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Disparities by sex in $P2Y_{12}$ 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 $P2Y_{12}$ inhibitor new user retrospective cohort analysis of US Medicare claims data

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ABSTRACT

Objectives To determine if comparable older women and men received different durations of $P2Y_{12}$ inhibitor therapy following acute myocardial infarction (AMI) and if therapy duration differences were justified by differences in ischaemic benefits and/or bleeding risks.

Design Retrospective cohort.

Setting 20% sample of 2007–2015 US Medicare fee-for-service administrative claims data.

Participants ≥66-year-old $P2Y_{12}$ inhibitor new users following 2008–2013 AMI hospitalisation (N=30 613). Older women compared to older men with similar predicted risks of study outcomes.

Primary and secondary outcome measures Primary outcome: $P2Y_{12}$ inhibitor duration (modelled as risk of therapy discontinuation). Secondary outcomes: clinical events while on $P2Y_{12}$ inhibitor therapy, including (1) death/hospice admission, (2) composite of ischaemic events (AMI/stroke/revascularisation) and (3) hospitalised bleeds. Cause-specific risks and relative risks (RRs) estimated using Aalen-Johansen cumulative incidence curves and bootstrapped 95% CIs.

Results 10 486 women matched to 10 486 men with comparable predicted risks of all 4 study outcomes. No difference in treatment discontinuation was observed at 12 months (women 31.2% risk; men 30.9% risk; RR 1.01; 95% CI 0.97 to 1.05), but women were more likely than men to discontinue therapy at 24 months (54.4% and 52.9% risk, respectively; RR 1.03; 95% CI 1.00 to 1.05). Among patients who did not discontinue $P2Y_{12}$ inhibitor therapy, women had lower 24-month risks of ischaemic outcomes than men (13.1% and 14.7%, respectively; RR 0.90; 95% CI 0.84 to 0.96), potentially lower 24-month risks of death/hospice admission (5.0% and 5.5%, respectively; RR 0.91; 95% CI 0.82 to 1.02), but women and men both had 2.5% 24-month bleeding risks (RR 0.98; 95% CI 0.82 to 1.14).

Strengths and limitations of this study

- Women experience acute myocardial infarctions differently than men, but matching on predicted risks of study outcomes allowed identification of women and men more likely to be clinically comparable.
- Using Aalen-Johansen cumulative incidence curves allowed calculation of cause-specific risks for all study outcomes without overinflating hazards as seen with cause-specific proportional hazards models.
- Medication stop dates are not available in administrative claims data, making treatment discontinuation misclassification as non-adherence—and vice versa—a measurement error concern that is only addressable through sensitivity analyses in this data source.
- Claims-based measures of medication utilisation may underestimate or overestimate a patient's actual medication use, but claims measures of medication utilisation have been shown to correlate well with other adherence measures and clinical outcomes.
- The rates of outcomes that may influence reasons to continue or stop $P2Y_{12}$ inhibitors—as well as patient characteristics predicting adherence behaviours—were adjusted for, but it was not possible to determine the reason patients discontinued $P2Y_{12}$ inhibitor therapy.

Conclusions Risks for death/hospice and ischaemic events were lower among women still taking a $P2Y_{12}$ inhibitor than comparable men, with no difference in bleeding risks. Shorter $P2Y_{12}$ inhibitor durations in older women than comparable men observed between 12 and 24 months post-AMI may reflect a disparity that is not justified by differences in clinical need.

INTRODUCTION

A coronary artery obstruction—blocking blood flow and delivery of oxygen and nutrients to heart muscle tissue, leading to necrosis—is the most common cause of an acute myocardial infarction (AMI).[1] Coronary artery disease has the largest global morbidity and mortality burden of any condition, with ~7 million AMIs occurring worldwide[2] and >600 000 AMI hospitalisations in the US annually.[3] Pharmacotherapies with significant benefit and minimal risk—each having a different mechanism for secondary prevention—are often recommended to continue indefinitely after AMI hospital discharge and include (1) statins; (2) either ACE inhibitors or angiotensin II receptor blockers (ARBs) and potentially, (3) beta-blockers.[4–10] However, dual antiplatelet therapy (DAPT)—consisting of low-dose aspirin plus a $P2Y_{12}$ inhibitor—comes with a substantial bleeding risk in addition to its benefit in preventing ischaemic events.

The increased bleeding risk of DAPT has led to considerable debate and several randomised clinical trials (RCTs) regarding the optimal $P2Y_{12}$ inhibitor duration.[11–17] Women and men experience AMIs differently, including differences in pathophysiology and symptom presentation,[18–20] and women may have a greater bleeding risk than men while taking a $P2Y_{12}$ inhibitor.[11 21] Additionally, several RCT subgroup analyses suggest women may not benefit as much as men from longer $P2Y_{12}$ inhibitor durations.[12–17] Despite these complexities, clinical guidelines recommend similar $P2Y_{12}$ inhibitor durations for men and women in most circumstances.[4–8 11 22–29]

Disparities by patient sex in receipt of guideline-recommended post-AMI secondary prevention are known to exist,[30–33] but the potential increased bleeding risks among women may justify shorter $P2Y_{12}$ inhibitor durations compared with men. In the Patterns of Non-Adherence to Antiplatelet Regimens in Stented Patients (PARIS) registry, physician-recommended discontinuation of DAPT was 11% more likely among women than men at any point in the 2 years following percutaneous coronary intervention (PCI) with stent placement.[21] However, this study did not account for rates of death, ischaemic events, and bleeding events while on DAPT, potentially valid clinical reasons for treatment duration to differ by patient sex. Thus, it is unclear how much of the observed difference in DAPT durations between men and women from PARIS is attributable to a disparity vs appropriate discontinuation based on differences in the ischaemic-benefit/bleeding-risk trade-off.

Additionally, among older US Medicare beneficiaries, the clinical differences in AMIs by sex are less striking than among younger patients,[18 19] and women account for ~50% of AMI hospitalisations.[34 35] The ischaemic-benefit/bleeding-risk trade-off is even more uncertain in these older women who are under-represented in RCTs.[12–15 36–38] This raises an important question of whether stopping $P2Y_{12}$ inhibitor therapy earlier in older women than older men post-AMI reflects appropriate benefit-risk trade-off or a quality-of-care disparity by patient sex.

Therefore, the primary purpose of this study was to determine—after accounting for baseline characteristics and potential differences in rates of death, ischaemic events and bleeding events—if older women compared with older men received different $P2Y_{12}$ inhibitor durations after an AMI. Additionally, this study aimed to determine if the risks of death, ischaemic events, and bleeding events following an AMI differed between older women and comparable older men while taking a $P2Y_{12}$ inhibitor.

METHODS

The primary data source was a 20% sample of 2007–2015 fee-for-service Medicare claims including enrolment summary, medical service claims and prescription claims. Medicare is available to nearly all US citizens and legal residents ≥65 years old, and in 2009, >95% received some coverage from Medicare.[39–42] Medicare beneficiaries ≥65 years old are fairly representative of the general 65+ US population. Over 70% of Medicare beneficiaries over 65 are covered by fee-for-service plans, which can include Parts A, B and D. Inpatient/hospital coverage (Part A) is available without a premium to most beneficiaries. Part B is optional coverage for outpatient services and procedures that ~90% of fee-for-service Medicare beneficiaries over 65 receive. Over 2/3 of Medicare beneficiaries have Part D coverage for prescription medications.[43]

Prescriber characteristics were identified by linking unique prescriber identifiers from prescription claims to Medicare Data on Provider Practice and Specialty files and linking National Provider Identifier numbers to CMS National Plan and Provider Enumeration System public files. Contextual characteristics were identified by geocoding patient 9-digit residential ZIP codes to US Census Block Groups and linking to publicly available US Census 2010 Summary Files and 2007–2011 American Community Survey 5-Year Summary Files.

Eligibility criteria (figure 1) included (1) index AMI hospitalisation (primary or secondary inpatient International Classification of Diseases, Ninth Revision (ICD-9) code 410.x1[44]) between 1 January 2008 and 30 September 2013; (2) ≥66 years old; (3) ≥12 months pre-AMI continuous enrolment in Medicare Parts A, B and D; (4) discharged to home/self-care and survived ≥30 days with continuous enrolment; (5) no AMI hospitalisation, PCI, coronary artery bypass graft surgery (CABG) or prescription claim for $P2Y_{12}$ inhibitors in 12 months pre-AMI; (6) no recurrent AMI, ischaemic stroke or hospitalised bleed in 30 days post-AMI and (7) $P2Y_{12}$ inhibitor prescription claim between hospital admission date and within 30

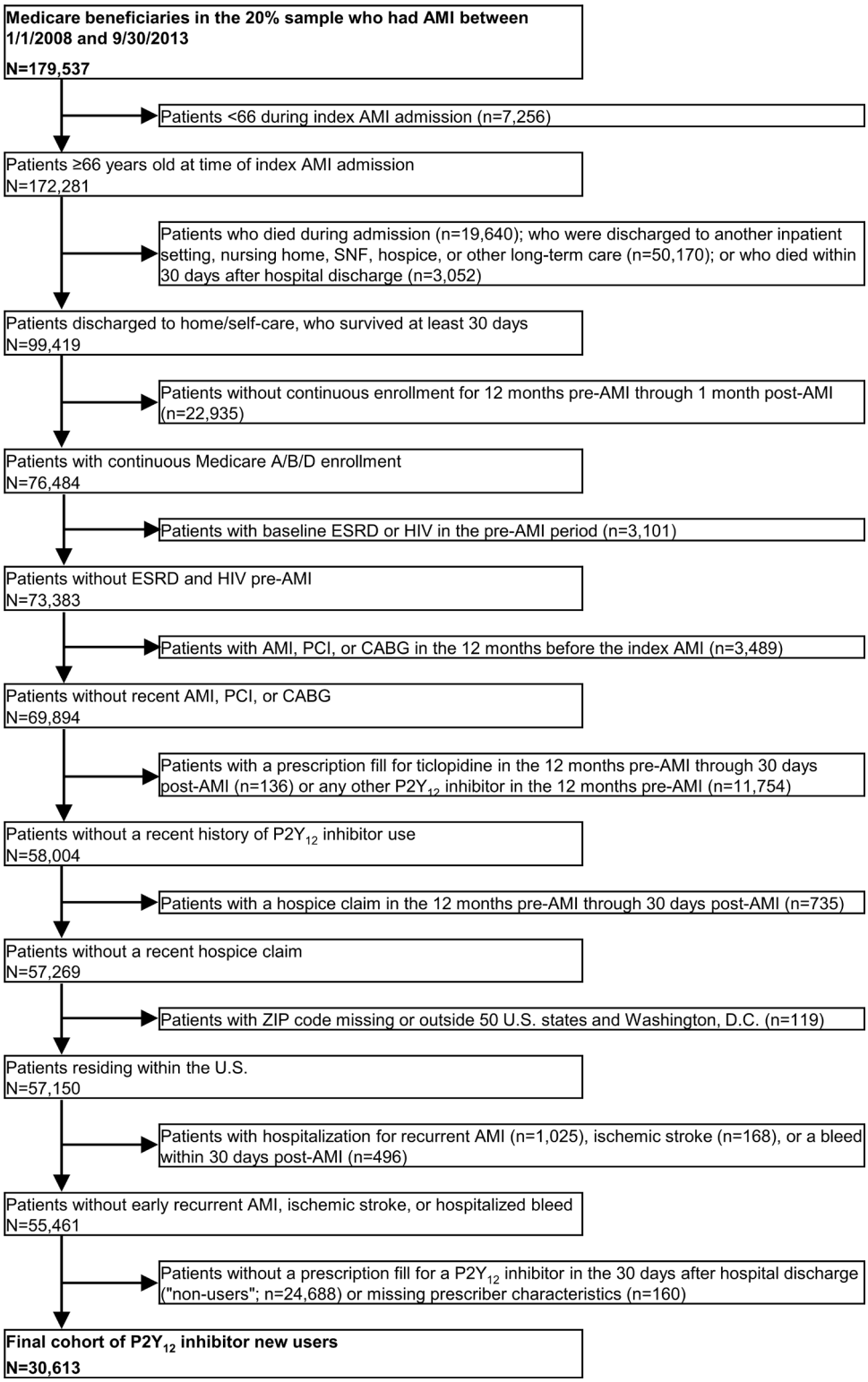


Figure 1 $P2Y_{12}$ inhibitor new user cohort eligibility. AMI, acute myocardial infarction; CABG, coronary artery bypass surgery; ESRD, end-stage renal disease; PCI, percutaneous coronary intervention; SNF, skilled nursing facility.

days postdischarge. Excluding patients in criterion (5)—previous indications for/use of $P2Y_{12}$ inhibitors—and including patients in criterion (7)—filling a $P2Y_{12}$ inhibitor—made this a 'new user' cohort.[45]

See online supplemental methods S1 for a detailed description and rationale for study eligibility criteria. While patients discharged to a nursing home or skilled nursing facility are an important and vulnerable population, their medications may be billed outside Part D plans[46]; our study was limited to home/self-care discharges where medication utilisation could be readily measured in Part D claims. Some exclusions were made

regarding important variables for the larger project associated with this cohort. There were 33/57 269 patients (<0.1%) excluded if ZIP code or neighbourhood measures needed to calculate contextual characteristics were missing, as well as 160/30 773 $P2Y_{12}$ inhibitor new users (0.5%) due to missing prescriber sex regarding $P2Y_{12}$ inhibitor prescription fills.

A retrospective cohort design was used (online supplemental figure S1). The 12 months pre-AMI were used to establish eligibility criteria and measure baseline comorbidities and healthcare utilisation. Concurrent medications were measured 6 months pre-AMI. The first month post-AMI discharge was used to identify $P2Y_{12}$ inhibitor new users and measure early post-AMI medications and follow-up with providers. Patients were followed until censored from loss of fee-for-service continuous enrolment, experiencing a study outcome or end of follow-up (720-day maximum).

Exposure

The exposure was patient sex, as reported in enrolment summary files. Male patients were the reference group.

Primary outcome

The primary outcome was $P2Y_{12}$ inhibitor therapy duration, defined as time to treatment discontinuation. In prescription claims data, no direct measure of treatment discontinuation exists. Using days supply reported in Part D prescription claims, $P2Y_{12}$ inhibitor therapy availability was measured during each day of follow-up, adjusting for oversupply and hospitalisations.[47 48] To differentiate therapy discontinuation from non-adherence in prescription claims data, the 'gap days' approach was used.[49] After 30 consecutive non-hospitalised days without therapy available, patients were assigned a therapy stop date of the last day of that 30-day drug-free interval. Inpatient days did not count towards the drug-free interval measurement; once patients were discharged, the counting of drug-free days resumed where it was before the hospitalisation began. Therapy duration was modelled as risk of treatment discontinuation.

Secondary outcomes

Secondary outcomes were clinical events that occurred while patients were still taking a $P2Y_{12}$ inhibitor. Clinical outcomes where prescribers would likely re-evaluate the ischaemic-benefit/bleeding-risk trade-off of $P2Y_{12}$ inhibitor therapy and make decisions to stop therapy earlier or continue therapy longer than originally planned were of interest. These outcomes included (1) death or hospice admission[50]; (2) a composite of ischaemic events (recurrent AMI, ischaemic stroke or coronary revascularisation procedures) and (3) hospitalised bleeding events. See online supplemental table S1 for details regarding these measures and their algorithms.

Covariates

Andersen's Behavioral Model of Health Services Use,[51] the Chronic Care Model,[52] and the Braveman conceptual framework on social determinants of health[53] were used to develop this study's research framework. Covariates of interest described below included patient, prescriber and contextual characteristics. For a full list of all covariates, see online supplemental table S2.

Patient characteristics

Based on Andersen's Behavioral Model,[51] patient characteristics were separated into (1) predisposing, (2) enabling, (3) patient-perceived need and (4) prescriber-perceived need characteristics.

Predisposing patient characteristics include individual sociodemographic characteristics such as age and race/ethnicity as well as individuals' health-seeking behaviours that are influenced by their attitudes, values and knowledge about health and health services. Specific measures included patient age (66–75, 76–85, 86+); race/ethnicity (white/non-Hispanic, black/non-Hispanic, Hispanic, Asian/non-Hispanic, other/non-Hispanic) and pre-AMI health-seeking behaviours (wellness visit and receipt of influenza or pneumococcal vaccine).

Enabling patient characteristics are personal resources that allow easier access to health services. These included dual Medicaid and Medicare eligibility and patient out-of-pocket cost for the first $P2Y_{12}$ inhibitor filled.

Patient-perceived need characteristics were split into factors associated with patients' pre-AMI understanding of their general health status, general experience during the index AMI admission which may indirectly influence understanding of their AMI severity and use of early post-discharge care recommended for nearly all post-AMI patients. These included pre-AMI healthcare utilisation (eg, primary care provider (PCP) visits and inpatient admissions); pre-AMI conditions (number of comorbidities measured by Charlson Comorbidity Index, depression, dementia/Alzheimer's disease); number of pre-AMI chronic medications; index AMI characteristics (length of stay and admission to intensive and/or coronary care unit); early post-AMI use of secondary prevention medications (statin, ACE inhibitor or ARB, beta-blocker) and early post-AMI follow-up with a PCP and/or cardiologist.

Prescriber-perceived need characteristics were related to prescribers' perceptions of patients' risk of future ischaemic and/or bleeding events based on clinically evaluated factors. These included pre-AMI conditions (eg, diabetes, heart failure, atrial fibrillation, history of bleeding); pre-AMI use of specific medications (eg, statin, ACE inhibitor/ARB, beta-blocker, anticoagulant and other medications with potential $P2Y_{12}$ inhibitor drug-drug interactions); index AMI hospitalisation characteristics (eg, index AMI intervention strategy (PCI with drug-eluting stent, PCI with bare-metal stent, PCI without mention of stent, CABG, medical management/fibrinolysis)); index AMI events (eg, bleeding event, acute kidney injury) and early post-AMI medication use (index $P2Y_{12}$ inhibitor (brand-name clopidogrel, generic clopidogrel, brand-name prasugrel, brand-name ticagrelor) and proton-pump inhibitor).

Prescriber characteristics

While claims data allow for easy identification of a medication's prescriber, no claims are submitted for discontinuing medications. To identify the prescriber most likely to make long-term decisions regarding secondary AMI prevention, a single prescriber was attributed to each patient who prescribed the greatest number of 30-day post-AMI cardiovascular medications.[54] This prescriber's sex, specialty (cardiologist vs PCP), and age were measured. Prescriber age was the only variable with missing values in the final cohort (1.3%) and was stochastically imputed.[55 56]

Contextual characteristics

Measured contextual characteristics included US Census Divisions to account for regional differences in post-AMI care patterns and outcomes,[57] residence within a metropolitan statistical area, neighbourhood segregation using location quotient (LQ) measures[58] and relative neighbourhood socioeconomic disadvantage using index of concentration at the extremes (ICE) measures.[59] See online supplemental equation S1 for additional details on LQ and ICE measures.

Statistical analysis

All analyses were conducted with SAS V.9.4 (SAS Institute). Distributions of characteristics were described in the full cohort and by patient sex. As described below, matching on disease risk scores was used to adjust for differences between men and women. Before and after matching, absolute standardised differences (ASDs) were calculated to assess differences in baseline characteristics between men and women (ASD ≥10% represent significant difference).[60 61] ASDs were estimated to help describe the balance of baseline characteristics between groups, but it is important to note that matching on DRSs balances groups on the risk of the outcome, NOT on the probability of exposure (like propensity scores). Therefore, we DID NOT expect all covariates to be well balanced between men and women after matching.

Disease risk score calculation and matching

DRS methodologies, like propensity scores, are used to adjust for confounding in observational studies.[62–64] Propensity scores predict the likelihood of receiving a given exposure (eg, treatment A vs B) based on measured covariates; patients in different exposure groups can then be matched or weighted using this propensity score, adjusting for confounding. DRSs are similar except they predict the likelihood of experiencing the outcome of interest. There are several ways to calculate DRSs and apply them to the final analysis to adjust for confounding.[62] The following paragraphs describe the DRS approach we used and includes references that guided our decisions when planning the analysis.

DRSs were used to match women to men with a similar likelihood of $P2Y_{12}$ inhibitor discontinuation, based on their baseline clinical ischaemic and bleeding risk factors as well as other patient, prescriber and contextual characteristics.[62 65] Using all covariates described above as well as patient sex, the likelihood of $P2Y_{12}$ inhibitor discontinuation was estimated in the full cohort using a subdistribution proportional hazards model (online supplemental equation S2).[63 66 67] A DRS was then calculated for each individual patient using log-hazard coefficients for all variables except patient sex (ie, all patients' DRSs calculated as though they belonged to male reference group; online supplemental equation S3).[63 65] However, rates of the secondary outcomes described above may differ between men and women, and these represent potentially valid clinical reasons to make a change to $P2Y_{12}$ inhibitor therapy (ie, continuing longer or stopping earlier than originally planned). Therefore, three additional DRSs were calculated for each of these secondary outcomes.[66] For each of these four subdistribution proportional hazards DRS models, all other outcome events were treated as competing risks.

Women were 1:1 nearest-neighbour matched to men on all four DRSs using Mahalanobis distance.[66 68] For a man and woman to be eligible for matching, all four DRSs had to fall within a calliper of 0.2 times the pooled standard deviation (ie, they had to have similar predicted risks of all four study outcomes).[64] After matching, ASDs were used to assess balance of all 4 DRSs between men and women.

Modelling outcome risk using Aalen-Johansen cumulative incidence curves

After matching men and women on the 4 DRSs, cause-specific risks for the outcomes of interest were estimated using the Aalen-Johansen estimator (online supplemental equation S4). Since $P2Y_{12}$ inhibitor treatment decisions would be re-evaluated when this study's secondary outcomes occurred, these clinical events were considered competing risks for the primary outcome of $P2Y_{12}$ inhibitor duration. Thus, we used the Aalen-Johansen estimator to appropriately model the risk of these events.[69] Instead of censoring competing risks, the Aalen-Johansen estimator takes into account the risks of all event types over time and does not inflate hazards like cause-specific proportional hazards models.[69] To avoid tied event times, a small amount of random noise between 0.0 and 0.1 days was attributed to all follow-up times.[69] Using Aalen-Johansen cumulative incidence curves, cause-specific risks—as well as risk differences (RDs) and relative risks (RRs) comparing women to men—were calculated at every 90-day interval for the primary outcome of $P2Y_{12}$ inhibitor discontinuation. Cause-specific risks, RDs and RRs were calculated at 360 and 720 days for secondary outcomes. Estimation of effect sizes—with CIs representing the precision and uncertainty of those estimates—was our approach for scientific inference from this analysis, not statistical significance testing.[70 71] Non-parametric 95% CIs were estimated with bootstrap resampling of matched-patient pairs with 2000 iterations.[69 72]

Sensitivity analyses

Two sets of sensitivity analyses were conducted. First, the 30-day drug-free interval to measure time to $P2Y_{12}$ inhibitor discontinuation was varied to shorter (15-day) and longer (45-day) intervals, as recommended when using prescription claims to measure medication discontinuation.[49] Second, analyses were stratified by index AMI discharge date: (1) patients discharged between 1 January 2008 and 30 June 2009 when only brand-name clopidogrel was available in the US market; (2) between 1 July 2009 and 30 June 2011 when only brand-name clopidogrel and prasugrel were available and (3) on/after 1 July 2011 once ticagrelor became available. Point estimates from sensitivity analyses that fell within 95% CIs from primary analyses were identified as consistent with primary findings.

Patient and public involvement

Neither patients nor the public were involved at any stage of this study.

RESULTS

Overall, 30 613 $P2Y_{12}$ inhibitor new users met study eligibility criteria (figure 1). The cohort was 51% female, 50% <76 years old, 88% white/non-Hispanic, 69% had their index AMI managed with PCI and coronary stents, and 90% filled clopidogrel as their index $P2Y_{12}$ inhibitor (table 1). This sample over-represents white/non-Hispanic and under-represents black/non-Hispanic and Hispanic individuals compared with the general 65+ US population; this sample is more similar compared with the 65+ Medicare population, but white/non-Hispanic and black/non-Hispanic beneficiaries are still slightly over-represented and under-represented, respectively.[41 42] Additionally, this population of $P2Y_{12}$ inhibitor new users that required no history of AMI or coronary revascularisation in the prior 12 months is younger and healthier compared with other post-AMI Medicare populations we have previously studied.[10 47 48 73]

Notable differences by patient sex within this study's sample included older age in women as compared with men, greater use of medications pre-AMI among women, lower likelihood of receiving post-AMI care from cardiologists among women, and greater likelihood of having the index AMI managed medically or with fibrinolytics among women (ASD >10% for all; table 1). See online supplemental table S2 for all patient characteristics.

When only death was considered a competing risk, median $P2Y_{12}$ inhibitor duration was 415 days (IQR 158–720); women were on therapy slightly longer than men in unadjusted analyses (online supplemental figure S2). When all event types were considered, the earliest event that occurred from most to least frequent was $P2Y_{12}$ inhibitor discontinuation (52%), coronary revascularisation (8%), recurrent AMI or ischaemic stroke (6%), death (3%), hospice admission (3%) and bleed (3%); 3% were censored from loss of fee-for-service enrolment, and 22% were administratively censored at 720 days.

In unadjusted Aalen-Johansen analyses (ie, before matching), the 720-day RD for $P2Y_{12}$ inhibitor discontinuation was −2.5% (95% CI −3.6 to −1.3) in women compared with men (online supplemental figure S3). The 360-day RD for ischaemic outcomes was −0.8% (95% CI −1.5 to −0.0) in women compared with men, but the magnitude of the 720-day RD was smaller (RD −0.6%; 95% CI −1.5 to 0.1; online supplemental figure S4). Women were more likely than men to experience death/hospice admission and bleeds, with 720-day RDs of +1.4% (95% CI 0.8 to 1.9) and +0.6% (95% CI 0.2 to 1.0), respectively.

Matching and overall Aalen-Johansen cumulative incidence

The four DRS distributions before matching can be seen in online supplemental figure S5. There were 10 486 women matched to 10 486 men. Because DRSs do not balance groups on the probability of exposure, some differences in baseline characteristics between men and women remained after matching, as expected (table 1 and online supplemental table S2), but all DRSs were well-balanced (all ASDs <10%; online supplemental table S3). Stacked Aalen-Johansen plots showing the cause-specific cumulative incidence curves for all event types are presented for men and women in figure 2A,B, respectively; each shaded region represents the cumulative incidence for that specific outcome, while the entire height of the stack is the composite cumulative incidence (ie, risk for experiencing any of the study outcomes). Among this matched sample, 24% of men and 25% of women were event-free at 720 days (ie, still taking a $P2Y_{12}$ inhibitor and had not yet experienced any of the secondary clinical outcomes). The cause-specific Aalen-Johansen cumulative incidence curves are evaluated individually for each outcome below, comparing female to male patients.

Primary outcome: $P2Y_{12}$ inhibitor discontinuation

After matching, the 90-day risk of $P2Y_{12}$ inhibitor discontinuation was ~10%–11% (figure 3), and women were potentially more likely to discontinue therapy compared with men (RD +0.7%; 95% CI −0.2 to 1.5; RR 1.07; 95% CI 0.98 to 1.15). There were no other differences in $P2Y_{12}$ inhibitor discontinuation in women compared with men through 540 days. During this period, the risk of $P2Y_{12}$ inhibitor therapy discontinuation increased from approximately a 31% 360-day risk to a 42% 450-day risk in both sexes. Between 540 and 720 days of follow-up, the cumulative incidence curves began to separate, with women being more likely than men to discontinue $P2Y_{12}$ inhibitor therapy (720-day RD +1.5%; 95% CI 0.1 to 2.8; 720-day RR 1.03; 95% CI 1.00 to 1.05).

Secondary outcomes: clinical events

After matching, the 360-day risk of death/hospice admission while taking a $P2Y_{12}$ inhibitor was between 3% and 4% in both men and women (figure 4A); the 720-day risk was ~5%–6%. Women were potentially less likely to

Table 1 Selected baseline characteristics in full cohort, by patient sex prematching, and by patient sex postmatching

Patient, prescriber and contextual characteristics	Prematch				Postmatch		
	Full cohort	Male	Female		Male	Female	
	N=30 613	n=14 943	n=15 670	ASD*	n=10 486	n=10 486	ASD*
	n (%)†	%†	%†	%	%†	%†	%
Predisposing patient characteristics							
Age							
66–75	15 297 (50.0)	58.6	41.7	34.3	56.3	46.1	20.6
76–85	11 154 (36.4)	32.4	40.3	16.5	34.6	40.5	12.1
86+	4162 (13.6)	9.0	18.0	26.4	9.1	13.5	14.0
Race/ethnicity							
White, non-Hispanic	27 033 (88.3)	89.8	86.9	9.3	90.4	88.0	7.7
Black, non-Hispanic	1837 (6.0)	4.6	7.3	11.6	4.6	6.7	9.2
Hispanic	730 (2.4)	2.1	2.7	4.0	2.0	2.5	3.0
Asian, non-Hispanic	644 (2.1)	2.2	2.0	1.2	1.8	1.9	0.9
Other	369 (1.2)	1.3	1.1	1.9	1.2	1.0	2.7
Enabling patient characteristics							
Dual Medicare/Medicaid eligibility‡	5578 (18.2)	14.2	22.1	20.7	14.4	19.1	12.5
Out-of-pocket index $P2Y_{12}$ inhibitor cost§							
US$0	1259 (4.1)	3.1	5.0	9.6	3.0	3.7	3.7
US$0.01–US$5.00	5926 (19.4)	15.8	22.8	17.8	16.4	21.0	11.9
US$5.01–US$10.00	5239 (17.1)	16.1	18.1	5.2	16.1	17.3	3.3
US$10.01–US$30.00	2407 (7.9)	8.3	7.5	3.0	8.5	7.4	4.0
US$30.01–US$90.00	12 412 (40.5)	44.3	36.9	15.2	44.7	39.8	9.9
>US$90.00	3370 (11.0)	12.3	9.8	8.2	11.3	10.8	1.8
Patient-perceived need							
Pre-AMI conditions¶							
Charlson Comorbidity Index							
0	11 365 (37.1)	39.1	35.3	7.8	37.8	41.0	6.6
1–2	12 358 (40.4)	38.4	42.2	7.7	40.6	42.2	3.1
3–4	4721 (15.4)	15.3	15.5	0.7	15.3	12.3	8.7
5–7	1678 (5.5)	5.5	5.4	0.3	4.9	3.7	6.4
8+	491 (1.6)	1.7	1.5	1.3	1.3	0.9	4.2
Depression	3417 (11.2)	7.6	14.5	22.0	7.6	12.9	17.4
Dementia/Alzheimer's**	1750 (5.7)	4.4	7.0	11.5	4.0	4.4	2.0
Pre-AMI medications††							
Chronic medications‡‡							
0	3493 (11.4)	14.8	8.2	20.6	13.5	9.9	11.4
1–3	10 112 (33.0)	36.5	29.7	14.5	35.9	34.1	3.9
4–6	9479 (31.0)	28.9	32.9	8.5	30.9	33.4	5.4
7–9	4889 (16.0)	13.4	18.4	13.7	13.8	15.6	5.3
10+	2640 (8.6)	6.4	10.8	15.8	5.9	7.1	4.7
Post-AMI secondary prevention medications§§							
Statin							
None	4416 (14.4)	14.0	14.8	2.1	12.9	13.0	0.4
Filled prescription	22 967 (75.0)	74.6	75.4	1.7	76.2	77.8	3.9
Remaining pre-AMI supply	3230 (10.6)	11.3	9.8	4.9	10.9	9.2	5.9

Continued

Table 1 Continued

Patient, prescriber and contextual characteristics	Prematch				Postmatch		
	Full cohort	Male	Female		Male	Female	
	N=30 613	n=14 943	n=15 670	ASD*	n=10 486	n=10 486	ASD*
	n (%)†	%†	%†	%	%†	%†	%
ACE inhibitor or ARB							
None	8002 (26.1)	27.6	24.8	6.3	26.0	24.5	3.5
Filled prescription	18 315 (59.8)	58.3	61.3	6.2	59.4	62.0	5.2
Remaining pre-AMI supply	4296 (14.0)	14.2	13.9	0.7	14.5	13.5	2.9
Beta-blocker							
None	3042 (9.9)	10.9	9.0	6.2	10.0	8.6	4.8
Filled prescription	24 992 (81.6)	80.5	82.7	5.7	81.3	83.3	5.1
Remaining pre-AMI supply	2579 (8.4)	8.6	8.3	1.3	8.6	8.1	2.0
Early post-AMI follow-up with providers§§							
None	2783 (9.1)	9.8	8.4	4.7	9.3	8.4	3.3
Primary care provider¶¶ only	7539 (24.6)	22.7	26.5	8.9	23.4	24.9	3.4
Cardiologist only	6937 (22.7)	25.5	20.0	13.1	23.8	22.0	4.3
Both	13 354 (43.6)	42.1	45.1	6.0	43.5	44.8	2.7
Prescriber-perceived need							
Pre-AMI conditions¶							
Diabetes	9942 (32.5)	31.6	33.3	3.6	31.8	30.0	3.8
Heart failure	3798 (12.4)	11.0	13.8	8.4	10.5	8.9	5.3
Coronary artery disease	9609 (31.4)	34.7	28.2	13.9	33.3	24.4	19.6
Cerebrovascular disease	1160 (3.8)	3.6	3.9	1.5	3.4	3.0	2.5
Peripheral vascular disease	3746 (12.2)	11.2	13.2	5.9	10.8	10.9	0.3
Cancer	3563 (11.6)	15.1	8.3	21.3	14.8	7.4	23.8
Previous venous thromboembolism	1982 (6.5)	6.3	6.7	1.8	5.9	5.7	1.0
Atrial fibrillation	2288 (7.5)	7.3	7.6	1.0	6.2	5.1	4.7
History of bleeding event	4649 (15.2)	16.0	14.4	4.5	15.3	12.4	8.6
Pre-AMI medications††							
Statin	13 021 (42.5)	43.3	41.8	2.9	43.7	39.9	7.6
ACE inhibitor or ARB	14 967 (48.9)	45.3	52.3	14.2	46.2	50.0	7.8
Beta-blocker	12 805 (41.8)	39.1	44.4	10.8	39.3	41.2	3.9
Anticoagulant	2267 (7.4)	7.6	7.2	1.8	6.4	5.1	5.7
Index AMI hospitalisation characteristics							
AMI intervention strategy***							
PCI with drug-eluting stent	14 554 (47.5)	50.0	45.2	9.5	53.7	47.9	11.5
PCI with bare-metal stent	6630 (21.7)	22.9	20.5	5.9	22.2	22.0	0.4
Other PCI	1862 (6.1)	7.0	5.3	7.1	7.0	5.7	5.1
Coronary artery bypass surgery	1001 (3.3)	4.4	2.2	12.6	1.7	1.7	0.3
Medical management or fibrinolytics	6566 (21.4)	15.8	26.9	27.4	15.4	22.6	18.3
Heart failure	8126 (26.5)	23.9	29.1	11.8	24.0	22.7	2.9
Bleeding event	1963 (6.4)	6.9	5.9	3.9	6.0	4.5	6.8
Acute kidney injury	3227 (10.5)	10.9	10.2	2.1	10.5	7.4	10.8
Post-AMI medications§§							
Index $P2Y_{12}$ inhibitor product							
Brand-name clopidogrel	22 182 (72.5)	70.7	74.1	7.6	72.8	74.3	3.3

Continued

Table 1 Continued

Patient, prescriber and contextual characteristics	Prematch				Postmatch		
	Full cohort	Male	Female		Male	Female	
	N=30 613	n=14 943	n=15 670	ASD*	n=10 486	n=10 486	ASD*
	n (%)†	%†	%†	%	%†	%†	%
Generic clopidogrel	6450 (21.1)	21.0	21.1	0.1	20.8	20.7	0.1
Brand-name prasugrel	1470 (4.8)	6.4	3.3	14.4	4.7	3.5	6.4
Brand-name ticagrelor	511 (1.7)	1.8	1.5	2.7	1.6	1.5	1.0
Proton pump inhibitor							
None	23 730 (77.5)	80.7	74.5	14.8	80.7	77.3	8.4
Omeprazole/esomeprazole	3756 (12.3)	10.2	14.2	12.3	10.2	12.7	7.8
Lansoprazole/dexlansoprazole	441 (1.4)	1.3	1.6	2.2	1.1	1.0	1.7
Pantoprazole/rabeprazole	2686 (8.8)	7.8	9.7	6.6	7.9	9.0	3.9
Prescriber managing post-AMI medications†††							
Male	23 601 (77.1)	78.5	75.7	6.6	78.6	75.6	7.2
Younger (born in/after 1975)	3651 (11.9)	12.0	11.9	0.3	12.2	11.6	1.7
Cardiologist	13 803 (45.1)	48.8	41.6	14.4	48.4	44.6	7.7

* ASD ≥10% considered significant difference between male and female patients.
†Column percentages.
‡Medicare beneficiaries dually enrolled with full Medicaid benefits at any point in 12 calendar months before through one calendar month after index AMI hospitalisation.
§Standardised to 30-day supply and adjusted for inflation to 2015 US$.
¶Measured 12 months pre-AMI admission date.
**Medicare Chronic Conditions Data Warehouse definition.
††Measured 6 months pre-AMI admission date.
‡‡≥2 prescription fills on separate dates for unique fourth-level ATC code.
§§Measured through 30 days post-AMI discharge date.
¶¶Primary care physician, physician assistant or nurse practitioner.
***Measured during index AMI hospitalisation; includes coronary revascularisation procedures through 30 days post-AMI discharge date.
†††Prescriber of most cardiovascular medications for patient during 30 days post-AMI.
AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; ASD, absolute standardised difference; ATC, Anatomical Therapeutic Chemical Classification System; PCI, percutaneous coronary intervention.;

experience death/hospice admission than comparable men (720-day RD −0.5%; 95% CI −1.0 to 0.1; 720-day RR 0.91; 95% CI 0.82 to 1.02).

Women were consistently less likely than men to experience the composite ischaemic outcome while taking a $P2Y_{12}$ inhibitor, with 360- and 720-day RDs of −1.4% (95% CI −2.2 to −0.5) and −1.5% (95% CI −2.4 to −0.6), respectively (figure 4B). The 360-day risk of this outcome was ~10%–12% (RR women compared with men 0.88; 95% CI 0.82 to 0.95), and the 720-day risk was ~13%–15% (RR 0.90; 95% CI 0.84 to 0.96).

The 360-day risk of hospitalised bleeds while taking a $P2Y_{12}$ inhibitor was ~2% (figure 4C); the 720-day risk only slightly increased to 2.5%. No differences were observed for bleeding risks in women compared with men (figure 4D).

Sensitivity analyses

As expected, when varying the drug-free interval from 30 days to 15-day and 45-day measures (ie, changing the definition of the time to treatment discontinuation measure), all absolute risk estimates for $P2Y_{12}$ inhibitor discontinuation were inconsistent with absolute risk estimates from primary analyses (online supplemental table S4). However, all RD and RR estimates were consistent and therefore did not impact our interpretation of RD and RR estimates from primary analyses. When evaluating secondary clinical outcomes, a few absolute risk estimates were inconsistent with results from the primary 30-day analyses, but all RD and RR estimates were again consistent with primary analyses (online supplemental table S5).

When analyses were stratified by the index AMI discharge date and sample sizes were greatly reduced, several risk estimates for $P2Y_{12}$ inhibitor discontinuation were inconsistent with primary analyses, but all RD and RR estimates from the most recent period (patients discharged after 1 July 2011) were consistent with primary analyses, increasing our confidence that study findings are relevant for current clinical practice (online supplemental table S6). Similarly, most estimates for secondary clinical outcomes from the most recent period were consistent with primary analysis findings (online supplemental table S7).

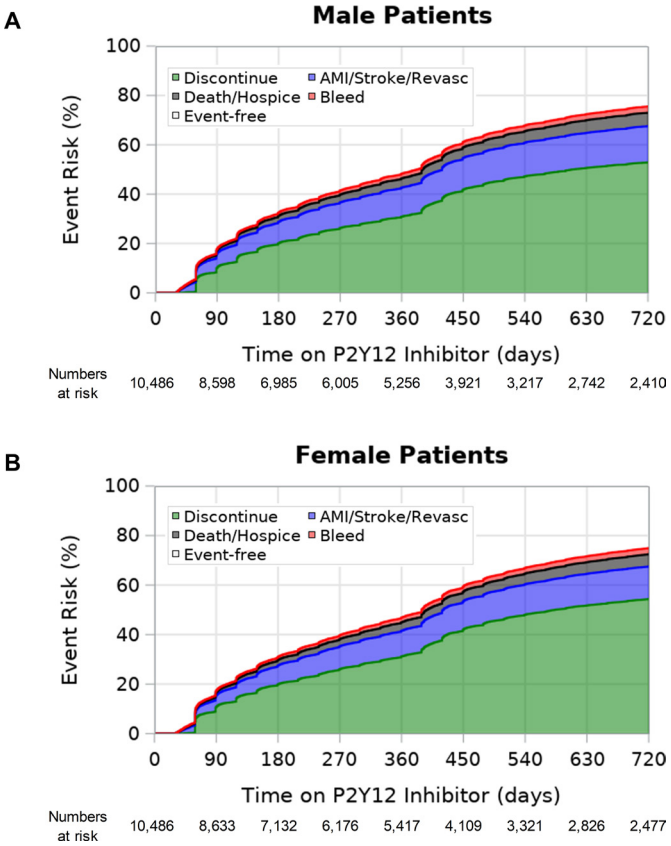


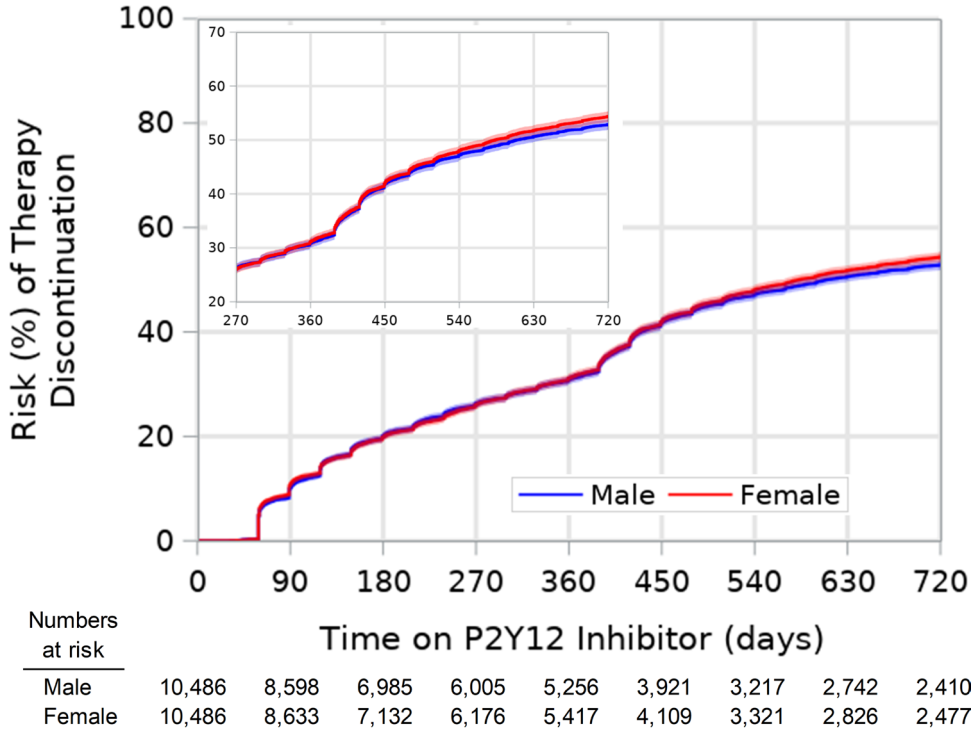
Figure 2 Stacked Aalen-Johansen cumulative incidence curves of $P2Y_{12}$ inhibitor discontinuation primary outcome and secondary clinical outcomes for (A) male patients and (B) female patients. Cumulative incidences from bottom to top are for (1) $P2Y_{12}$ inhibitor discontinuation, (2) composite ischaemic events, (3) death/hospice admission and (4) hospitalised bleed. AMI, acute myocardial infarctions; Revasc, revascularisation.

DISCUSSION

In this study of older adults hospitalised for AMI and then initiated on $P2Y_{12}$ inhibitor therapy, women were matched to men who had similar DRSs for four separate outcomes: (1) $P2Y_{12}$ inhibitor discontinuation, (2) death/hospice admission, (3) composite ischaemic outcomes and (4) hospitalised bleed. We observed several key findings. First, among women and men with comparable predicted risks for all four outcomes, there was no observed difference in the risk of $P2Y_{12}$ inhibitor discontinuation during the first 540 days (1.5 years) of follow-up, but by 720 days (2 years), cumulative incidence curves began to separate with women being 1.5% more likely (95% CI 0.1 to 2.8) to discontinue $P2Y_{12}$ inhibitor therapy than their matched male counterparts. Second, among patients who had not discontinued $P2Y_{12}$ inhibitor therapy, women had a lower 2-year risk than men of death/hospice admission and the composite ischaemic outcome (RR ~0.9 for both outcomes). Third, no difference in hospitalised bleeds was observed among matched women and men while taking a $P2Y_{12}$ inhibitor. Fourth, among matched women and men, more than 20% of patients had not experienced a clinical event and were still taking their $P2Y_{12}$ inhibitor at 2 years.

The pattern of antiplatelet discontinuation in our study was similar to that observed in the PARIS study,[21] with a sharp increase in discontinuation near the 1-year mark of follow-up. The PARIS study results suggested that physician-recommended discontinuation was more common in women than men at any point during 2 years of follow-up (HR 1.11; 95% CI 1.00 to 1.22), while we found (1) no difference in the risk of therapy discontinuation during the first 1.5 years of follow-up and (2) women were more likely than comparable men to discontinue therapy at 2 years (RR 1.03; 95% CI 1.00 to 1.05). Additionally, the clinical outcome findings were different between our study and PARIS. In women compared with men, the PARIS study observed no difference for the outcomes of major adverse cardiac events (HR 1.04; 95% CI 0.86 to 1.27) or death (HR 1.16; 95% CI 0.87 to 1.54),[21] while we found women were less likely than comparable men to experience the composite ischaemic outcome (2-year RR 0.90; 95% CI 0.84 to 0.96) and potentially death/hospice admission (2-year RR 0.91; 95% CI 0.82 to 1.02). The PARIS study also showed that women were more likely to experience bleeding (HR 1.39; 95% CI 1.02 to 1.89)[21]; no difference in the risk of hospitalised bleeds was observed between comparable women and men in our study (2-year RR 0.98; 95% CI 0.82 to 1.14).

The discrepancies between these two studies may be explained by a younger population who underwent PCI with stents—only 41% for acute coronary syndromes—in PARIS,[21] while our study included patients≥66 years old hospitalised for AMI—69% had PCI with stent(s)—with no recent indication for or use of $P2Y_{12}$ inhibitors. Additionally, some discrepancies are likely attributed to differences in measures, design and analyses. By restricting matching to comparable men and women with similar DRSs, we attempted to emulate an experimental setting where prescribers are randomised to make treatment decisions for simulated patient cases where the only difference between cases is patient sex.[30 31] PARIS had a specific physician-recommended discontinuation measure,[21] while we adjusted for baseline characteristics to address differential bias in adherence behaviours by sex and completed 15-day and 45-day sensitivity analyses to test our 30-day drug-free interval measure's robustness to differentiate medication discontinuation from non-adherence. The PARIS study also measured discontinuation of any DAPT component ($P2Y_{12}$ inhibitor or aspirin); 87% of all discontinuations were for $P2Y_{12}$ inhibitors.[74] Finally, since PARIS did not use an interaction term between sex and time, the HR for DAPT discontinuation is assumed to be constant during all of follow-up.[75] While this may be true, our results suggest that among comparable male and female Medicare beneficiaries, the relative rate of discontinuation begins to change after 1.5 years. Our use of the Aalen-Johansen estimator avoids this assumption and allows for estimating time-specific



Numbers at risk									
Male	10,486	8,598	6,985	6,005	5,256	3,921	3,217	2,742	2,410
Female	10,486	8,633	7,132	6,176	5,417	4,109	3,321	2,826	2,477

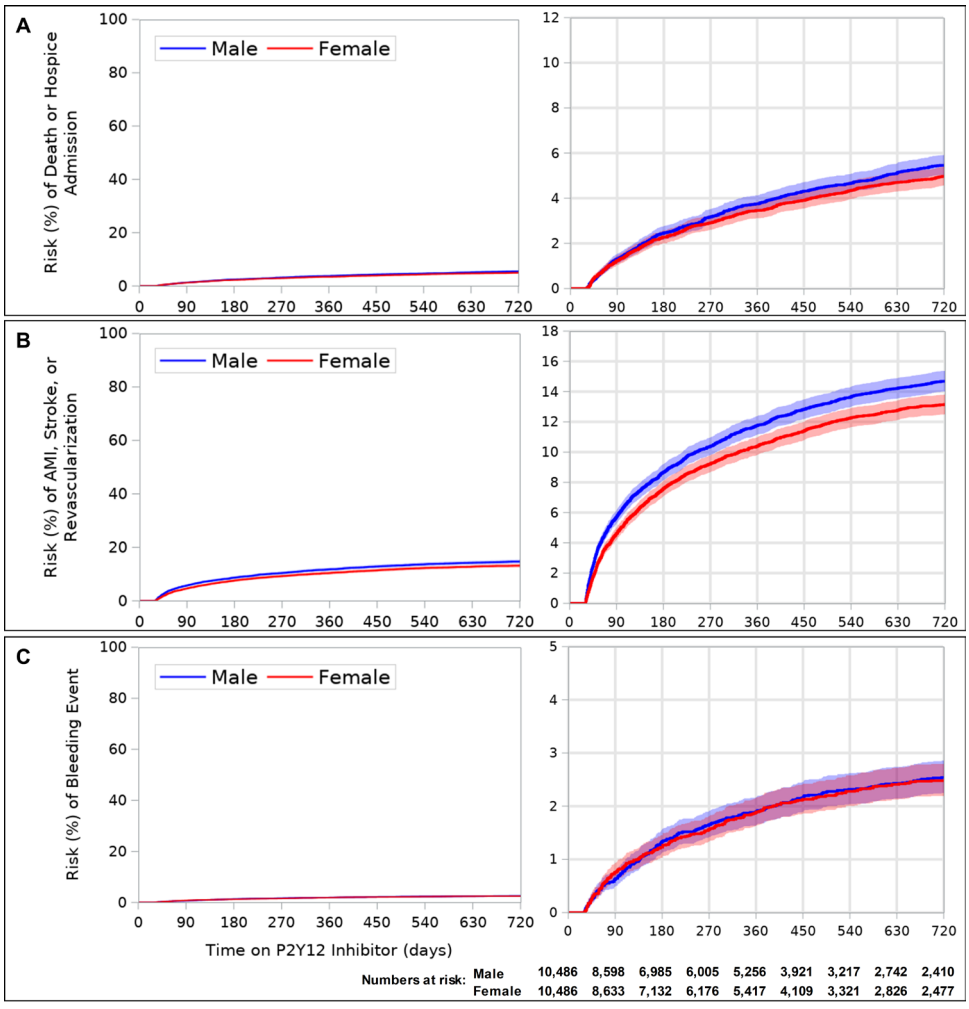
		Risk %	RD %	RR
90 days	Male	10.2 (9.7, 10.8)	0.	1.
	Female	10.9 (10.3, 11.5)	0.7 (-0.2, 1.5)	1.07 (0.98, 1.15)
180 days	Male	20.1 (19.4, 20.9)	0.	1.
	Female	19.9 (19.1, 20.7)	-0.2 (-1.3, 0.8)	0.99 (0.94, 1.04)
270 days	Male	26.3 (25.5, 27.1)	0.	1.
	Female	26.0 (25.2, 26.9)	-0.3 (-1.4, 0.9)	0.99 (0.95, 1.04)
360 days	Male	30.9 (30.0, 31.8)	0.	1.
	Female	31.2 (30.3, 32.1)	0.3 (-0.9, 1.5)	1.01 (0.97, 1.05)
450 days	Male	41.9 (40.9, 42.9)	0.	1.
	Female	42.1 (41.1, 43.1)	0.2 (-1.2, 1.6)	1.00 (0.97, 1.04)
540 days	Male	47.2 (46.2, 48.2)	0.	1.
	Female	48.1 (47.1, 49.0)	0.9 (-0.5, 2.2)	1.02 (0.99, 1.05)
630 days	Male	50.6 (49.7, 51.6)	0.	1.
	Female	51.8 (50.8, 52.8)	1.2 (-0.2, 2.5)	1.02 (1.00, 1.05)
720 days	Male	52.9 (52.0, 53.9)	0.	1.
	Female	54.4 (53.4, 55.3)	1.5 (0.1, 2.8)	1.03 (1.00, 1.05)

Each estimate followed by 95% CIs in parentheses. Abbreviations: CI, confidence interval; RD, risk difference; RR, relative risk

Figure 3 Aalen-Johansen cause-specific cumulative incidence of $P2Y_{12}$ inhibitor discontinuation with 95% confidence bands and risk, RD and RR estimates by patient sex. These cumulative incidence curves share the same denominator of numbers at risk with other study outcomes as part of the Aalen-Johansen estimator presented in figure 2.

RDs and RRs, which are easier to interpret and avoid other issues of HRs.[69 75]

When patients experience clinical events like recurrent AMIs or hospitalised bleeds while taking a $P2Y_{12}$ inhibitor, the ischaemic benefits and/or bleeding risks attributable to continuing therapy are often evident. However, clinicians wishing to prevent these negative outcomes must make difficult decisions about stopping or continuing $P2Y_{12}$ inhibitor therapy, and the most beneficial choice is often not clear. We found that when older women and men have characteristics suggesting similar predicted risks of experiencing this study's outcomes, there was no evidence that $P2Y_{12}$ inhibitor therapy should be stopped earlier in women. We also found that women received a similar or even greater benefit from continuing therapy regarding ischaemic and death/hospice outcomes. Therefore, women in this population should be given similar (or even greater) consideration for continuing $P2Y_{12}$ inhibitor therapy than clinically comparable men during the first 2 years of post-AMI follow-up. These findings suggest that—in most cases—women being more likely to discontinue $P2Y_{12}$ inhibitor therapy than comparable men between 1.5 and 2 years post-AMI may not be justifiable by clinical differences and may represent disparities in care by sex. Since these differences just began emerging after 1.5–2 years post-AMI, future research should evaluate



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			Risk %	RD %	RR
Death or Hospice Admission	360 days	Male	3.7 (3.4, 4.1)	0.	1.
		Female	3.5 (3.1, 3.8)	-0.3 (-0.8, 0.2)	0.92 (0.81, 1.06)
	720 days	Male	5.5 (5.0, 5.9)	0.	1.
		Female	5.0 (4.6, 5.4)	-0.5 (-1.0, 0.1)	0.91 (0.82, 1.02)
AMI, Stroke, or Revasc.	360 days	Male	11.8 (11.1, 12.4)	0.	1.
		Female	10.4 (9.8, 11.0)	-1.4 (-2.2, -0.5)	0.88 (0.82, 0.95)
	720 days	Male	14.7 (14.0, 15.3)	0.	1.
		Female	13.1 (12.5, 13.8)	-1.5 (-2.4, -0.6)	0.90 (0.84, 0.96)
Bleeding Event	360 days	Male	1.9 (1.6, 2.2)	0.	1.
		Female	1.9 (1.6, 2.1)	0.0 (-0.4, 0.4)	1.00 (0.82, 1.20)
	720 days	Male	2.5 (2.2, 2.8)	0.	1.
		Female	2.5 (2.2, 2.8)	-0.1 (-0.5, 0.3)	0.98 (0.82, 1.14)

Each estimate followed by 95% CIs in parentheses. Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; RD, risk difference; Revasc, revascularization; RR, relative risk

Figure 4 Aalen-Johansen cause-specific cumulative incidences for secondary clinical outcomes while taking a $P2Y_{12}$ inhibitor by patient sex. Cumulative incidence with 95% confidence bands for the secondary outcome of death or hospice admission (A), composite ischaemic events (B) and hospitalised bleed (C). Estimates of risk, RD and RR for all secondary clinical outcomes can be found in (D). All figures on the left are presented with the full 0%–100% risk scale, but please note, each corresponding magnified figure on the right has a different risk scale. All curves share the same denominator of numbers at risk as part of the Aalen-Johansen estimator presented in figure 2.

if these differences increase more over time and if any differences after longer follow-up are justified by clinical differences between women and men. Finally, it is important to note that these findings should not be used to make general recommendations for therapy duration; instead, they suggest that $P2Y_{12}$ inhibitor therapy should not be stopped earlier simply because a patient is a woman. Research is underway using dynamic marginal structural models to directly evaluate the clinical effectiveness and safety of different $P2Y_{12}$ inhibitor durations in older women and older men.

Limitations

The limitation of greatest concern was misclassification of treatment discontinuation as non-adherence and vice versa, which is unavoidable when using drug-free intervals

to measure treatment discontinuation in prescriptions claims. However, our comparative RD and RR estimates were robust to varying the drug-free interval, lessening concerns regarding this limitation. Additionally, adherence-related approaches in claims data may overestimate—if patients are not actually taking medication—or underestimate—if medications are received outside of prescription plans—time to treatment discontinuation. However, claims measures correlate with other adherence measures and outcomes, and medication fills outside prescription plans are less common in Medicare than other US claims data.[47]

Second, our goal was to attribute treatment discontinuation to prescriber recommendations. We accounted for outcome rates of death/hospice admission, ischaemic events, and hospitalised bleeds. However, regarding patient behaviours, we only adjusted for baseline healthy-user/sick-stopper factors to address differential bias between men and women; specific measures of reasons for discontinuation would be ideal[21 74] and would improve the accuracy of absolute risk estimates for treatment discontinuation.

Third, DRS and propensity score analyses share similar limitations, including residual confounding from unmeasured variables being possible. Additionally, we initially matched on DRSs for six outcomes (discontinuation, death, hospice, AMI/stroke, revascularisation, bleeding); however, matching six DRSs within callipers made the final sample too small, so some outcomes were combined.

Finally, our findings may not be generalisable to patients <66 years old, nursing home residents or healthcare settings outside the USA. Also, our study did not include patients who experienced a clinical outcome (death/hospice, AMI/stroke/revascularisation and bleeding) in the 30-day postindex AMI period.

Conclusions

Among new users of $P2Y_{12}$ inhibitors in Medicare, older women were more likely to discontinue therapy than clinically comparable men between 1.5 and 2 years post-AMI. However, our analysis found that the risks for death/hospice admission and composite ischaemic outcomes were lower among women than clinically comparable men among patients who had not discontinued $P2Y_{12}$ inhibitor therapy, with no observed differences in bleeding risks. Thus, our findings suggest that shorter $P2Y_{12}$ inhibitor durations received by older women than comparable older men may reflect a disparity that is not justified by differences in clinical need.

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Contributors RPH: study conception, design, data acquisition, analysis and interpretation; manuscript drafting; critical review of study content; approval of the final manuscript; overall content guarantor. AMK-N: study conception, design and interpretation; critical review of study content; approval of the final manuscript. JER: study conception, design, and interpretation; critical review of study content; approval of the final manuscript. BLS: study conception, design and interpretation; critical review of study content; approval of the final manuscript. GF: study conception, design and interpretation; critical review of study content; approval of the final manuscript.

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