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Fewer gastrointestinal bleeds with ticagrelor and prasugrel compared with clopidogrel in patients with acute coronary syndrome following percutaneous coronary intervention

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Summary

Background: Gastrointestinal bleeding (GIB) frequently occurs following percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) with the prescription of $P2Y_{12}$ inhibiting antiplatelet agents. Compared with clopidogrel, the newer $P2Y_{12}$ inhibitors lower major adverse cardiac events with similar or possibly higher major bleeding events. The comparative GIB rates of these medications remains poorly understood.

Aims: To compare GIB rates associated with clopidogrel, prasugrel and ticagrelor using national medical and pharmacy claims data from privately insured and Medicare Advantage enrollees.

Methods: Propensity score and inverse probability treatment weighting were used to balance baseline characteristics among treatment groups. The 1-year GIB risk was calculated using weighted Cox proportional hazard models and expressed as hazard ratios (HR) with 95% confidence intervals (CI) and number needed to harm (NNH).

Results: We identified 37 019 patients with ACS (non-ST elevation ACS [NSTE-ACS] and ST-elevation myocardial infarction [STEMI]) within 14 days of a PCI (mean age 63 years and 70% male). Clopidogrel prescription was most common (69%) with prasugrel (16%) and ticagrelor (14%) prescribed less frequently. When compared with clopidogrel, ticagrelor was associated with a 34% risk reduction (HR 0.66; 95% CI: 0.54–0.81) in GIB overall and with NSTE-ACS, and a 37% GIB risk reduction (HR 0.63; 95% CI: 0.42–0.93) in STEMI patients. When compared with clopidogrel, prasugrel was associated with a 21% risk reduction (HR 0.79; 95% CI: 0.64–0.97) overall, a 36% GIB risk reduction (HR 0.64; 95% CI: 0.49–0.85) in STEMI patients but no reduction of GIB risk in NSTE-ACS patients.

Conclusions: In the first year following PCI, ticagrelor or prasugrel are associated with fewer GIB events compared with clopidogrel.

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1 | INTRODUCTION

Following percutaneous coronary intervention (PCI), adjunctive platelet inhibition with a second-generation (ie clopidogrel) or newer (ie prasugrel, ticagrelor) thienopyridine agents is recommended for a minimum of 12 months in patients presenting with acute coronary syndromes (ACS).[1] This intense antiplatelet activity increases the risk of procedure and nonprocedure-related major bleeding complications. Compared to clopidogrel, the newer P2Y$_{12}$ inhibitors lower major adverse cardiac events in patients undergoing PCI for ACS with similar or possibly higher major bleeding events.[2] Post-PCI bleeding is a serious event associated with increased morbidity and mortality.[3]

Gastrointestinal bleeding (GIB) is a frequent adverse event in the first year following PCI often necessitating temporary interruption of the antiplatelet regimen during identification and treatment of the bleeding source.[4] Systematic reviews of randomised clinical trials have suggested higher bleeding rates with the newer P2Y$_{12}$ inhibitors compared to clopidogrel.[2] However, the comparative bleeding rates of these medications in real-world populations are poorly understood. This gap in the literature is noteworthy as there has been gradual uptake of these newer agents. More than one-third of patients receive these newer agents after PCI.[5,6]

We have previously demonstrated the average 1-year GIB risk following initiation of P2Y$_{12}$ inhibitors in routine clinical practice is 4.2% and increases to >8% for those over the age of 75.[4] However, it remains unclear if the risk of GIB differs among the three P2Y$_{12}$ inhibitors. We aimed to compare the safety of clopidogrel, prasugrel and ticagrelor by quantifying the GIB risk in patients with ACS following PCI, using a real-world population.

2 | METHODS

2.1 | Data source

We used medical, and pharmacy claims data from the OptumLabs Data Warehouse. A national data source that includes physician, hospital and prescription drug claims of >100 million privately insured and Medicare Advantage enrolees across the United States.[7,8] Medical claims include International Classification of Diseases Clinical Modification (ICD-9-CM & ICD-10-CM) diagnosis codes, ICD-9 & ICD-10 procedure codes, Current Procedural Terminology, Version 4 (CPT-4) procedure codes, Healthcare Common Procedure Coding System procedure codes, site of service codes and provider specialty codes. This study was exempt from Institutional Review Board approval as it involved analysis of pre-existing, de-identified data.

2.2 | Study population

We identified patients 18 years of age or older with an index prescription of clopidogrel, prasugrel or ticagrelor between 01/01/10

and 07/31/18. The date of the first prescription fill was defined as the index date and used to stratify patients to their exposure group. We required at least 12 months of health plan enrollment before the index date and excluded patients with evidence of a dispensed prescription in the 12 months before the index date to ensure a new-user cohort. We excluded patients with a cancer diagnosis at risk of malignancy-associated GIB and missing gender data. All patients were required to have a diagnosis of ACS within 90 days of index date and evidence of a recent PCI, within 14 days of index prescription (Appendix 1).

2.3 | Patient characteristics

Baseline demographic characteristics (age, gender) and CHA2DS2-VASC score (hypertension, age, diabetes mellitus, congestive heart failure, stroke/transient ischaemic attack/thromboembolic event). Concomitantly prescribed medications, including prescription acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors, anticoagulants and gastroprotective agents, were assessed as potential confounding variables. Administrative codes identified co-morbid conditions in the primary or secondary position on any claim during the baseline period, and overall comorbidity burden determined using the Charlson-Deyo index.

2.4 | Study outcomes

The primary outcome of interest was total GIB using administrative codes as previously described and validated in prior publications[7-9] (Appendix 1), with each event identified using inpatient hospital claims for relevant primary and secondary discharge diagnoses. Total GIB included upper (including small intestinal) and lower GIB. Drug exposure was considered continuous from the index prescription until GIB or censoring occurred due to end of enrollment (including mortality), switch to another treatment strategy or treatment termination as defined by the absence of prescription supply for 30 days following the last identified prescription fill date for the index medication. Secondary outcomes included GIB-related transfusions and hospital length of stay.

2.5 | Statistical analysis

Propensity score and inverse probability treatment weighting (IPTW) were used to balance the differences in baseline characteristics (Appendix 2) among three treatment groups (clopidogrel, prasugrel and ticagrelor). The propensity score was estimated using generalised boosted modeling, which uses an iterative estimation procedure to find a model with the best balance among treatment groups.[10] This method is particularly suited to comparing more than two treatment groups and has been used in

numerous previous studies.[11-13] The propensity score model included the baseline characteristics listed in Appendix 2. Weights were calculated independently for the overall, non-ST elevated ACS (NSTE-ACS) and ST-elevated myocardial infarction (STEMI) groups. Baseline characteristics are displayed after the inverse probability treatment weighting. Standardised differences are calculated to assess the balance of covariates, with a difference of <10% considered acceptable[14]; whereas covariates that exceed the 10% threshold treated as independent variables in subsequent survival models.

The outcome of interest was calculated using Weighted Cox Proportional Hazards models with a robust variance estimator, stratified by ACS event type (STEMI or NSTE-ACS). Schoenfeld residuals[15] was used to test the proportional hazards assumption. We calculated the event rates per 100 person-years and hazard ratios (HR) with 95% confidence interval (CI) in the overall cohort, and the STEMI and NSTE-ACS subgroups. The number needed to harm (NNH) is used to express the magnitude of risk reduction for each comparison. In addition, we calculated the event rates of GIB-related inpatient transfusions. We examined three independent outcomes (chronic obstructive pulmonary disease, pneumonia and fracture) as falsification tests to assess for residual confounding. We used a Sidak correction to adjust for multiple comparisons.[16] These falsification endpoints[17] could be associated with patient frailty but are unlikely to be related to the choice of antiplatelet agent. Finally, we conducted a sensitivity analysis excluding patients prescribed ASA, NSAIDS and anticoagulants to assess the influence of these important GIB-related covariates on the estimates. The analytic data set was created and manipulated using SAS 9.3 (SAS Institute Inc) and Stata 15.1 (Stata Corp).

3 | RESULTS

3.1 | Patient characteristics

Between 01/01/2010 and 7/31/2018, we identified 80 355 patients with ACS and an index prescription, of whom 51 190 underwent PCI within 14 days of index prescription. Of these patients, it was possible to classify 37 019 as STEMI or NSTE-ACS using the claims data source (Figure 1). The baseline characteristics of the cohort after IPTW are shown in Table 1. Examination of the standardised differences reveals patients were well-balanced after weighting was applied.

The mean age and gender of the overall cohort were 63 years and ~70% male. Approximately 20% of our population was 75 years or older. Cardiac co-morbidity was significant, with the majority of patients having of CHA2DS2VASC score of 2 or higher. Approximately a third of the cohort each had a HAS-BLED score of 0-2, 3 or greater than 4, respectively (Table 1). Other chronic cardiac and noncardiac comorbidities, pharmacological risk modifiers (including concomitant anticoagulant and ASA prescription), NSAIDs and history of GIB (18%) were well-balanced among the three exposure groups.

3.2 | Outcomes

Figure 2 outlines the overall GIB outcomes by treatment group (per-protocol analysis) and when stratified by STEMI vs NSTE-ACS. We highlight the magnitude of risk reduction with the absolute risk reduction (ARR) and the NNH for each drug comparison in Figure 2.

3.2.1 | Clopidogrel compared with prasugrel

Throughout observation, 5.1% (95% CI: 4.8%-5.3%) of patients in the clopidogrel group experienced a GIB compared to 4.1% (95% CI: 3.3%-5%) in the prasugrel group overall suggesting a 21% reduction in GIB risk when prasugrel is compared with clopidogrel (HR 0.79; 95% CI 0.64-0.97). Similar rates between the two agents are observed in the NSTE-ACS group (Figure 2). However, in the STEMI subgroup prasugrel was associated with a 36% reduction in GIB risk when compared with clopidogrel (HR 0.64; 95% CI: 0.49-0.85).

3.2.2 | Clopidogrel compared with ticagrelor

Ticagrelor patients experienced fewer GIB events overall and in both ACS subgroups. As few as 62 patients overall would need to be prescribed clopidogrel, as opposed to ticagrelor, to cause an additional GIB (Figure 2). When compared with clopidogrel, ticagrelor was associated with 34% fewer events overall (HR 0.66, 95% 0.54-0.81) and 37% fewer GIB in the STEMI subgroup (HR 0.63, 95% CI: 0.42-0.93) (Figure 2). In the NSTE-ACS subgroup, ticagrelor was again associated with 34% fewer GIB when compared with clopidogrel (HR 0.66, 95% CI: 0.52-0.83).

3.2.3 | Prasugrel compared with ticagrelor

Similar GIB rates between the two agents are observed overall and in the STEMI and NSTE-ACS groups (Figure 2).

The breakdown of GI bleed subtype (total, upper and lower GIB) is shown in Table 2 demonstrating more frequent upper GIB vs lower GIB among all exposures (P < 0.0001). The associated GIB-related inpatient transfusion rates are shown in Table 3. The lowest transfusion burden was associated with ticagrelor (0.42; 95% CI: 0.26, 0.73), corresponding to a 41% reduction in overall transfusion burden when compared with clopidogrel. There was no significant difference in the transfusion burden associated with prasugrel when compared with clopidogrel.

Once admitted with their GIB, all three agents had similar inpatient lengths of stay (clopidogrel 6.5 days [SD 8.9], prasugrel 5.2 days [SD 4.3] and ticagrelor 6.5 days [SD 6.0]; P = 0.46). The median duration of exposure to each agent (stratified by age and gender), as shown in Table 4, reveals patients spend fewer days on ticagrelor then clopidogrel or prasugrel post-PCI. Older adults (>75 years) spent the fewest days on ticagrelor, regardless of the type of ACS event.
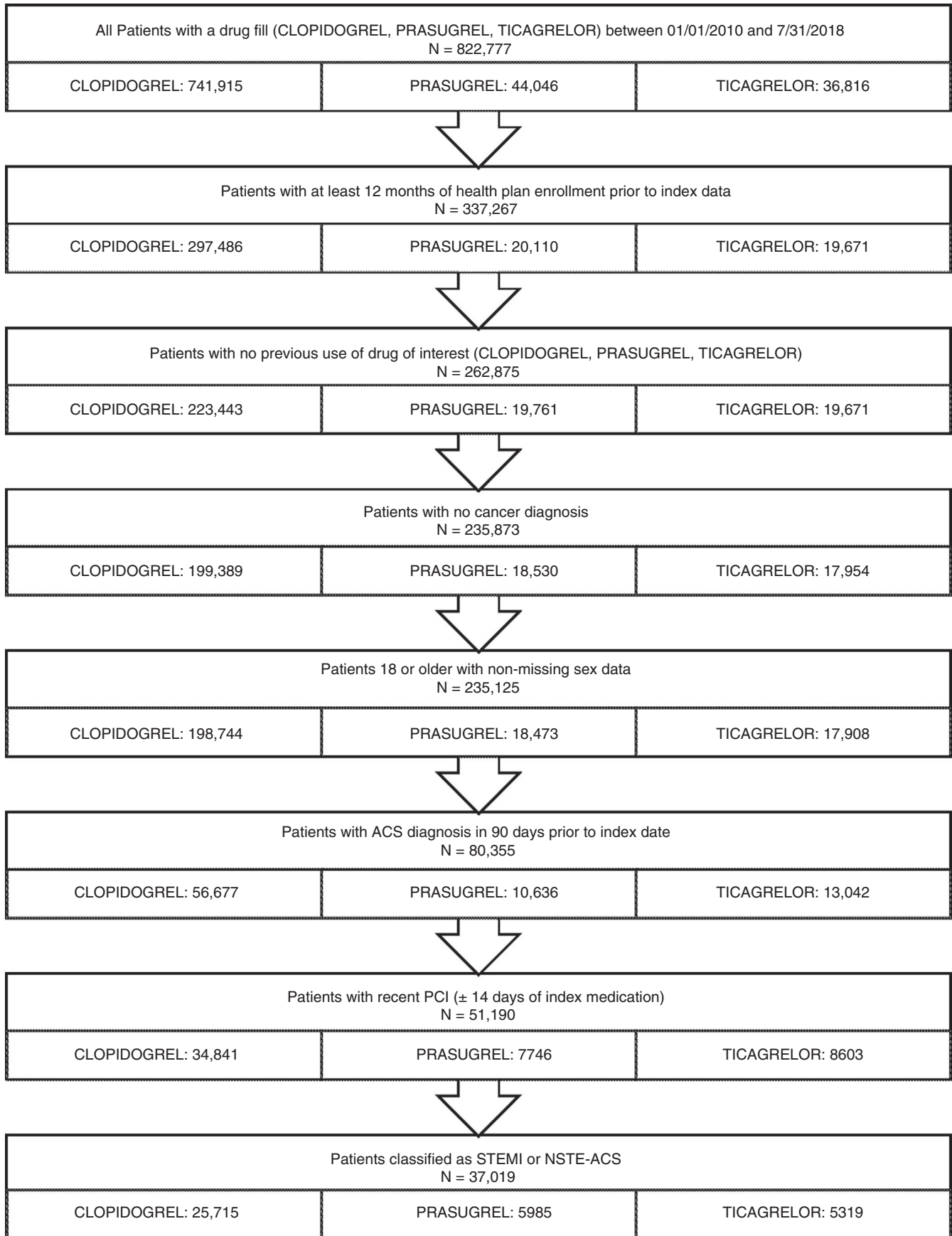
FIGURE 1 Study flow diagram

TABLE 1 Baseline characteristics after inverse probability treatment weighting

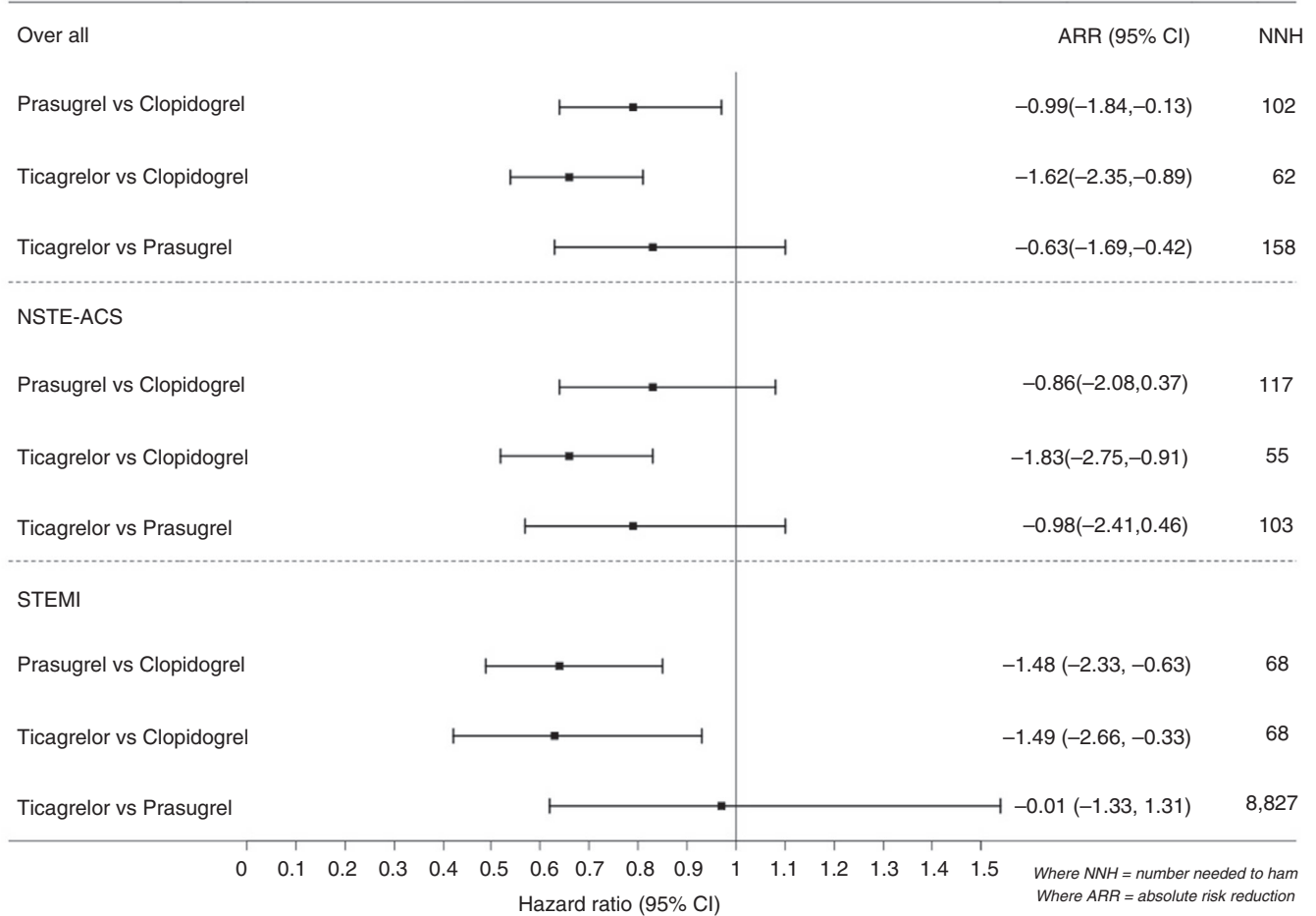| Characteristic	Clopidogrel (N = 25 552)	Prasugrel (N = 5609)	Ticagrelor (N = 4907)	Standardized differences		
				Clopidogrel vs prasugrel	Clopidogrel vs ticagrelor	Prasugrel vs ticagrelor
Age, y, Mean (SD)	63.4 (11.9)	62.9 (11.4)	63.4 (11.3)	0.047	0.003	0.045
Male	17 720 (69.3)	3965 (70.7)	3452 (70.3)	0.029	0.022	0.006
White	18 063 (70.7)	3963 (70.7)	3456 (70.4)	0.001	0.006	0.004
STEMI	16 555 (64.8)	3575 (63.7)	3240 (66)	0.022	0.026	0.039
NSTE-ACS	8997 (35.2)	2034 (36.3)	1667 (34)	0.022	0.026	0.039
CHA2DS2VASC 0-1	1850 (7.2)	435 (7.8)	311 (6.3)	0.020	0.036	0.045
CHA2DS2VASC 2-3	11 506 (45)	2586 (46.1)	2233 (45.5)	0.022	0.010	0.010
CHA2DS2VASC 4+	12 196 (47.7)	2588 (46.1)	2363 (48.2)	0.032	0.009	0.033
Charlson-Deyo score 0-1	8370 (32.8)	1901 (33.9)	1591 (32.4)	0.024	0.007	0.025
Charlson-Deyo score 2-3	10 436 (40.8)	2318 (41.3)	1994 (40.6)	0.010	0.004	0.011
Charlson-Deyo score 4+	6746 (26.4)	1390 (24.8)	1322 (26.9)	0.037	0.012	0.040
Coronary artery bypass graft surgery (CABG)	2163 (8.5)	429 (7.7)	380 (7.7)	0.030	0.027	0.003
History of GIB	4790 (18.7)	1065 (19)	909 (18.5)	0.006	0.006	0.009
Hypertension	21 729 (85)	4731 (84.3)	4201 (85.6)	0.019	0.016	0.029
Smoking	13 049 (51.1)	2873 (51.2)	2492 (50.8)	0.003	0.006	0.007
ASA (Aspirin)	1856 (7.3)	405 (7.2)	384 (7.8)	0.002	0.022	0.019
Gastroprotective agents	6038 (23.6)	1324 (23.6)	1165 (23.7)	0.000	0.003	0.003
Nonsteroidal anti-inflammatory drugs (NSAIDs)	4397 (17.2)	987 (17.6)	859 (17.5)	0.010	0.008	0.002
Selective serotonin reuptake inhibitors (SSRI)	2223 (8.7)	476 (8.5)	455 (9.3)	0.008	0.020	0.023
Warfarin	1197 (4.7)	232 (4.1)	211 (4.3)	0.026	0.018	0.007
Dabigatran	91 (0.4)	12 (0.2)	11 (0.2)	0.028	0.030	0.002
Apixaban	264 (1)	42 (0.7)	51 (1)	0.031	0.001	0.027
Rivaroxaban	234 (0.9)	43 (0.8)	37 (0.7)	0.017	0.019	0.002

3.3 | Sensitivity analysis

The sensitivity analysis to assess unmeasured confounders between pharmacological exposure and GIB using falsification endpoints suggested the potential for significance with ticagrelor and fracture. However, after using the Sidak correction for multiple comparisons ($P = 0.006$), no statistically significant relationship exists between exposure and the falsification endpoints (data not shown). There were no significant differences in the risk of pneumonia, fracture or COPD between each of the comparison groups. We also completed a sensitivity analysis excluding patients prescribed NSAIDs, aspirin and other anticoagulants to ascertain if the magnitude and direction of risk estimates would change. There was no significant difference in the exposure and outcome relationships after the exclusion of patients with concomitant pharmacological risk factors for GIB (Appendix 3).

4 | DISCUSSION

In this study of 37 019 real-world ACS patients who underwent PCI, we demonstrate fewer GIB events in patients treated with ticagrelor, when compared with clopidogrel in all subgroups (overall, NSTE-ACS and STEMI). Prasugrel was also associated with fewer GIB events overall and in the STEMI group, but not in the NSTE-ACS group. There was no observed difference in GIB events with ticagrelor vs prasugrel in all three subgroups (Figure 2). With all three antiplatelet agents, upper GIB was more frequent than lower GIB. The clinical severity of

		ARR (95% CI)	NNH
Over all			
Prasugrel vs Clopidogrel		−0.99(−1.84,−0.13)	102
Ticagrelor vs Clopidogrel		−1.62(−2.35,−0.89)	62
Ticagrelor vs Prasugrel		−0.63(−1.69,−0.42)	158
NSTE-ACS			
Prasugrel vs Clopidogrel		−0.86(−2.08,0.37)	117
Ticagrelor vs Clopidogrel		−1.83(−2.75,−0.91)	55
Ticagrelor vs Prasugrel		−0.98(−2.41,0.46)	103
STEMI			
Prasugrel vs Clopidogrel		−1.48 (−2.33, −0.63)	68
Ticagrelor vs Clopidogrel		−1.49 (−2.66, −0.33)	68
Ticagrelor vs Prasugrel		−0.01 (−1.33, 1.31)	8,827

Hazard ratio (95% CI)

Where NNH = number needed to ham
Where ARR = absolute risk reduction

FIGURE 2 Comparative risk of GIB of prasugrel, clopidogrel and ticagrelor overall and in the ACS subgroups of NSTE-ACS and STEMI: expressed as absolute risk reduction (ARR) and the number needed to harm (NNH)

TABLE 2 GIB subtype per exposure group -after inverse probability treatment weighting

Treatment	No GIB	Lower GIB	Upper GIB	Total	P value*
Clopidogrel	23 054.4 (90.3%)	640.7 (2.5%)	1846.9 (7.2%)	25 542.0 (71%)	<0.0001
Prasugrel	5023.2 (90.7%)	131.4 (2.4%)	381.3 (6.9%)	5535.9 (15.4%)	
Ticagrelor	4571.7 (93.1%)	90.8 (1.9%)	247.4 (5%)	4909.9 (13.6%)	
Total	32 649.3 (90.7%)	863.0 (2.4%)	2475.6 (6.9%)	35 987.8 (100%)	

Abbreviation: GIB, gastrointestinal bleed.
*Weighted chi-square test.

TABLE 3 Number of GIB-related transfusions per exposure group

Treatment	N	Events	Person years	Event rate (95% CI)	HR (95% CI) vs clopidogrel
Clopidogrel	25 552	169	254.2	0.67 (0.57, 0.78)	ref
Prasugrel	5609	41	51.7	0.79 (0.47, 1.42)	1.14 (0.67, 1.94)
Ticagrelor	4907	18	43.8	0.42 (0.26, 0.73)	0.59 (0.35, 1.00)

Abbreviations: CI, confidence interval; HR, hazard ratio (95% CI).

the bleeding event is demonstrated by inpatient admissions that exceeded 5 days regardless of exposure. The latter is not surprising given the significant co-morbidity burden of ACS patients. Interestingly, ticagrelor was associated with fewer transfusions when compared to clopidogrel, but no statistical significant difference was observed in transfusion rates between clopidogrel and prasugrel.

TABLE 4 Duration of antiplatelet exposure

	Age	Gender	Clopidogrel			Prasugrel			Ticagrelor		
			N	Mean (SD)	Median (Q1, Q3)	N	Mean (SD)	Median (Q1, Q3)	N	Mean (SD)	Median (Q1, Q3)
Overall	<75	Female	5147	398.2 (405.4)	312 (126, 496)	1201	265.4 (257.5)	210 (61, 380)	1155	210.7 (211.1)	163 (43, 323)
		Male	13 790	403.4 (405.4)	319 (120, 510)	4436	303.2 (296.5)	250 (85, 401)	3039	239.3 (205.3)	200 (73, 355)
	75+	Female	2929	392.3 (391.8)	312 (116, 497)	105	270.5 (280.6)	205 (86, 351)	482	191.4 (182.6)	120 (30, 320)
		Male	3218	364.6 (376.2)	276 (102, 457)	168	249.4 (273.7)	186 (33.5, 353)	546	190.3 (179.6)	142.5 (30, 303)
NSTE-ACS	<75	Female	3450	375.7 (362.2)	302 (128, 478)	723	260.2 (240.8)	218 (62, 377)	944	203.3 (193.8)	163 (45, 303)
		Male	8187	368.5 (367.2)	293 (113, 468)	2302	293.5 (270)	250.5 (87, 394)	2336	229.9 (188.1)	196 (76.5, 346)
	75+	Female	2118	365.5 (357.6)	290 (117, 459)	68	290.9 (283.8)	213.5 (96.5, 376.5)	383	196.2 (181.8)	138 (30, 326)
		Male	2400	349.8 (334.2)	277 (114, 448.5)	103	206.2 (181.3)	180 (30, 303)	426	190.2 (176.1)	150.5 (30, 301)
STEMI	<75	Female	1697	444.1 (478.3)	334 (120, 551)	478	273.3 (280.9)	190 (58, 388)	211	243.5 (273.6)	171 (30, 359)
		Male	5603	454.4 (450.7)	354 (135, 587)	2134	313.7 (322.5)	250 (83, 413)	703	270.4 (251.8)	225 (65, 377)
	75+	Female	811	462.4 (462.4)	352 (112, 610)	37	233.1 (274.6)	111 (78, 289)	99	173 (185.8)	94 (30, 272)
		Male	818	408.2 (476.4)	273.5 (90, 500)	65	317.9 (367.8)	191 (45, 412)	120	190.8 (192.2)	131.5 (30, 303.5)

Data from prior randomised clinical trials of ticagrelor and prasugrel vs clopidogrel have shown variable GIB risks in the post-ACS population. Ticagrelor is associated with a nonsignificant trend towards increased GIB when compared with clopidogrel (relative risk [RR] 1.23; 95% CI: 0.93-1.64) in the Platelet Inhibition and Patient Outcome Trial (PLATO).[18] Prasugrel had a significantly higher risk of GIB (RR 1.31; 95% CI: 1.07-1.61) compared to clopidogrel in the Trial to Assess Improvement with Prasugrel-Thrombolysis in Myocardial Infarction 38 Trial (TRITON-TIMI 38).[19] A meta-analysis of all randomised controlled trials of ticagrelor and prasugrel (including trials for peripheral artery disease and medical management of ACS) demonstrated no significant increase in the risk of GIB with ticagrelor and an increased risk of GIB with prasugrel (RR = 1.28; 95% CI: 1.13-1.46).[20] However, the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial[21] comparing prasugrel to ticagrelor showed a similar rate of major bleeding for patients treated with prasugrel compared to ticagrelor; but the use of a lower dose of prasugrel (5 mg vs 10 mg) in patients over the age of 75 or those weighing less than 60 kg likely contributed to the observed bleeding rates.[21]

Prior real-world studies have investigated the overall risk of bleeding with ticagrelor or prasugrel compared to clopidogrel but fail to clarify the risk of GIB. In a large study of 45 073 Swedish patients with ACS, an increased risk for readmission with bleeding is seen with ticagrelor when compared to clopidogrel (5.5% vs 5.2% HR 1.2 [1.04-1.40].[5] A Swiss registry of 7621 ACS patients showed that prasugrel was associated with an increased risk of bleeding compared to clopidogrel (4.1% vs. 2.8%, P = 0.024).[6] However, neither of these studies described the rates of GIB.

Our study provides real-world evidence to specifically investigate the risk of GIB in ACS patients following PCI and treatment with P2Y12 inhibitors. These data are complementary to the efficacy data obtained from RCTs and provides valuable outcomes in an unselected patient population (patients of all ages and with concomitant prescription of NSAIDs, ASA or anticoagulants) that would normally be excluded from an RCT. Ticagrelor was associated with a lower risk of GIB compared to clopidogrel and prasugrel was associated with lower rates of GIB in the STEMI subgroup.

Data from a large retrospective multicentre observational study of 19 913 ACS patients in the US between 2010 and 2013[22] may explain our observation of fewer adverse events associated with prasugrel (when compared with clopidogrel) in the STEMI population. In this large study, STEMI patients were more likely to receive prasugrel (vs clopidogrel) at discharge when compared to NSTE-ACS patients. The observed attenuated cardiac adverse events with prasugrel (when compared with clopidogrel) were attributed to preferential use of prasugrel in lower-risk patients.[22] A large French observational study further highlighted the narrow prescribing window recommended for a prasugrel prescription (younger, higher body mass index and less frequent stroke history).[23] In this latter study, the baseline characteristics differed between STEMI patients prescribed prasugrel vs clopidogrel, and this preferential prescription to 'lower risk patients' was likely the factor contributing to fewer cardiac adverse events.[23]

Before adjustment, STEMI patients prescribed prasugrel had fewer co-morbidities and were younger when compared with clopidogrel patients (data not shown). However, after the IPTW, baseline characteristics were equally distributed among exposure groups. It is possible that despite adjustment residual unknown confounding related to clinical heuristic may have contributed to this finding.

Taken together our results are compelling because, despite significant reductions in major adverse cardiac events in ACS patients undergoing PCI, many clinicians remain reticent to use ticagrelor due to concerns for increased risk of bleeding.[5,6] Our data suggest that limiting ticagrelor due to concerns of GIB may be unnecessary.

4.1 | Strengths and weaknesses

One must interpret our study within the framework of its observational study design. First, the associations between antiplatelet drug

exposure and the outcome of interest may not be causal. Second, with the observational study design, there exists the potential for unmeasured confounders. However, our sensitivity analysis of falsification endpoints suggests no unmeasured confounders related to patient frailty or co-morbidity that could modify GIB risk. Third, the measurement of ASA exposure is limited to prescription drug claims and does not include potential over-the-counter (OTC) ASA use. Thus, measured ASA use in this population is likely under-representative of actual ASA use as part of dual antiplatelet therapy. However, we know from published registry data[24,25] that ASA use exceeds 95%-98% in patients in the first year following coronary reperfusion therapy, consistent with published cardiac guidelines.[1] Since we ascertained GIB outcomes within the first year of index prescription we assume that most (if not all) of our patients are exposed to dual antiplatelet therapy (with concomitant prescribed or OTC ASA) and have no reason to believe there exists a differential miss-classification bias of ASA exposure in our cohort that could influence the outcome of interest.

Despite these limitations, this study has important strengths worth considering. Our finding of a reduction in GIB adverse events associated with ticagrelor prescription is novel. Our ability to ascertain outcomes in a large, geographically diverse, national cohort of patients of different backgrounds provides clinically relevant data for physicians as they choose between the three $P2Y_{12}$ inhibitors following coronary reperfusion therapy. Finally, these data help to clarify the risk reduction associated with the prescription of ticagrelor that has previously been difficult to ascertain in a real-world population.

4.2 | Implications for healthcare professionals and patients

In RCTs, ticagrelor and prasugrel use in ACS patients undergoing PCI reduce major adverse cardiac events compared to clopidogrel. However, concerns for increased bleeding have resulted in limited use of ticagrelor and prasugrel.[5,6] GIB is the most common cause of bleeding in post-PCI patients treated with DAPT. The results of the current study show that in a real-world population of ACS patients treated with PCI, ticagrelor appears to have a reduced rate of GIB compared to clopidogrel in both STEMI and NSTE-ACS patients. Prasugrel was found to have lower rates of GIB compared to clopidogrel in the select subgroup of STEMI patients.

5 | CONCLUSIONS

We clarify the comparative GIB risk associated with three $P2Y_{12}$ inhibitors in a national cohort of ACS patients following coronary reperfusion therapy in routine practice. Prescription of ticagrelor is associated with up to a 37% reduction of GIB within the first year following index prescription when compared to clopidogrel in all patients undergoing PCI for ACS. Prasugrel is associated with a 36% reduction in GIB among STEMI patients.

AUTHORSHIP

Guarantor of the article: Dr Abraham.

Authors' contributions: Dr Abraham involved in study concept, design and supervision of the article. Drs. Shah, Abraham, Herrin; Mr Inselman and Ms Sangaralingham involved in acquisition and analysis of data. Dr Herrin and Mr Inselman had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis. Drs. Abraham, Yang, Shah, Yao, Noseworthy, Herrin, Ngufor; Mr Inselman and Ms Sangaralingham performed interpretation of data. Drs. Abraham, Yang and Noseworthy carried out drafting of the manuscript. All authors gave critical revision of the manuscript for relevant intellectual content. Dr Herrin, Mr Inselman and Ms Sangaralingham also performed statistical analysis of the article. All authors have reviewed the final version of the manuscript, including the authorship list.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.