalized bleeds in populations using anticoagulants or antiplatelets [38,43], and the bleeding outcomes missed by algorithms using primary diagnosis positions only may be more likely to be bleeding that occurred during a hospitalization (as opposed to the bleed being the primary reason the hospitalization occurred) [38]. We would argue that hospitalization specifically for a bleeding event is a clinically distinct and meaningful outcome in this population.

Finally, when using “gap days” to measure treatment duration in prescription claims, measurement error is a substantial concern [28]; however, nearly all sensitivity analyses were consistent when varying 30-day drug-free intervals to shorter and longer intervals, lessening concerns regarding this limitation. Additionally, our data source did not have information about why patients discontinued $P2Y_{12}$ inhibitor therapy. We did adjust for baseline and time-varying patient-perceived need and prescriber-perceived need characteristics, as well as time-varying prescriber characteristics. Therefore, our models estimate risks attributed to time on therapy but as a weighted average between prescriber-recommended discontinuation and patient-nonadherence discontinuation, assuming no residual confounding attributed to reasons for therapy discontinuation.

5. Conclusions

Among patients ≥66 years old who started a new course of $P2Y_{12}$ inhibitor therapy (primarily clopidogrel) following an AMI and remained on therapy for at least 12 months, our clone-censor-weight analysis of observational data to emulate a randomized trial found different optimal durations of therapy for men and women. In older men, up to 23+ months of therapy compared to shorter durations resulted in the greatest benefit in reducing the risk of composite death and ischemic outcomes without substantially increasing bleeding risk. In older women, continuing $P2Y_{12}$ inhibitor therapy beyond 15–17 months post-AMI

resulted in an increased bleeding risk without a benefit in the reduction of composite death and ischemic outcomes. Future research should evaluate how the type of AMI and AMI intervention strategy, use of different $P2Y_{12}$ inhibitor products, and strategies of switching from more potent $P2Y_{12}$ inhibitors to clopidogrel impact the benefit-risk tradeoff of different $P2Y_{12}$ inhibitor durations, separately in older men and older women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank (1) Allison E Aiello, PhD for her feedback on this project as a member of Dr. Hickson's dissertation committee; and (2) Izabela E Annis, MS; Alan C Kinlaw, PhD; and Carolyn T Thorpe, PhD, MPH for assistance and feedback on previous versions of this research.

Sources of funding

The database infrastructure used for this project was funded by the Pharmacoepidemiology Gillings Innovation Lab (PEGIL) for the Population-Based Evaluation of Drug Benefits and Harms in Older US Adults (GIL200811.0010); the Center for Pharmacoepidemiology, Department of Epidemiology, UNC Gillings School of Global Public Health; the CER Strategic Initiative of UNC's Clinical and Translational Science Award (UL1TR001111); the Cecil G. Sheps Center for Health Services Research, UNC; and the UNC School of Medicine. Dr. Hickson received support from the NIH National Heart, Lung, and Blood Institute (NHLBI) (National Research Service Award Training Grant No. 4T32HL007055-43) as a post-doctoral research fellow with the Cardiovascular Disease Epidemiology Program at The University of North Carolina at Chapel Hill and from the American Foundation for Pharmaceutical Education (AFPE) Pre-Doctoral Fellowship in Health Outcome Disparities. At the time of submission, Dr. Hickson was supported as a Postdoctoral Fellow in Advanced Geriatrics with the Geriatric Research, Education, and Clinical Center at the Veterans Affairs Healthcare System, Pittsburgh, PA. At the time of acceptance, Dr. Hickson was employed by the US Food and Drug Administration (FDA). The contents do not represent the views of the U.S. Department of Veterans Affairs, the FDA, or the United States Government.

References

[1]. Levine GN, Bates ER, Bittl JA, et al. , 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, J. Am. Coll. Cardiol. 68 (10) (2016) 1082–1115. [PubMed: 27036918]

[2]. Helft G, Steg PG, Le Feuvre C, et al. , Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial, Eur. Heart J. 37 (4) (2016) 365–374. [PubMed: 26364288]

[3]. Gilard M, Barragan P, Noryani AAL, et al. , 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial, J. Am. Coll. Cardiol. 65 (8) (2015) 777–786. [PubMed: 25461690]

[4]. Gwon HC, Hahn JY, Park KW, et al. , Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study, Circulation 125 (3) (2012) 505–513. [PubMed: 22179532]

[5]. Park SJ, Park DW, Kim YH, et al. , Duration of dual antiplatelet therapy after implantation of drug-eluting stents, N. Engl. J. Med. 362 (15) (2010) 1374–1382. [PubMed: 20231231]

[6]. Schulz-Schupke S, Byrne RA, Ten Berg JM, et al. , ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting, Eur. Heart J. 36 (20) (2015) 1252–1263. [PubMed: 25616646]

[7]. Valgimigli M, Campo G, Monti M, et al. , Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial, Circulation 125 (16) (2012) 2015–2026. [PubMed: 22438530]

[8]. Collet JP, Silvain J, Barthelemy O, et al. , Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-interruption): a randomised trial, Lancet (London, England) 384 (9954) (2014) 1577–1585. [PubMed: 25037988]

[9]. Feres F, Costa RA, Abizaid A, et al. , Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial, Jama 310 (23) (2013) 2510–2522. [PubMed: 24177257]

[10]. Kim BK, Hong MK, Shin DH, et al. , A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation), J. Am. Coll. Cardiol. 60 (15) (2012) 1340–1348. [PubMed: 22999717]

[11]. Lee CW, Ahn JM, Park DW, et al. , Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized, controlled trial, Circulation 129 (3) (2014) 304–312. [PubMed: 24097439]

[12]. Mauri L, Kereiakes DJ, Yeh RW, et al. , Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents, N. Engl. J. Med. 371 (23) (2014) 2155–2166. [PubMed: 25399658]

[13]. Colombo A, Chieffo A, Frasheri A, et al. , Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial, J. Am. Coll. Cardiol. 64 (20) (2014) 2086–2097. [PubMed: 25236346]

[14]. Bairey Merz CN, Shaw LJ, Reis SE, et al. , Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study: part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease, J. Am. Coll. Cardiol. 47 (3 Suppl) (2006) S21–S29. [PubMed: 16458167]

[15]. Shaw LJ, Bairey Merz CN, Pepine CJ, et al. , Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study: part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies, J. Am. Coll. Cardiol. 47 (3 Suppl) (2006) S4–s20. [PubMed: 16458170]

[16]. Sawaya FJ, Morice MC, Spaziano M, et al. , Short-versus long-term dual antiplatelet therapy after drug-eluting stent implantation in women versus men: a sex-specific patient-level pooled-analysis of six randomized trials, Catheter. Cardiovasc. Interv. 89 (2) (2017) 178–189. [PubMed: 27426936]

[17]. Virani SS, Alonso A, Benjamin EJ, et al. , Heart disease and stroke statistics-2020 update: a report from the American Heart Association, Circulation 141 (9) (2020) e139–e596. [PubMed: 31992061]

[18]. Krumholz HM, Normand SL, Wang Y, Trends in hospitalizations and outcomes for acute cardiovascular disease and stroke, 1999–2011, Circulation 130 (12) (2014) 966–975. [PubMed: 25135276]

[19]. Hickson RP, Kucharska-Newton AM, Rodgers JE, Sleath BL, Fang G, Disparities by sex in P2Y12 inhibitor therapy duration, or differences in the balance of ischaemic-benefit and bleeding-risk clinical outcomes in older women versus comparable men following acute myocardial infarction? A P2Y12 inhibitor new user retrospective cohort analysis of US Medicare claims data, BMJ Open 11 (12) (2021), e050236.

[20]. Hickson RP, Robinson JG, Annis IE, et al. , Changes in statin adherence following an acute myocardial infarction among older adults: patient predictors and the association with follow-up with primary care providers and/or cardiologists, J. Am. Heart Assoc. 6 (10) (2017), e007106. [PubMed: 29051213]

[21]. Yu J, Baber U, Mastoris I, et al. , Sex-based differences in cessation of dual-antiplatelet therapy following percutaneous coronary intervention with stents, JACC Cardiovasc. Interv. 9 (14) (2016) 1461–1469. [PubMed: 27478113]

[22]. Chichareon P, Modolo R, Kerkmeijer L, et al. , Association of sex with outcomes in patients undergoing percutaneous coronary intervention: a subgroup analysis of the global leaders randomized clinical trial, JAMA Cardiol. 5 (1) (2020) 21–29. [PubMed: 31693078]

[23]. Medicare Data (20% Sample) Database Description. UNC The Cecil G. Sheps Center for Health Services Research. https://www.shepscenter.unc.edu/data/medicare-data-20-sample/database-description/. Accessed June 24, 2022.

[24]. Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH, Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records, Am. Heart J. 148 (1) (2004) 99–104. [PubMed: 15215798]

[25]. Lund JL, Richardson DB, Sturmer T, The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application, Curr. Epidemiol. Rep. 2 (4) (2015) 221–228. [PubMed: 26954351]

[26]. Enders CK, Applied Missing Data Analysis, Guilford press, 2010.

[27]. Multiple Imputation in SAS Part 1, UCLA Institute for Digital Research & Education Statistical Consulting, 2017. https://stats.idre.ucla.edu/sas/seminars/multiple-imputation-in-sas/mi_new_1/. Accessed September 17, 2021.

[28]. van Wijk BL, Shrank WH, Klungel OH, Schneeweiss S, Brookhart MA, Avorn J, A cross-national study of the persistence of antihypertensive medication use in the elderly, J. Hypertens. 26 (1) (2008) 145–153. [PubMed: 18090552]

[29]. Suissa S, Immeasurable time bias in observational studies of drug effects on mortality, Am. J. Epidemiol. 168 (3) (2008) 329–335. [PubMed: 18515793]

[30]. Andrade SE, Harrold LR, Tjia J, et al. , A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data, Pharmacoepidemiol. Drug Saf. 21 (Suppl. 1) (2012) 100–128. [PubMed: 22262598]

[31]. Kokotailo RA, Hill MD, Coding of stroke and stroke risk factors using international classification of diseases, revisions 9 and 10, Stroke 36 (8) (2005) 1776–1781. [PubMed: 16020772]

[32]. Lauffenburger JC, Farley JF, Gehi AK, Rhoney DH, Brookhart MA, Fang G, Effectiveness and safety of dabigatran and warfarin in real-world US patients with non-valvular atrial fibrillation: a retrospective cohort study, J. Am. Heart Assoc. 4 (4) (2015).

[33]. Lauffenburger JC, Rhoney DH, Farley JF, Gehi AK, Fang G, Predictors of gastrointestinal bleeding among patients with atrial fibrillation after initiating dabigatran therapy, Pharmacotherapy 35 (6) (2015) 560–568. [PubMed: 26044889]

[34]. Roumie CL, Mitchel E, Gideon PS, Varas-Lorenzo C, Castellsague J, Griffin MR, Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data, Pharmacoepidemiol. Drug Saf. 17 (1) (2008) 20–26. [PubMed: 17979142]

[35]. Tirschwell DL, Longstreth WT Jr., Validating administrative data in stroke research, Stroke 33 (10) (2002) 2465–2470. [PubMed: 12364739]

[36]. Kumamaru H, Judd SE, Curtis JR, et al. , Validity of claims-based stroke algorithms in contemporary Medicare data: reasons for geographic and racial differences in stroke (REGARDS) study linked with medicare claims, Circ. Cardiovasc. Qual. Outcomes 7 (4) (2014) 611–619. [PubMed: 24963021]

[37]. McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA, Validity of diagnostic codes for acute stroke in administrative databases: a systematic review, PLoS One 10 (8) (2015), e0135834. [PubMed: 26292280]

[38]. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA, An automated database case definition for serious bleeding related to oral anticoagulant use, Pharmacoepidemiol. Drug Saf. 20 (6) (2011) 560–566. [PubMed: 21387461]

[39]. Fang MC, Go AS, Chang Y, et al. , A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study, J. Am. Coll. Cardiol. 58 (4) (2011) 395–401. [PubMed: 21757117]

[40]. Graham DJ, Reichman ME, Wernecke M, et al. , Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation, Circulation 131 (2) (2015) 157–164. [PubMed: 25359164]

[41]. Thigpen JL, Dillon C, Forster KB, et al. , Validity of international classification of disease codes to identify ischemic stroke and intracranial hemorrhage among individuals with associated diagnosis of atrial fibrillation, Circ. Cardiovasc. Qual. Outcomes 8 (1) (2015) 8–14. [PubMed: 25587093]

[42]. Wahl PM, Rodgers K, Schneeweiss S, et al. , Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population, Pharmacoepidemiol. Drug Saf. 19 (6) (2010) 596–603. [PubMed: 20140892]

[43]. Guimarães PO, Krishnamoorthy A, Kaltenbach LA, et al. , Accuracy of medical claims for identifying cardiovascular and bleeding events after myocardial infarction : a secondary analysis of the TRANSLATE-ACS study, JAMA Cardiol. 2 (7) (2017) 750–757. [PubMed: 28538984]

[44]. Tchetgen Tchetgen E, The control outcome calibration approach for causal inference with unobserved confounding, Am. J. Epidemiol. 179 (5) (2014) 633–640. [PubMed: 24363326]

[45]. Iribarren C, Karter AJ, Go AS, et al. , Glycemic control and heart failure among adult patients with diabetes, Circulation 103 (22) (2001) 2668–2673. [PubMed: 11390335]

[46]. Jong P, Gong Y, Liu PP, Austin PC, Lee DS, Tu JV, Care and outcomes of patients newly hospitalized for heart failure in the community treated by cardiologists compared with other specialists, Circulation 108 (2) (2003) 184–191. [PubMed: 12821540]

[47]. Kucharska-Newton AM, Heiss G, Ni H, et al. , Identification of heart failure events in Medicare claims: the atherosclerosis risk in communities (ARIC) study, J. Card. Fail. 22 (1) (2016) 48–55. [PubMed: 26211720]

[48]. Saczynski JS, Andrade SE, Harrold LR, et al. , A systematic review of validated methods for identifying heart failure using administrative data, Pharmacoepidemiol. Drug Saf. 21 (Suppl. 1) (2012) 129–140. [PubMed: 22262599]

[49]. Brookhart MA, Sturmer T, Glynn RJ, Rassen J, Schneeweiss S, Confounding control in healthcare database research: challenges and potential approaches, Med. Care 48 (6 Suppl) (2010) S114–S120. [PubMed: 20473199]

[50]. Choudhry NK, Improving the pathway from cardiovascular medication prescribing to longer-term adherence: new results about old issues, Circ. Cardiovasc. Qual. Outcomes 3 (3) (2010) 223–225. [PubMed: 20484200]

[51]. Desai RJ, Solomon DH, Shadick N, Iannaccone C, Kim SC, Identification of smoking using Medicare data–a validation study of claims-based algorithms, Pharmacoepidemiol. Drug Saf. 25 (4) (2016) 472–475. [PubMed: 26764576]

[52]. Neugebauer R, Fireman B, Roy JA, O'Connor PJ, Selby JV, Dynamic marginal structural modeling to evaluate the comparative effectiveness of more or less aggressive treatment intensification strategies in adults with type 2 diabetes, Pharmacoepidemiol. Drug Saf. 21 (Suppl. 2) (2012) 99–113. [PubMed: 22552985]

[53]. García-Albéniz X, Hernán MA, Logan RW, Price M, Armstrong K, Hsu J, Continuation of annual screening mammography and breast cancer mortality in women older than 70 years, Ann. Intern. Med. 172 (6) (2020) 381–389. [PubMed: 32092767]

[54]. Hernan MA, Brumback B, Robins JM, Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men, Epidemiology 11 (5) (2000) 561–570. [PubMed: 10955409]

[55]. Robins JM, Hernan MA, Brumback B, Marginal structural models and causal inference in epidemiology, Epidemiology 11 (5) (2000) 550–560. [PubMed: 10955408]

[56]. Cuisset T, Deharo P, Quilici J, et al. , Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study, Eur. Heart J. 38 (41) (2017) 3070–3078. [PubMed: 28510646]

[57]. Jencks SF, Williams MV, Coleman EA, Rehospitalizations among patients in the Medicare fee-for-service program, N. Engl. J. Med. 360 (14) (2009) 1418–1428. [PubMed: 19339721]

[58]. Korhonen MJ, Robinson JG, Annis IE, et al. , Adherence tradeoff to multiple preventive therapies and all-cause mortality after acute myocardial infarction, J. Am. Coll. Cardiol. 70 (13) (2017) 1543–1554. [PubMed: 28935030]

[59]. Hernan MA, How to estimate the effect of treatment duration on survival outcomes using observational data, BMJ (Clinical research ed) 360 (2018), k182.

[60]. Zhao SS, Lyu H, Yoshida K, Versatility of the clone-censor-weight approach: response to 'trial emulation in the presence of immortal-time bias, Int. J. Epidemiol. 50 (2) (2020) 694–695.

[61]. Gokhale M, Buse JB, DeFilippo Mack C., et al. , Calendar time as an instrumental variable in assessing the risk of heart failure with antihyperglycemic drugs, Pharmacoepidemiol. Drug Saf. 27 (8) (2018) 857–866. [PubMed: 29943442]

[62]. Hernan MA, Robins JM, Estimating causal effects from epidemiological data, J. Epidemiol. Community Health 60 (7) (2006) 578–586. [PubMed: 16790829]

[63]. Li F, Morgan KL, Zaslavsky AM, Balancing covariates via propensity score weighting, J. Am. Stat. Assoc. 113 (521) (2018) 390–400.

[64]. Orellana L, Rotnitzky A, Robins JM, Dynamic regime marginal structural mean models for estimation of optimal dynamic treatment regimes, part I: main content, Int. J. Biostat. 6 (2) (2010) Article 8.

[65]. Cain LE, Robins JM, Lanoy E, Logan R, Costagliola D, Hernán MA, When to start treatment? A systematic approach to the comparison of dynamic regimes using observational data, Int. J. Biostat. 6 (2) (2010) Article 18.

[66]. Sturmer T, Rothman KJ, Avorn J, Glynn RJ, Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution–a simulation study, Am. J. Epidemiol. 172 (7) (2010) 843–854. [PubMed: 20716704]

[67]. Hernan MA, Hernandez-Diaz S, Robins JM, A structural approach to selection bias, Epidemiology 15 (5) (2004) 615–625. [PubMed: 15308962]

[68]. Cole SR, Hernan MA, Constructing inverse probability weights for marginal structural models, Am. J. Epidemiol. 168 (6) (2008) 656–664. [PubMed: 18682488]

[69]. Cain LE, Logan R, Robins JM, et al. , When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: an observational study, Ann. Intern. Med. 154 (8) (2011) 509–515. [PubMed: 21502648]

[70]. Association AS, Statement on statistical significance and p-values, Am. Stat. 70 (2016) 129–133.

[71]. Greenland S, Senn SJ, Rothman KJ, et al. , Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations, Eur. J. Epidemiol. 31 (4) (2016) 337–350. [PubMed: 27209009]

[72]. Hernán MA, The hazards of hazard ratios, Epidemiology 21 (1) (2010) 13–15. [PubMed: 20010207]

[73]. Collet JP, Thiele H, Barbato E, et al. , 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, Eur. Heart J. 42 (14) (2021) 1289–1367. [PubMed: 32860058]

[74]. Ibanez B, James S, Agewall S, et al. , 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC), Eur. Heart J. 39 (2) (2018) 119–177. [PubMed: 28886621]

[75]. You SC, Gupta A, Krumholz HM, Ticagrelor vs clopidogrel for patients with acute coronary syndrome undergoing percutaneous intervention-reply, Jama 325 (9) (2021) 890–891.

[76]. Zhao X, Zhang J, Guo J, et al. , Comparison of safety and efficacy between clopidogrel and ticagrelor in elderly patients with acute coronary syndrome: a systematic review and meta-analysis, Front. Pharmacol. 12 (2021), 743259. [PubMed: 34721032]

[77]. Faridi KF, Garratt KN, Kennedy KF, et al. , Physician and hospital utilization of P2Y12 inhibitors in ST-segment-elevation myocardial infarction in the United States: a study from the National Cardiovascular Data Registry's research to practice initiative, Circ. Cardiovasc. Qual. Outcomes 13 (3) (2020), e006275. [PubMed: 32156164]

[78]. Christensen DM, Schjerning AM, Sindet-Pedersen C, et al. , Outcomes of prolonged dual anti-platelet therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a nationwide registry-based study, Am. Heart J. 245 (2021) 81–89. [PubMed: 34902311]

[79]. Angiolillo DJ, Bhatt DL, Cannon CP, et al. , Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective: 2021 update, Circulation 143 (6) (2021) 583–596. [PubMed: 33555916]

[80]. O'Gara PT, Kushner FG, Ascheim DD, et al. , 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, Circulation 127 (4) (2013) e362–e425. [PubMed: 23247304]

[81]. Jneid H, Anderson JL, Wright RS, et al. , 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines, Circulation 126 (7) (2012) 875–910. [PubMed: 22800849]

[82]. Kushner FG, Hand M, Smith SC Jr., et al. , 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, J. Am. Coll. Cardiol. 54 (23) (2009) 2205–2241. [PubMed: 19942100]

[83]. Wright RS, Anderson JL, Adams CD, et al. , 2011 ACCF/AHA focused update of the guidelines for the Management of Patients with Unstable Angina/ non-ST-elevation myocardial infarction (updating the 2007 guideline): a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines, Circulation 123 (18) (2011) 2022–2060. [PubMed: 21444889]

[84]. Nanna MG, Chen ST, Nelson AJ, Navar AM, Peterson ED, Representation of older adults in cardiovascular disease trials since the inclusion across the lifespan policy, JAMA Intern. Med. 180 (11) (2020) 1531–1533. [PubMed: 32897289]

[85]. Benjamin EJ, Blaha MJ, Chiuve SE, et al. , Heart disease and stroke statistics-2017 update: a report from the American Heart Association, Circulation 135 (10) (2017) e146–e603. [PubMed: 28122885]

[86]. Neugebauer R, Schmittdiel JA, van der Laan MJ, A case study of the impact of data-adaptive versus model-based estimation of the propensity scores on causal inferences from three inverse probability weighting estimators, Int. J. Biostat. 12 (1) (2016) 131–155. [PubMed: 27227720]

[87]. Faridi KF, Tamez H, Butala NM, et al. , Comparability of event adjudication versus administrative billing claims for outcome ascertainment in the DAPT study: findings from the EXTEND-DAPT study, Circ. Cardiovasc. Qual. Outcomes 14 (1) (2021), e006589. [PubMed: 33435731]

[88]. Butala NM, Faridi KF, Tamez H, et al. , Estimation of DAPT study treatment effects in contemporary clinical practice: findings from the EXTEND-DAPT study, Circulation 145 (2) (2022) 97–106. [PubMed: 34743530]

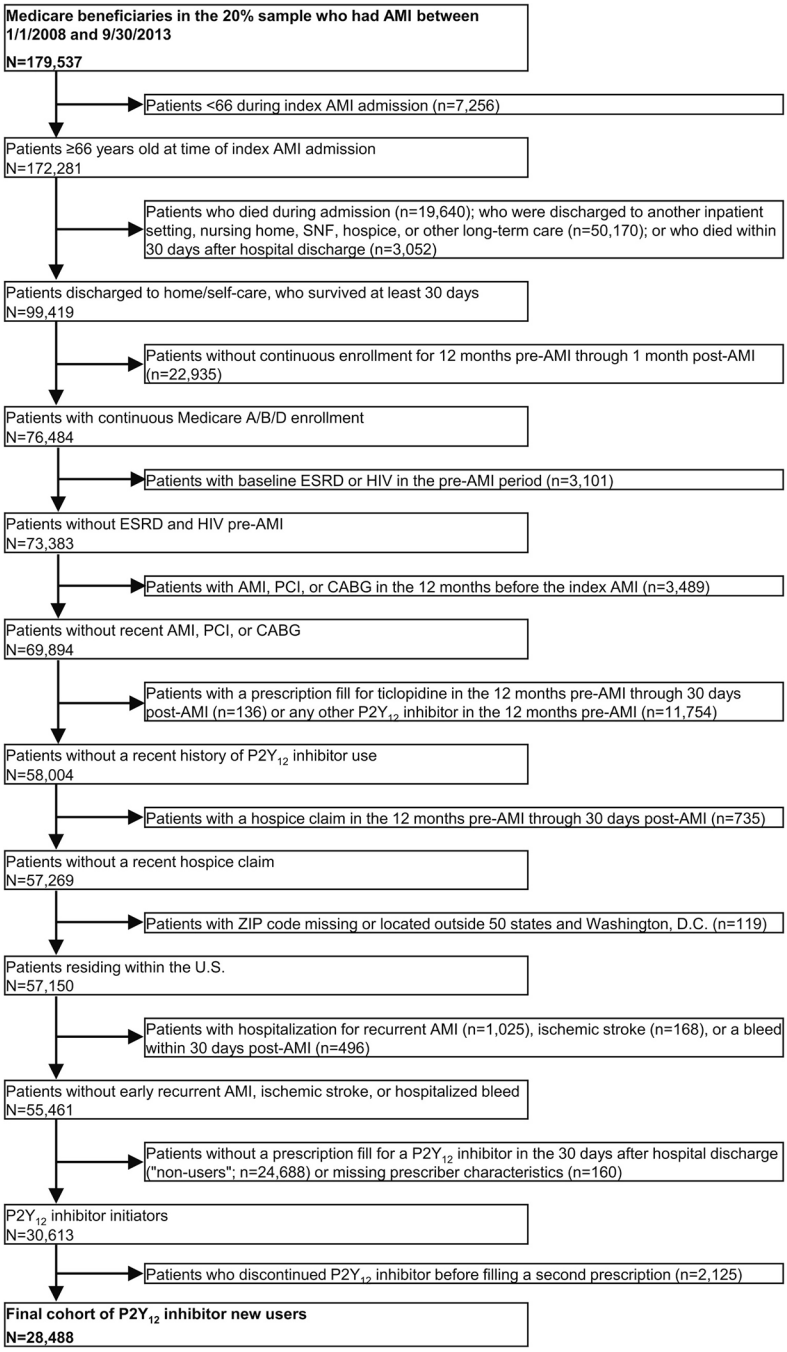


Fig. 1.

$P2Y_{12}$ inhibitor new user cohort study flowchart. Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass surgery; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; PCI, percutaneous coronary intervention; SNF, skilled nursing facility.

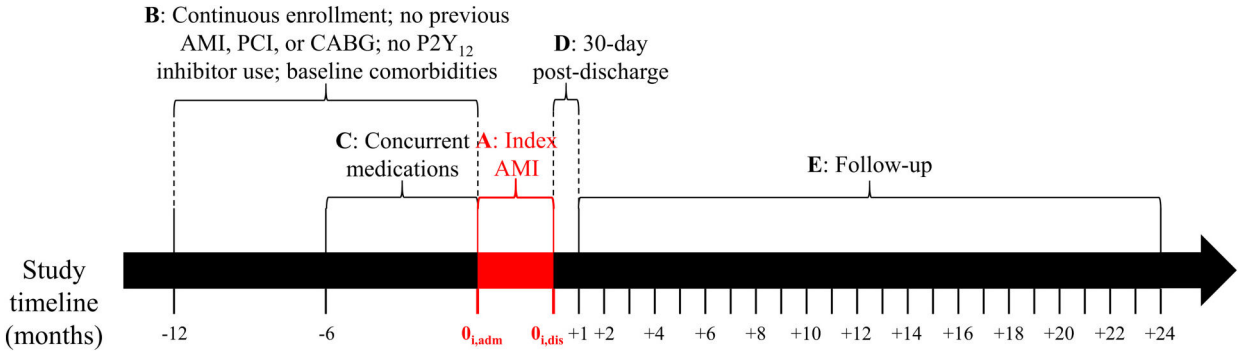
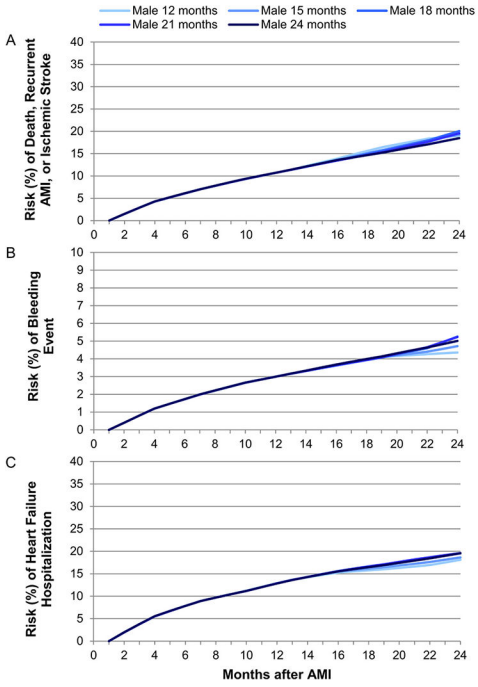


Fig. 2.

Study design. Index AMI hospitalization (A) from date of admission ($0_{i,adm}$) to discharge ($0_{i,dis}$). Baseline conditions and previous $P2Y_{12}$ inhibitor use/indication (B) and use of other medications (C) measured pre-AMI. $P2Y_{12}$ inhibitor prescription fill and event-free survival required during first 30 days post-AMI (D). Follow-up (E) began in month 2 (day 31) and occurred in 30-day increments (person-months).

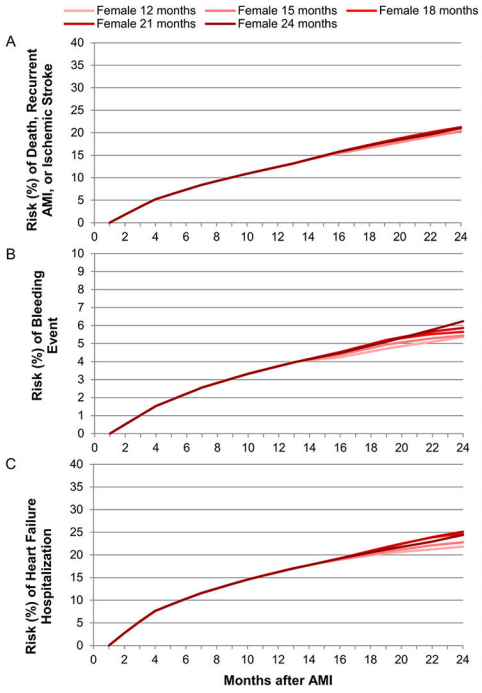
Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass surgery; PCI percutaneous coronary intervention.



Assigned treatment duration	Risk (%) at 24mo	RR at 24mo	RD (%) at 24mo
Male 12 months	19.0 (17.4, 20.6)	1.03 (0.94, 1.12)	0.5 (-1.0, 2.3)
Male 13 months	19.3 (17.8, 20.6)	1.04 (0.96, 1.13)	0.8 (-0.8, 2.2)
Male 14 months	19.2 (18.0, 20.3)	1.04 (0.96, 1.11)	0.7 (-0.7, 1.9)
Male 15 months	19.3 (18.1, 20.2)	1.04 (0.97, 1.11)	0.8 (-0.5, 1.9)
Male 16 months	19.9 (18.6, 20.9)	1.08 (1.00, 1.15)	1.4 (0.0, 2.6)
Male 17 months	19.8 (18.5, 21.0)	1.07 (1.00, 1.15)	1.4 (0.0, 2.8)
Male 18 months	20.0 (18.8, 21.4)	1.08 (1.01, 1.18)	1.6 (0.2, 3.1)
Male 19 months	20.2 (19.0, 21.8)	1.09 (1.02, 1.18)	1.8 (0.3, 3.3)
Male 20 months	19.8 (18.6, 21.2)	1.07 (1.01, 1.14)	1.3 (0.2, 2.6)
Male 21 months	19.6 (18.5, 20.8)	1.06 (1.01, 1.11)	1.1 (0.2, 2.0)
Male 22 months	19.2 (18.1, 20.1)	1.04 (1.00, 1.07)	0.7 (0.1, 1.3)
Male 23 months	18.8 (17.8, 19.7)	1.02 (1.00, 1.03)	0.3 (0.0, 0.6)
Male 24 months	**18.5 (17.5, 19.5)**	**1.**	**0.**
Male 12 months	**4.4 (3.8, 5.2)**	**0.87 (0.76, 1.02)**	**-0.6 (-1.3, 0.1)**
Male 13 months	4.5 (3.9, 5.1)	0.89 (0.78, 1.02)	-0.5 (-1.2, 0.1)
Male 14 months	4.6 (4.0, 5.1)	0.91 (0.80, 1.03)	-0.4 (-1.1, 0.1)
Male 15 months	4.7 (4.1, 5.2)	0.94 (0.82, 1.05)	-0.3 (-0.9, 0.2)
Male 16 months	4.9 (4.3, 5.6)	0.98 (0.85, 1.13)	-0.1 (-0.8, 0.6)
Male 17 months	5.1 (4.4, 6.0)	1.02 (0.86, 1.23)	0.1 (-0.7, 1.1)
Male 18 months	5.3 (4.5, 6.4)	1.05 (0.87, 1.34)	0.3 (-0.7, 1.5)
Male 19 months	5.3 (4.6, 6.5)	1.06 (0.89, 1.35)	0.3 (-0.6, 1.6)
Male 20 months	5.3 (4.6, 6.2)	1.05 (0.91, 1.28)	0.3 (-0.5, 1.3)
Male 21 months	5.2 (4.7, 6.0)	1.04 (0.92, 1.19)	0.2 (-0.4, 0.9)
Male 22 months	5.1 (4.6, 5.7)	1.03 (0.94, 1.11)	0.1 (-0.3, 0.6)
Male 23 months	5.1 (4.6, 5.6)	1.01 (0.97, 1.05)	0.1 (-0.2, 0.2)
Male 24 months	5.0 (4.4, 5.6)	1.	0.
Male 12 months	18.1 (16.8, 19.4)	0.93 (0.86, 1.01)	-1.4 (-2.7, 0.2)
Male 13 months	18.3 (17.1, 19.4)	0.94 (0.87, 1.01)	-1.2 (-2.5, 0.2)
Male 14 months	18.5 (17.3, 19.5)	0.95 (0.89, 1.01)	-1.0 (-2.2, 0.2)
Male 15 months	18.6 (17.5, 19.6)	0.95 (0.90, 1.01)	-0.9 (-2.0, 0.2)
Male 16 months	**19.0 (17.9, 20.1)**	**0.97 (0.92, 1.03)**	**-0.5 (-1.5, 0.6)**
Male 17 months	**19.4 (18.2, 20.5)**	**0.99 (0.94, 1.06)**	**-0.2 (-1.2, 1.1)**
Male 18 months	**19.5 (18.3, 20.7)**	**1.00 (0.95, 1.07)**	**0.0 (-1.0, 1.2)**
Male 19 months	**19.7 (18.5, 21.0)**	**1.01 (0.96, 1.08)**	**0.2 (-0.8, 1.5)**
Male 20 months	**19.7 (18.5, 20.9)**	**1.01 (0.96, 1.06)**	**0.1 (-0.7, 1.2)**
Male 21 months	**19.6 (18.5, 20.7)**	**1.00 (0.97, 1.05)**	**0.0 (-0.7, 0.8)**
Male 22 months	**19.6 (18.6, 20.6)**	**1.00 (0.97, 1.03)**	**0.0 (-0.5, 0.6)**
Male 23 months	**19.6 (18.6, 20.6)**	**1.00 (0.99, 1.02)**	**0.0 (-0.3, 0.3)**
Male 24 months	**19.6 (18.4, 20.6)**	**1.**	**0.**

Fig. 3.

Effectiveness, safety, and negative control outcome cumulative incidences of $P2Y_{12}$ inhibitor durations in men. Estimates are presented for all durations, but cumulative incidence curves are only presented in 3-month intervals (12-, 15-, 18-, 21-, and 24-month durations). Lighter colors are shorter $P2Y_{12}$ inhibitor durations; darker colors are longer durations. Estimates (95 % CIs) for composite effectiveness (A), bleeds (B), and heart failure (C) outcomes. For (A) and (B), duration with lowest risk is bolded; for (C), comparable durations are bolded. Please note, the y-axis risk scale for bleeds (B) is different than other outcomes. Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; RD risk difference; RR, relative risk.



Assigned treatment duration	Risk (%) at 24mo	RR at 24mo	RD (%) at 24mo
Female 12 months	20.4 (18.9, 22.1)	0.97 (0.90, 1.05)	-0.6 (-2.3, 1.0)
Female 13 months	20.4 (19.1, 21.6)	0.97 (0.90, 1.04)	-0.7 (-2.1, 0.7)
Female 14 months	**20.1 (18.9, 21.1)**	**0.96 (0.89, 1.01)**	**-0.9 (-2.3, 0.3)**
Female 15 months	20.3 (19.1, 21.2)	0.96 (0.91, 1.02)	-0.8 (-2.0, 0.4)
Female 16 months	20.6 (19.5, 21.6)	0.98 (0.92, 1.04)	-0.4 (-1.7, 0.8)
Female 17 months	20.8 (19.7, 21.9)	0.99 (0.93, 1.05)	-0.2 (-1.5, 1.1)
Female 18 months	21.0 (19.9, 22.2)	1.00 (0.94, 1.06)	0.0 (-1.3, 1.2)
Female 19 months	21.2 (20.2, 22.3)	1.01 (0.95, 1.06)	0.1 (-1.0, 1.3)
Female 20 months	21.4 (20.4, 22.4)	1.02 (0.97, 1.07)	0.4 (-0.7, 1.4)
Female 21 months	21.3 (20.3, 22.2)	1.01 (0.97, 1.05)	0.2 (-0.6, 1.0)
Female 22 months	21.2 (20.3, 22.1)	1.01 (0.98, 1.03)	0.1 (-0.5, 0.7)
Female 23 months	21.1 (20.2, 22.1)	1.00 (0.99, 1.01)	0.0 (-0.3, 0.3)
Female 24 months	21.0 (20.1, 22.2)	1.	0.
Female 12 months	**5.4 (4.6, 6.4)**	**0.86 (0.74, 1.03)**	**-0.9 (-1.7, 0.2)**
Female 13 months	5.4 (4.7, 6.1)	0.86 (0.75, 0.99)	-0.8 (-1.6, -0.1)
Female 14 months	5.4 (4.7, 6.0)	0.86 (0.76, 0.96)	-0.8 (-1.5, -0.2)
Female 15 months	5.4 (4.8, 6.0)	0.87 (0.78, 0.96)	-0.8 (-1.5, -0.2)
Female 16 months	5.5 (4.9, 6.0)	0.88 (0.80, 0.96)	-0.7 (-1.3, -0.2)
Female 17 months	5.6 (5.0, 6.1)	0.89 (0.81, 0.98)	-0.7 (-1.3, -0.1)
Female 18 months	5.7 (5.0, 6.2)	0.91 (0.82, 1.01)	-0.6 (-1.1, 0.0)
Female 19 months	5.7 (5.1, 6.3)	0.92 (0.84, 1.02)	-0.5 (-1.1, 0.1)
Female 20 months	5.8 (5.2, 6.4)	0.93 (0.85, 1.03)	-0.5 (-0.9, 0.2)
Female 21 months	5.9 (5.2, 6.5)	0.94 (0.87, 1.03)	-0.4 (-0.8, 0.2)
Female 22 months	5.9 (5.3, 6.5)	0.95 (0.89, 1.02)	-0.3 (-0.7, 0.1)
Female 23 months	6.1 (5.4, 6.7)	0.97 (0.93, 1.01)	-0.2 (-0.4, 0.0)
Female 24 months	6.2 (5.6, 6.9)	1.	0.
Female 12 months	21.8 (20.6, 23.1)	0.89 (0.84, 0.95)	-2.6 (-3.9, -1.1)
Female 13 months	22.2 (21.0, 23.3)	0.91 (0.85, 0.96)	-2.2 (-3.6, -0.9)
Female 14 months	22.3 (21.2, 23.3)	0.91 (0.87, 0.97)	-2.1 (-3.4, -0.8)
Female 15 months	22.8 (21.8, 23.8)	0.93 (0.89, 0.99)	-1.6 (-2.9, -0.3)
Female 16 months	**23.7 (22.6, 24.7)**	**0.97 (0.92, 1.02)**	**-0.7 (-2.0, 0.6)**
Female 17 months	**24.0 (22.9, 25.2)**	**0.98 (0.94, 1.04)**	**-0.4 (-1.6, 1.0)**
Female 18 months	**24.7 (23.5, 26.0)**	**1.01 (0.96, 1.08)**	**0.3 (-1.1, 1.8)**
Female 19 months	**25.0 (23.8, 26.2)**	**1.02 (0.97, 1.09)**	**0.5 (-0.8, 2.0)**
Female 20 months	**25.2 (24.0, 26.5)**	**1.03 (0.98, 1.09)**	**0.8 (-0.5, 2.2)**
Female 21 months	**25.1 (24.0, 26.3)**	**1.03 (0.99, 1.07)**	**0.7 (-0.4, 1.8)**
Female 22 months	**24.8 (23.8, 25.9)**	**1.02 (0.99, 1.04)**	**0.4 (-0.4, 1.1)**
Female 23 months	**24.6 (23.6, 25.6)**	**1.01 (0.99, 1.02)**	**0.2 (-0.2, 0.5)**
Female 24 months	**24.4 (23.2, 25.5)**	**1.**	**0.**

Fig. 4.

Effectiveness, safety, and negative control outcome cumulative incidences of $P2Y_{12}$ inhibitor durations in women. Estimates are presented for all durations, but cumulative incidence curves are only presented in 3-month intervals (12-, 15-, 18-, 21-, and 24-month durations). Lighter colors are shorter $P2Y_{12}$ inhibitor durations; darker colors are longer durations. Estimates (95 % CIs) for composite effectiveness (A), bleeds (B), and heart failure (C) outcomes. For (A) and (B), duration with lowest risk is bolded; for (C) comparable durations are bolded. Please note, the y-axis risk scale for bleeds (B) is different than other outcomes. Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; RD risk difference; RR, relative risk.

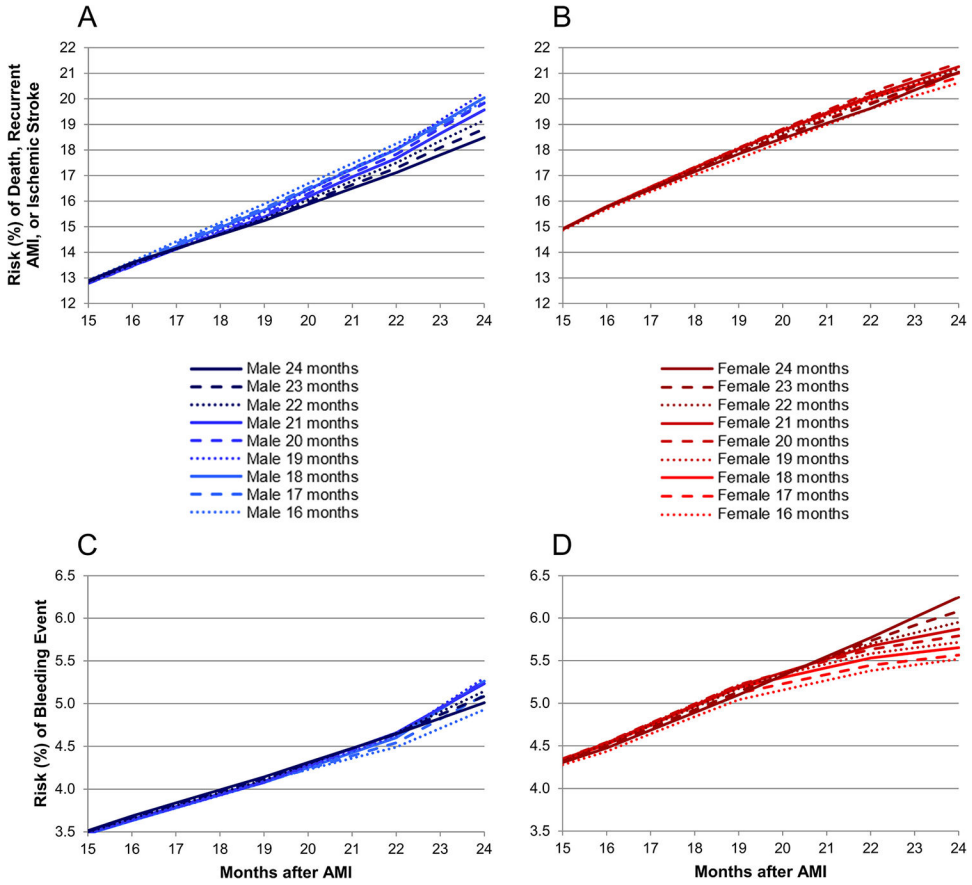


Fig. 5.

Magnified cumulative incidences of 16- to 24-month $P2Y_{12}$ inhibitor durations for the composite effectiveness outcome in men (A) and women (B), and the safety bleeding outcome in men (C) and women (D). Results for only 16- to 24-month $P2Y_{12}$ inhibitor durations (identified as comparable for causal inference) are presented here. Please note, the x-axis time scale goes from 15 to 24 months after AMI, and the y-axis risk scales are different for effectiveness vs. safety outcomes.

Abbreviations: AMI, acute myocardial infarction.

Table 1

ICD-9 codes and algorithms used to measure study outcomes.

Outcome	ICD-9 codes	Source of diagnosis code	Diagnosis field position
Composite clinical effectiveness outcome (all-cause mortality and hospitalized ischemic events)			
All-cause mortality[a]	Date of death	Beneficiary summary file	
Recurrent AMI [24]	410.x1	Inpatient	Primary or secondary
Ischemic stroke [30–37]	433.x1, 434 (excluding 434.x0), 436	Inpatient	Primary
Clinical safety outcome (hospitalized bleeding events)			
Intracranial hemorrhage [30–35,38–41]	430, 431, 432	Inpatient	Primary
Gastrointestinal hemorrhage [32,33,38–40,42]	455.2, 455.5, 455.8, 456.0, 456.20, 530.7, 531.0–531.6, 532.6, 533.6, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.0, 578.1, 578.9	Inpatient	Primary
Other bleeding events [32,33,38–40]		Inpatient	Primary
Choroidal hemorrhage	363.6		
Conjunctival hemorrhage	372.72		
Orbital hemorrhage	376.32		
Optic nerve hemorrhage	377.42		
Vitreous hemorrhage	379.23		
Hemopericardium	423.0		
Hematuria	599.7		
Hemarthrosis	719.1		
Hematoma	729.92		
Adrenal hemorrhage	772.5		
Epistaxis	784.7		
Hemorrhage from throat	784.8		
Hemoptysis	786.3		
Injury to kidney	866.01–866.02, 866.11–866.12		
Other	285.1, 459.0		
Negative control outcome (hospitalized heart failure)			
Heart failure [45–48]	428.x, 402.01, 402.11, 402.91	Inpatient	Any

Abbreviations: AMI, acute myocardial infarction; ICD-9, International Classification of Diseases, Ninth Revision, Clinical Modification.

[a]Measured using date of death in annual beneficiary summary file.

Table 2

Selected baseline characteristics in male and female patients.

Patient baseline characteristics	Male patients N = 13,920 No. (%)[a]	Female patients N = 14,568 No. (%)[a]
Predisposing patient characteristics		
Age		
66–75	8222 (59.1)	6125 (42.0)
76–85	4467 (32.1)	5870 (40.3)
86+	1231 (8.8)	2573 (17.7)
Race/ethnicity		
White, non-Hispanic	12,498 (89.8)	12,670 (87.0)
Black, non-Hispanic	626 (4.5)	1059 (7.3)
Hispanic	298 (2.1)	393 (2.7)
Asian, non-Hispanic	314 (2.3)	297 (2.0)
Other	184 (1.3)	149 (1.0)
Enabling patient characteristics		
Dual Medicare/Medicaid eligibility[b]	1993 (14.3)	3224 (22.1)
Patient-perceived need		
Pre-AMI conditions[c]		
Charlson comorbidity index		
0	5460 (39.2)	5191 (35.6)
1–2	5374 (38.6)	6158 (42.3)
3–4	2105 (15.1)	2236 (15.3)
5–7	753 (5.4)	766 (5.3)
8+	228 (1.6)	217 (1.5)
Depression	1075 (7.7)	2120 (14.6)
Dementia/Alzheimer's[d]	605 (4.3)	1015 (7.0)
Pre-AMI medications[e]		
Chronic medications[f]		
0	2012 (14.5)	1194 (8.2)
1 –3	5087 (36.5)	4328 (29.7)
4–6	4062 (29.2)	4797 (32.9)
7–9	1868 (13.4)	2684 (18.4)
10+	891 (6.4)	1565 (10.7)
Prescriber-perceived need		
Pre-AMI conditions[c]		
Diabetes	4404 (31.6)	4870 (33.4)
Heart failure	1504 (10.8)	1949 (13.4)

Patient baseline characteristics	Male patients N = 13,920	Female patients N = 14,568
	No. (%)[a]	No. (%)[a]
Coronary artery disease	4791 (34.4)	4068 (27.9)
Cerebrovascular disease	509 (3.7)	560 (3.8)
Peripheral vascular disease	1542 (11.1)	1893 (13.0)
Cancer	2088 (15.0)	1178 (8.1)
Previous venous thromboembolism	865 (6.2)	941 (6.5)
History of smoking[g]	5443 (39.1)	3983 (27.3)
Atrial fibrillation	974 (7.0)	1043 (7.2)
History of bleeding event	2201 (15.8)	2061 (14.1)
Pre-AMI medications[e]		
Statin	6081 (43.7)	6091 (41.8)
ACE inhibitor or ARB	6345 (45.6)	7645 (52.5)
Beta-blocker	5461 (39.2)	6458 (44.3)
Anticoagulant	1017 (7.3)	974 (6.7)
Index AMI hospitalization characteristics		
Year of index admission		
2008	2334 (16.8)	2657 (18.2)
2009	2254 (16.2)	2493 (17.1)
2010	2304 (16.6)	2547 (17.5)
2011	2453 (17.6)	2519 (17.3)
2012	2539 (18.2)	2510 (17.2)
2013	2036 (14.6)	1842 (12.6)
AMI intervention strategy[h]		
PCI with drug-eluting stent	7307 (52.5)	7004 (48.1)
PCI with bare-metal stent	3099 (22.3)	2888 (19.8)
Other PCI	893 (6.4)	716 (4.9)
Coronary artery bypass surgery	543 (3.9)	282 (1.9)
Medical management or fibrinolytics	2078 (14.9)	3678 (25.2)
Heart failure	3278 (23.5)	4187 (28.7)
Bleeding event	918 (6.6)	851 (5.8)
Acute kidney injury	1477 (10.6)	1486 (10.2)
Index $P2Y_{12}$ inhibitor product[i]		
Brand-name clopidogrel	9822 (70.6)	10,794 (74.1)
Generic clopidogrel	2928 (21.0)	3066 (21.0)
Brand-name prasugrel	905 (6.5)	490 (3.4)
Brand-name ticagrelor	265 (1.9)	218 (1.5)

Abbreviations: ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; ATC, Anatomical Therapeutic Chemical Classification System; PCI, percutaneous coronary intervention.

[a]Column percentages of total male or female patients included in cohort.

[b] Medicare beneficiaries dually enrolled with full Medicaid benefits at any point in 12 calendar months before through 1 calendar month after index AMI hospitalization.

[c] Measured 12 months pre-AMI admission date.

[d] Medicare Chronic Conditions Data Warehouse definition.

[e] Measured 6 months pre-AMI admission date.

[f] ≥2 prescription fills on separate dates for unique 4th-level ATC code.

[g] Measured 12 months pre-AMI admission date through 30 days post-AMI discharge date using Desai algorithm including diagnoses codes and prescription medication fill data.

[h] Measured during index AMI hospitalization; includes coronary revascularization procedures through 30 days post-AMI discharge date. Variable is hierarchical with categories officially being (1) any PCI with drug-eluting stent; (2) PCI with bare-metal stent but no drug-eluting stent; (3) PCI with no mention of coronary stent; (4) patients undergoing coronary artery bypass surgery but did not receive PCI; and (5) patients who (a) did not receive PCI, (b) did not receive coronary artery bypass surgery, and (c) either received fibrinolytics or had no record of other intervention strategies.

[i] Measured between index AMI admission date and 30 days post-AMI discharge date. Variable not included in clone-censor-weight marginal structural models; presented here to simply describe the percentage of patients filling each type of product as their first $P2Y_{12}$ inhibitor.