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ORIGINAL RESEARCH

Impact of Society Guidelines on Trends in Use of Newer $P2Y_{12}$ Inhibitors for Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention

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BACKGROUND: Over the past decade, major society guidelines have recommended the use of newer $P2Y_{12}$ inhibitors over clopidogrel for those undergoing percutaneous coronary intervention for acute coronary syndrome. It is unclear what impact these recommendations had on clinical practice.

METHODS AND RESULTS: All percutaneous coronary intervention procedures (n=534 210) for acute coronary syndrome in England and Wales (April 1, 2010, to March 31, 2022) were retrospectively analyzed, stratified by choice of preprocedural $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, and prasugrel). Multivariable logistic regression models were used to examine odds ratios of receipt of ticagrelor and prasugrel (versus clopidogrel) over time, and predictors of their receipt. Overall, there was a significant increase in receipt of newer $P2Y_{12}$ inhibitors from 2010 to 2020 (2022 versus 2010: ticagrelor odds ratio, 8.12 [95% CI, 7.67–8.60]; prasugrel odds ratio, 6.14 [95% CI, 5.53–6.81]), more so in ST-segment–elevation myocardial infarction than non–ST-segment–elevation acute coronary syndrome indication. The most significant increase in odds of receipt of prasugrel was observed between 2020 and 2022 ($P<0.001$), following a decline/plateau in its use in earlier years (2011–2019). In contrast, the odds of receipt of ticagrelor significantly increased in earlier years (2012–2017, $P_{trend}<0.001$), after which the trend was stable ($P_{trend}=0.093$).

CONCLUSIONS: Over a 13-year-period, there has been a significant increase in use of newer $P2Y_{12}$ inhibitors, although uptake of prasugrel use remained significantly lower than ticagrelor. Earlier society guidelines (pre-2017) were associated with the highest rates of ticagrelor use for non–ST-segment–elevation acute coronary syndrome and ST-segment–elevation myocardial infarction cases while the ISAR-REACT 5 (Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndrome) trial and later society guidelines were associated with higher prasugrel use, mainly for ST-segment–elevation myocardial infarction indication.

Key Words: acute coronary syndrome ■ newer $P2Y_{12}$ inhibitors ■ outcomes ■ percutaneous coronary intervention ■ trends

Dual antiplatelet therapy, including aspirin and an oral $P2Y_{12}$ inhibitor, is an integral part of management of acute coronary syndromes (ACSs). Numerous randomized controlled trials over the past 2 decades have demonstrated a significant reduction in rates of reinfarction and stent thrombosis with dual antiplatelet therapy use after percutaneous coronary intervention (PCI).[1–4] Large randomized trials, including PLATO (A Comparison of Ticagrelor [AZD6140] and Clopidogrel in Patients With Acute Coronary Syndrome)

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CLINICAL PERSPECTIVE

What Is New?

- Major society guidelines from the United States and Europe had a significant yet time-limited impact on uptake of ticagrelor and prasugrel use for patients with acute coronary syndrome undergoing percutaneous coronary intervention in England and Wales (8- and 6-fold, respectively) over a 13-year period.
- Earlier guidelines (pre-2017) were associated with an increased use of ticagrelor, while later guidelines (2017 onward) and the ISAR-REACT 5 (Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndrome) trial led to higher use of prasugrel.
- Despite the increased use of both ticagrelor and prasugrel over a 13-year horizon, prasugrel use remained significantly low compared with ticagrelor as of 2022.

What Are the Clinical Implications?

- National society working groups for quality standards, including clinicians and stakeholders, should systematically delineate and address factors behind suboptimal prescription rates for newer $P2Y_{12}$ inhibitors among patients with acute coronary syndrome undergoing percutaneous coronary intervention.

Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
AHA	American Heart Association
BCIS	British Cardiovascular Intervention Society
ESC	European Society of Cardiology
ISAR-REACT 5	Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndrome
NSTE-ACS	non–ST-segment–elevation acute coronary syndrome
PLATO	A Comparison of Ticagrelor (AZD6140) and Clopidogrel in Patients With Acute Coronary Syndrome
SCAI	Society for Cardiovascular Angiography and Interventions
TRITON-TIMI 38	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction

and TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction), have shown that newer $P2Y_{12}$ inhibitors, including ticagrelor and prasugrel, are superior to clopidogrel in terms their reduction of reinfarction, stent thrombosis and restenosis events, albeit with a cost in terms of increased bleeding.[2,3] Consequently, major international guidelines including the European Society of Cardiology (ESC), American Heart Association (AHA), American College of Cardiology (ACC), and Society of Cardiovascular Angiography and Interventions (SCAI) have recommended their use over clopidogrel in patients with ACS undergoing PCI, including ST-segment–elevation myocardial infarction (STEMI) and non–ST-segment–elevation ACS (NSTE-ACS).[5–7] However, it is unclear what impact major guidelines have had on trends in the adoption of newer $P2Y_{12}$ inhibitors, particularly given the obvious differences between populations recruited into the randomized trials according to strict inclusion/exclusion criteria and patients in the real world.

The present study sought to examine national trends and predictors of use of newer $P2Y_{12}$ inhibitors among patients with ACS undergoing PCI, from the BCIS (British Cardiovascular Intervention Society) registry, over a 13-year period commensurate with publication of relevant major trials and society guideline recommendations from Europe and the United States.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Source, Study Design, and Population

All PCI procedures for patients with ACS between April 1, 2010, and March 31, 2022, in England and Wales were retrospectively analyzed from the BCIS registry, stratified by preprocedural $P2Y_{12}$ inhibitor use into 3 groups: clopidogrel, ticagrelor, and prasugrel.

The BCIS registry comprises clinical and procedural data, and in-hospital outcomes (death, bleeding, arterial complications) for all procedures undertaken in England and Wales.[8] Exclusion criteria included age <18 years, missing data for antiplatelets, exclusions for newer $P2Y_{12}$ inhibitor use (previous stroke/transient ischemic attack for prasugrel and recent thrombolysis or concomitant warfarin use for both prasugrel and ticagrelor). This represented 5.3% (n=30 314) of the data set. Institutional review board approval was not required for this study, as it does not apply to the use of routinely collected national pseudoanonymized registry data for audit purposes.

Outcome

The primary outcome was receipt of newer $P2Y_{12}$ inhibitors (versus clopidogrel), stratified by clinical syndrome (STEMI versus NSTE-ACS).

Statistical Analysis

All statistical analyses were performed using Stata 16 MP (StataCorp, College Station, TX). Patient and procedural characteristics were compared between antiplatelet groups. Continuous variables that were normally distributed were presented as mean values with SD, while those that were not, we presented as medians with 25th and 75th centiles. For comparing these variables between 2 groups, we used *t* tests for the former, Mann–Whitney tests for the latter, and where there were ≥3 groups, we used ANOVA test. Categorical variables are summarized as percentages and compared between groups using χ^2 tests. Multivariable logistic regression modeling was performed to quantify the odds of receipt of newer $P2Y_{12}$ inhibitors (ticagrelor and prasugrel) versus clopidogrel, using 2010 as the reference year, stratified by clinical syndrome. Further modeling was undertaken to identify predictors of receipt of newer $P2Y_{12}$ inhibitors (versus clopidogrel). All associations are reported as odds ratios (ORs) with corresponding 95% CIs. We also performed segment regression modeling, analyzing the data as a time series (in weeks) using the xtbreak command in Stata, which implements multiple tests for structural breaks in the trend of use of ticagrelor and prasugrel (versus clopidogrel) over the study period,[9] which was compared with the observed trends in adjusted odds of receipt of either agent.

All models were adjusted for the following variables, which were selected a priori: age, sex, race or ethnicity (White as reference, South Asian, Black, and Other), clinical syndrome (STEMI versus non–ST-segment–elevation myocardial infarction), stent thrombosis indication, previous myocardial infarction, previous PCI, previous coronary artery bypass graft surgery, diabetes, renal failure (creatinine >200 μmoL/L and/or dialysis), cardiac transplant, left ventricular function category (good [ejection fraction, <50%], moderate [ejection fraction, 30%–49%], poor [ejection fraction <30%]), hypercholesterolemia, peripheral vascular disease, hypertension, smoking, out-of-hospital cardiac arrest, mechanical ventilation, circulatory support (intra-aortic balloon pump or left ventricular assist device), vascular access (radial versus femoral), number of stents, number of vessels and lesions attempted, calcium modification (rotablation, laser angioplasty), and vessel attempted (left main, proximal left anterior descending, and grafts).

Multiple imputation with chained equations was performed for variables with missingness before model fitting, with a total of 10 imputations. Combined estimates, using Rubin's rules, were then used for analyses.[10]

RESULTS

A total of 534 210 patients with a diagnosis of ACS undergoing PCI between April 1, 2010, and March 31, 2022, were included. Overall, clopidogrel was the most prescribed $P2Y_{12}$ inhibitor (n=282 768, 52.9%), followed by ticagrelor (n=213 012, 39.9%) and prasugrel (n=38 430, 7.2%). This pattern was consistent in the NSTE-ACS subgroup (clopidogrel: 204, 285, 62.1%; ticagrelor: 118961, 36.2%; prasugrel: 5542, 1.7%). However, within the STEMI group, ticagrelor was the most prescribed agent (n=94 051, 45.8%), followed by clopidogrel (n=78 483, 38.2%) and prasugrel (n=32 888, 16.0%) (Figure 1). Several differences in baseline characteristics were observed between patients in receipt of newer $P2Y_{12}$ inhibitors and clopidogrel, as follows.

Predictors of Receipt of Newer $P2Y_{12}$ Inhibitors

Overall, patients in receipt of newer $P2Y_{12}$ inhibitors were younger and more likely to present with STEMI or stent thrombosis indication, and less likely to have a history of previous myocardial infarction, PCI or coronary artery bypass graft, renal failure, peripheral vascular disease, and hypertension, compared with those in receipt of clopidogrel (Table 1).

In multivariable regression analysis, certain patient and procedural characteristics correlated with receipt of newer $P2Y_{12}$ inhibitors (versus clopidogrel) (Table 2). Specifically, older age was a negative predictor of receipt of newer $P2Y_{12}$ inhibitors, while there was no difference in receipt of newer $P2Y_{12}$ inhibitors between sexes. All non-White races and ethnicities were more likely to receive ticagrelor compared with White patients, while South Asian patients were the only ethnicity more likely to receive prasugrel (OR, 1.27 [95% CI, 1.21–1.34]).

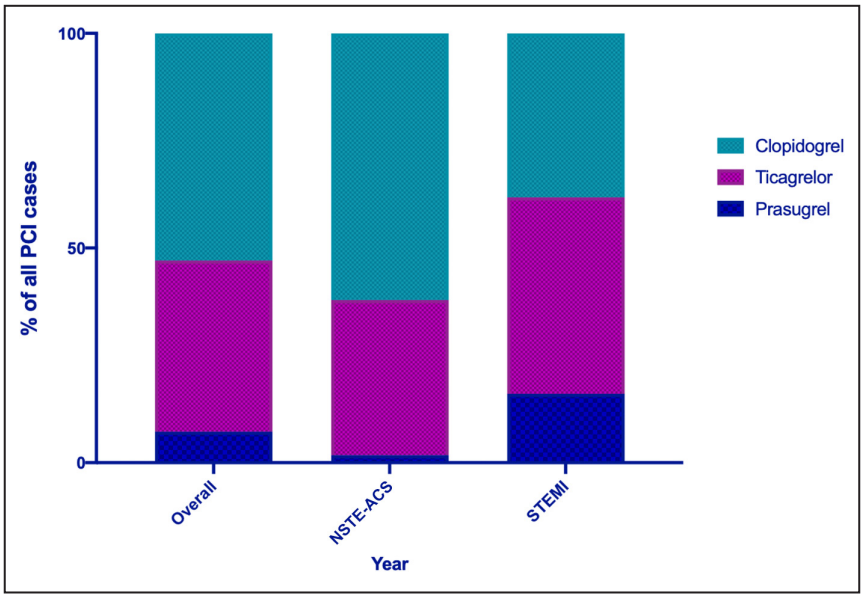

Figure 1. Overall rates of $P2Y_{12}$ inhibitor use.
NSTE-ACS indicates non–ST-segment–elevation acute coronary syndrome; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

STEMI presentation was a significant positive predictor of receipt of newer $P2Y_{12}$ inhibitors, more so with prasugrel (OR, 15.04 [95% CI, 14.55–15.56]) than ticagrelor (OR, 1.99 [95% CI, 1.96–2.02]). Stent thrombosis and previous PCI was associated with increased odds of receipt of ticagrelor and prasugrel, respectively. Previous coronary artery bypass graft, renal failure, and peripheral vascular disease were all associated with reduced odds of receipt of newer $P2Y_{12}$ inhibitors. Certain procedural factors were associated with increased odds of receipt of newer $P2Y_{12}$ inhibitors, including radial access (versus femoral), greater number of lesions or stents, left main stem (LMS) PCI (only ticagrelor), and graft PCI.

Trends of $P2Y_{12}$ Inhibitor Use

Overall, the rates of prescription of new $P2Y_{12}$ inhibitors increased between 2010 and 2020 (ticagrelor: 13.3%–50.5%; prasugrel: 4.7%–11.1%; P_{trend}<0.001). (Figure 2A) A similar pattern was observed in both STEMI and NSTE-ACS subgroups (P_{trend}<0.001 for both; Figure 2B). Figure 3 demonstrates the estimated break time points at which the rate of use of newer $P2Y_{12}$ inhibitors (versus clopidogrel) changed between 2010 and 2022, stratified by clinical syndrome. Overall, the trend of use of ticagrelor has significantly increased at the following time points: 2012 (week 45), 2014 (week 41), 2016 (week 49), and 2020 (week 10). In contrast, the trend of use of prasugrel significantly increased until 2011 (week 44), then followed further notable declines around 2013 (week 37) and 2016 (week 18) before a significant increase in utilization in 2020 (week 22). A similar pattern was observed in the STEMI and NSTE-ACS subgroups.

Figure 4 demonstrates the odds of receipt of newer $P2Y_{12}$ inhibitors (versus clopidogrel) over the study period, using 2010 as the reference year, commensurate with US and European guidelines over that period. After adjustment for baseline variables, there was a significant increase in overall odds of receipt of newer $P2Y_{12}$ inhibitors (versus clopidogrel) over the study period (2022 versus 2010: ticagrelor OR, 8.12 [95% CI, 7.67–8.60]; prasugrel OR, 6.14 [95% CI, 5.53–6.81]; P_{trend}<0.001; Figure 4A, Table S1). While the odds of receipt of prasugrel (versus clopidogrel) were consistently higher in the years 2011 to 2019, the most significant increase in odds was observed between 2020 and 2022, coinciding with the ISAR-REACT 5 (Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndrome) trial and the 2020 ESC guidelines for NSTE-ACS. In contrast, there was a significant increase in the odds of receipt of ticagrelor in earlier years (2012–2017; P_{trend}<0.001), compared with 2010, suggesting that earlier ESC and AHA/ACC/SCAI guidelines had a positive impact on its uptake in clinical practice. However, the increase in odds of receipt of ticagrelor was stable from 2018 onward (P_{trend}=0.093), following the 2017 ESC focused update on dual antiplatelet therapy.

When stratified by ACS subtype, the odds of receipt of both prasugrel and ticagrelor (versus clopidogrel) increased between 2011 and 2022, compared with 2010, in the STEMI subgroup, although this was more significant for ticagrelor than prasugrel (2022 versus

Table 1. Patient and Procedural Characteristics of Patients With ACS Undergoing PCI According to P2Y12 Inhibitor Group

	Clopidogrel (n=282 768)	Ticagrelor (n=213 012)	Prasugrel (n=38 430)	*P* value
Age, y, median (IQR)	67 (57–76)	64 (55–73)	61 (53–69)	<0.001
Age groups, y, %				<0.001
<60	30.8	37.3	46.5	
60–69	26.5	27.9	30.8	
70–79	26.3	23.2	17.4	
≥80	16.5	11.5	5.3	
Male sex, %	72.2	73.9	77.7	<0.001
Race or ethnicity, %				<0.001
White	86.1	83.5	87.6	
Black	3.7	4.6	3.1	
South Asian	5.6	7.5	6.7	
Other	4.6	4.5	2.6	
Clinical syndrome, %				<0.001
NSTE-ACS	72.2	55.8	14.4	
STEMI	27.8	44.2	85.6	
Stent thrombosis indication, %	2.1	3.0	3.2	<0.001
Previous MI, %	25.5	20.6	15.3	<0.001
Previous PCI, %	20.1	18.0	13.2	<0.001
Previous CABG, %	7.4	5.3	2.5	<0.001
Previous CVA, %	5.0	3.6	0.0	<0.001
Diabetes, %	22.7	21.8	16.9	<0.001
Renal failure, %	3.1	1.9	1.0	<0.001
Left ventricular function (ejection fraction), %*				<0.001
Good (>50%)	65.7	58.3	49.9	
Moderate (30%–50%)	30.6	38.6	47.2	
Poor (<30%)	3.7	3.1	2.8	
Hypercholesterolemia, %	50.2	42.6	37.0	<0.001
Peripheral vascular disease, %	5.0	3.3	2.3	<0.001
Hypertension, %	55.8	49.8	38.9	<0.001
Current/previous smoker, %	63.3	61.1	67.8	<0.001
Valvular heart disease, %	1.9	1.4	0.6	<0.001
Preprocedural cardiogenic shock, %	3.0	4.1	5.4	<0.001
Out-of-hospital cardiac arrest, %	2.6	4.1	5.1	<0.001
Mechanical ventilation, %	1.8	2.8	2.7	<0.001
Mechanical circulatory support, %	2.3	2.7	3.8	<0.001
Access route*				<0.001
Radial, %	73.6	84.7	83.2	
Femoral, %	28.8	17.5	19.5	
No. of vessels, %				<0.001
1	79.8	80.5	85.6	
2	16.5	16.0	12.0	
3	3.2	3.0	1.9	
4	0.6	0.5	0.5	
No. of lesions, %				<0.001
1	63.8	58.9	61.4	
2	27.2	30.5	29.8	
3	6.9	8.1	6.7	
≥4	2.2	2.5	2.2	

(*Continued*)

Table 1. Continued

	Clopidogrel (n=282 768)	Ticagrelor (n=213 012)	Prasugrel (n=38 430)	*P* value
No. of stents, mean ±SD	1.36±0.93	1.36±0.91	1.36±0.82	0.716
Drug-eluting stents, %	71.2	74.1	70.7	<0.001
First generation, %[†]	35.1	39.5	44.0	<0.001
Second/third generation, %[†]	56.5	64.6	65.5	<0.001
Drug-coated balloon, %	0.5	0.8	0.7	<0.001
Intravascular imaging, %[‡]	9.9	9.9	6.3	<0.001
Calcium modification, %	3.1	3.1	1.8	<0.001
Left main stem, %	4.7	4.6	2.7	<0.001
Proximal LAD, %	30.1	29.4	28.8	<0.001
Grafts, %	3.5	2.6	1.6	<0.001
Chronic total occlusion, %	1.0	1.3	0.7	<0.001
Glycoprotein 2b/3a inhibitor, %	29.7	37.8	51.8	<0.001
Bivalirudin, %	2.6	1.9	15.8	<0.001

CABG indicates coronary artery bypass graft; CVA, cerebrovascular accident; IQR, interquartile range; LAD, left anterior descending artery; MI, myocardial infarction; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*Patients had >1 access route in some cases.

†There was an overlap in stent generations in a subset of cases.

‡Intravascular ultrasound or optical coherence tomography.

2010: ticagrelor OR, 16.50 [95% CI, 14.82–18.38]; prasugrel OR, 7.52 [95% CI, 6.63–8.52]; Figure 4B) The increase in odds of receipt of ticagrelor was more significant in earlier years (2012–2017; P_{trend}<0.001), while the increase in odds of receipt of prasugrel was more significant after 2019 (2020–2022; P_{trend}<0.001), a similar trend to that observed in the overall cohort and in relation to major society guidelines. Within the NSTE-ACS subgroup, the odds of receipt of ticagrelor and prasugrel (versus clopidogrel) were consistently high. However, there was no significant change in the odds of receipt of prasugrel at the start and end of the 11-year period (2011–2022; P_{trend}>0.05), while the odds of receipt of ticagrelor significantly increased from 2012 to 2017 (P_{trend}<0.001), after which they were stable (P_{trend}=0.085).

DISCUSSION

This is the largest study to examine national trends and predictors of use of newer $P2Y_{12}$ inhibitors among patients with ACS undergoing PCI in a contemporary procedural cohort over a 13-year period, commensurate with practice guideline recommendations over the same period. Our findings can be summarized as follows. First, newer $P2Y_{12}$ inhibitor use has significantly increased over the study period, although this was primarily in patients with STEMI. As of 2022, >80% of patients with STEMI were treated with newer $P2Y_{12}$ inhibitors, most commonly ticagrelor, while only 50% of patients with NSTE-ACS were in receipt of newer $P2Y_{12}$ inhibitors. However, the rate of prasugrel use remained relatively low, with only 26% of patients with STEMI and 2.5% of patients with NSTE-ACS in receipt of prasugrel in 2022. Our trend analysis shows that society guidelines between 2011 and 2017 were associated with an increased use of ticagrelor, while subsequent guidelines had limited effect on its trend of use. In contrast, earlier guidelines had no obvious association with the trend in prasugrel use (if anything, a downward trend), although the highest uptake of prasugrel use coincided with the ISAR-REACT 5 trial and 2020 ESC NSTE-ACS guidelines. Finally, our analysis identifies several patient and procedural predictors associated with preferential use of newer $P2Y_{12}$ inhibitors over clopidogrel, including younger age, non-White race or ethnicity, prior PCI, stent thrombosis, and greater number of lesions or stents, as well as LMS and graft PCI cases. In contrast, patients with peripheral vascular disease and renal failure were less likely to receive newer $P2Y_{12}$ inhibitors than clopidogrel.

Dual antiplatelet therapy is a central pillar of the management of ACS and holds a class 1 recommendation in all international society guidelines.[5–7] Newer $P2Y_{12}$ inhibitors have been shown to be superior to clopidogrel in terms of reduction of reinfarction and cardiac death, and stent thrombosis, although they are also associated with a greater risk of bleeding.[1,5,11] Consequently, major society guidelines by the ESC and AHA/ACC/SCAI have recommended their preferential use over clopidogrel, in the absence of contraindications, as early as 2011, a recommendation that has only been

Table 2. Predictors of Receipt of Newer $P2Y_{12}$ Inhibitors

Predictor/group	Prasugrel		Ticagrelor	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	0.97 (0.97–0.97)	<0.001	0.99 (0.99–0.99)	<0.001
Male sex	1.01 (0.98–1.04)	0.692	0.99 (0.98–1.01)	0.216
Ethnicity				
White	Reference		Reference	
Black	1.01 (0.94–1.08)	0.886	1.26 (1.22–1.30)	<0.001
South Asian	1.27 (1.21–1.34)	<0.001	1.46 (1.42–1.50)	<0.001
Other	0.65 (0.60–0.70)	<0.001	1.09 (1.06–1.12)	<0.001
STEMI (vs NSTE-ACS)	15.04 (14.55–15.56)	<0.001	1.99 (1.96–2.02)	<0.001
Stent thrombosis	0.83 (0.77–0.89)	<0.001	1.29 (1.24–1.34)	<0.001
Previous MI	1.04 (0.99–1.09)	0.111	0.92 (0.90–0.94)	<0.001
Previous PCI	1.25 (1.19–1.31)	<0.001	1.00 (0.98–1.02)	0.899
Previous CABG	0.74 (0.67–0.81)	<0.001	0.93 (0.90–0.97)	<0.001
Previous CVA	…	…	0.83 (0.80–0.85)	<0.001
Renal failure	0.69 (0.62–0.78)	<0.001	0.71 (0.69–0.75)	<0.001
Left ventricular function				
Good	Reference		Reference	
Moderate	1.34 (1.30–1.37)	<0.001	1.27 (1.25–1.29)	<0.001
Poor	1.14 (1.06–1.23)	<0.001	0.94 (0.91–0.98)	0.002
Peripheral vascular disease	0.83 (0.76–0.90)	<0.001	0.90 (0.87–0.93)	<0.001
Cardiogenic shock preoperative	1.02 (0.95–1.08)	0.668	0.99 (0.95–1.03)	0.565
Out-of-hospital cardiac arrest	0.97 (0.91–1.04)	0.404	1.16 (1.11–1.21)	<0.001
Radial access	2.06 (1.91–2.21)	<0.001	1.05 (1.01–1.09)	0.021
Number of vessels	1.03 (0.99–1.07)	0.097	0.975 (0.96–0.99)	0.002
Number of lesions	1.07 (1.04–1.10)	<0.001	1.05 (1.03–1.06)	<0.001
Number of stents	1.09 (1.07–1.11)	<0.001	1.03 (1.02–1.04)	<0.001
Left main stem	0.94 (0.86–1.02)	0.126	1.10 (1.07–1.14)	<0.001
Proximal LAD	0.88 (0.86–0.91)	<0.001	0.92 (0.90–0.93)	<0.001
Grafts	1.40 (1.25–1.57)	<0.001	1.10 (1.05–1.15)	<0.001

CABG indicates coronary artery bypass graft; CVA, cerebrovascular accident; DES, drug eluting stent; LAD, left anterior descending artery; MI, myocardial infarction; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; OR, odds ratio; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; and STEMI, ST-segment–elevation myocardial infarction.

reiterated and/or strengthened in subsequent guidelines.[12,13] However, the rate of adoption of these guidelines in clinical practice remains unclear. Moreover, further trials have evolved during the past decade that further strengthened the argument for use of newer $P2Y_{12}$ inhibitors and even demonstrated differences in outcomes between newer $P2Y_{12}$ inhibitors. For example, the ISAR-REACT 5 was a multicenter, randomized controlled trial that enrolled ≈4000 patients with ACS undergoing angiography randomized to prasugrel or ticagrelor and demonstrated a significant reduction in the primary end point, a composite of death, myocardial infarction, or stroke at 1 year (hazard ratio, 1.36 [95% CI, 1.09–1.70]; *P*=0.006), in favor of prasugrel.[14]

Our findings show that the use of newer $P2Y_{12}$ inhibitors, compared with clopidogrel, has generally increased over the past 13 years, although this has been primarily due to greater use of ticagrelor in both STEMI and NSTE-ACS indications. However, since 2017 there has been no increase in the use of ticagrelor year on year for both NSTE-ACS and STEMI, while prasugrel use was static until 2019, after which it significantly increased in STEMI but not for NSTE-ACS. These findings are particularly interesting, given the publication of several guidelines during that period, all of which recommend the use of prasugrel or ticagrelor over clopidogrel in both patients with STEMI and patients with NSTE-ACS, including the 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease, 2017 ESC guidelines on STEMI, the 2020 ESC guidelines for NSTE-ACS, and the 2021 AHA/ACC/SCAI guidelines on coronary revascularization.[6,7,11,15] Our findings suggest that earlier guidelines and trials, before 2017, correlated with significant uptake of ticagrelor

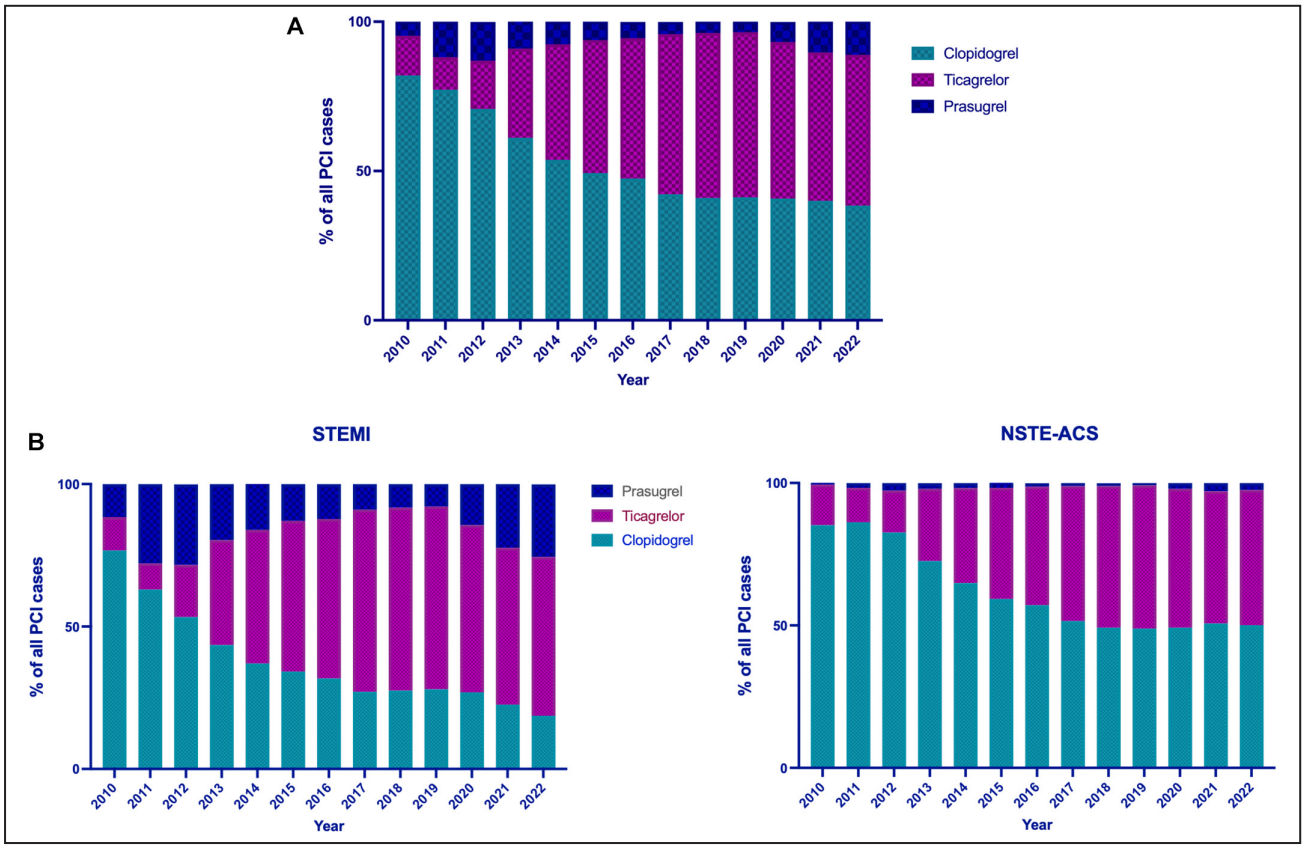

Figure 2. Rates of $P2Y_{12}$ use among ACS undergoing PCI (2010–2022) in the (A) overall cohort and (B) by clinical syndrome. P_{trend}<0.001 for all. NSTE-ACS indicates non–ST-segment–elevation acute coronary syndrome; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

use whereas prasugrel use only coincided with the 2020 ESC guidelines for NSTE-ACS and 2021 AHA/ACC/SCAI guidelines on coronary revascularization. A study of 62 423 patients with ACS who underwent PCI in the United States demonstrated a shift toward newer $P2Y_{12}$ inhibitor use (ticagrelor or prasugrel) between 2010 (22.5%) and 2019 (60.4%), mainly driven by a significant rise in ticagrelor use, while prasugrel use was stable in their later study years.[16] However, their trend analysis was unadjusted and did not stratify usage by type of clinical syndrome (NSTE-ACS versus STEMI). While this pattern is consistent with our findings, their analysis was only until 2019, and, therefore, the observed increase in prasugrel use among patients with STEMI in our study could not be compared.

A notable finding in our study is the overall low rate of use of prasugrel, especially in earlier years, which has not changed over the study period for NSTE-ACS and only increased in patients with STEMI after 2019 as previously discussed, which likely coincides with the publication of the ISAR-REACT 5 trial. Even as late as 2022, only 1 in 4 patients with STEMI and 1 in 20 patients with NSTE-ACS were prescribed prasugrel, and half of patients with NSTE-ACS were in receipt of clopidogrel. The slow uptake of newer $P2Y_{12}$ inhibitor use as of 2022 is particularly surprising given the robust evidence on superiority of prasugrel over clopidogrel, demonstrated from 2007 in the TRITON-TIMI 38 trial, and ticagrelor, as shown in the ISAR-REACT 5 trial, in addition to international guideline recommendations for newer $P2Y_{12}$ inhibitor use over clopidogrel as early as 2011.[2,14] Even at a national level, the National Institute for Health and Care Excellence guidelines for ACS outline similar recommendations regarding preferential $P2Y_{12}$ inhibitor use in the absence of contraindications.[17] A proportion of patients will have received clopidogrel due to certain contraindications (eg, concomitant use of anticoagulants or allergy/intolerance to newer $P2Y_{12}$ inhibitors) or high bleeding risk, although risk factors such as old age and renal failure were not highly prevalent in the clopidogrel group. The lack of early temporal association between the recommendations in the guidelines and clinical use of the newer agents cannot be explained from our data, but it could have several possible explanations. First, clinicians may have concerns about using the newer agents in real-world environments because of the high prevalence of patients with perceived high bleeding risk. Second,

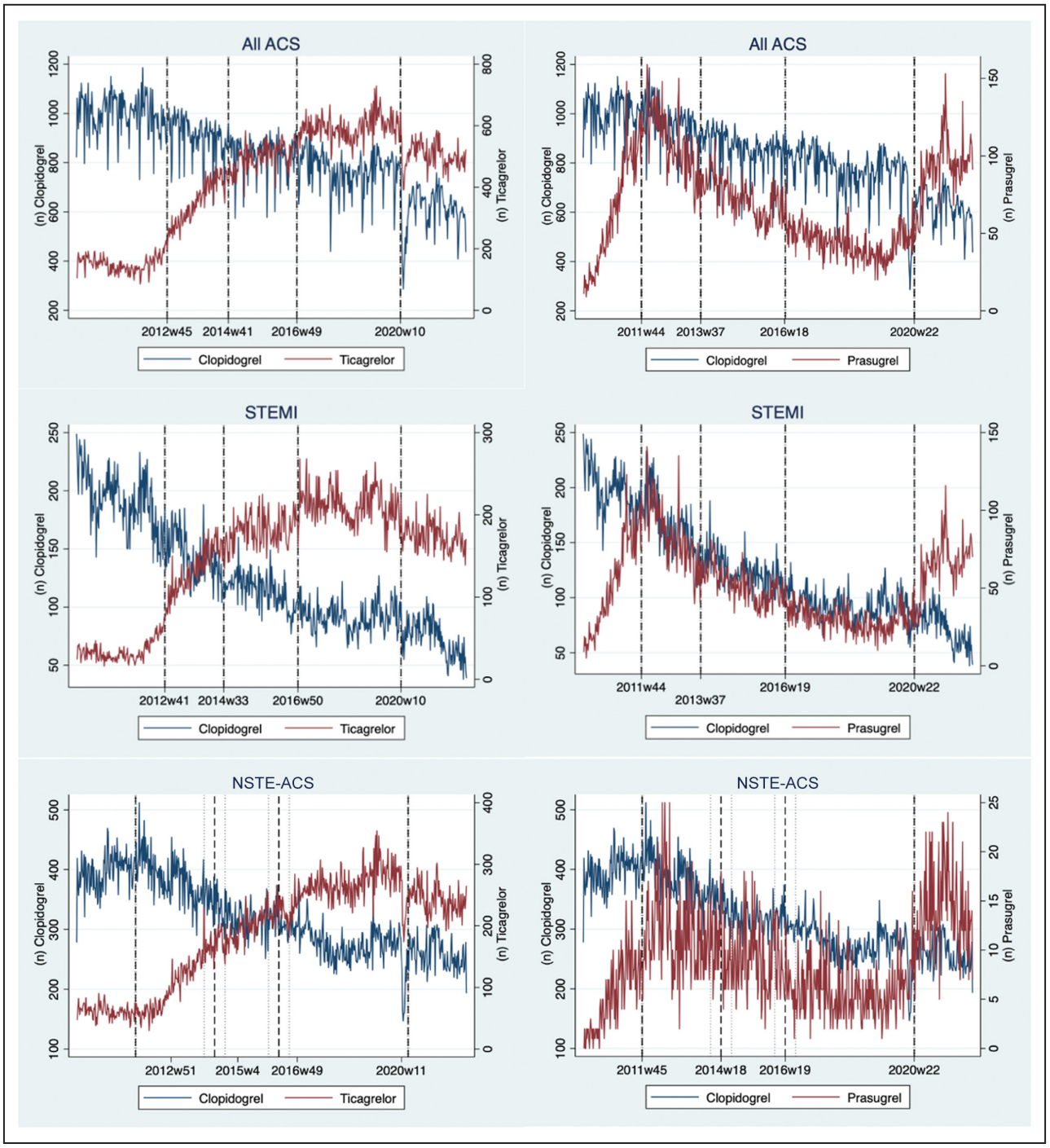

Figure 3. Estimated break points in the trend of use of newer P2Y$_{12}$ inhibitors (vs clopidogrel) between 2010 and 2020.
ACS indicates acute coronary syndrome; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; and STEMI, ST-segment–elevation myocardial infarction.

there is a large cost differential between the newer agents and clopidogrel, although National Institute for Health and Care Excellence guidelines, which recommend the use of newer P2Y$_{12}$ inhibitors over clopidogrel, were based on economic evaluations and incremental cost-effectiveness ratios in favour of newer P2Y$_{12}$ inhibitors.[18] It is possible that in nonuniversal health settings, such as the United States, cost implications for individual patients would discourage physicians from prescribing newer P2Y$_{12}$ inhibitors despite their greater efficacy. Third, many frontline healthcare workers (such as emergency and internal medicine physicians) may have chosen clopidogrel as a more familiar and less risky choice, and changing hospital

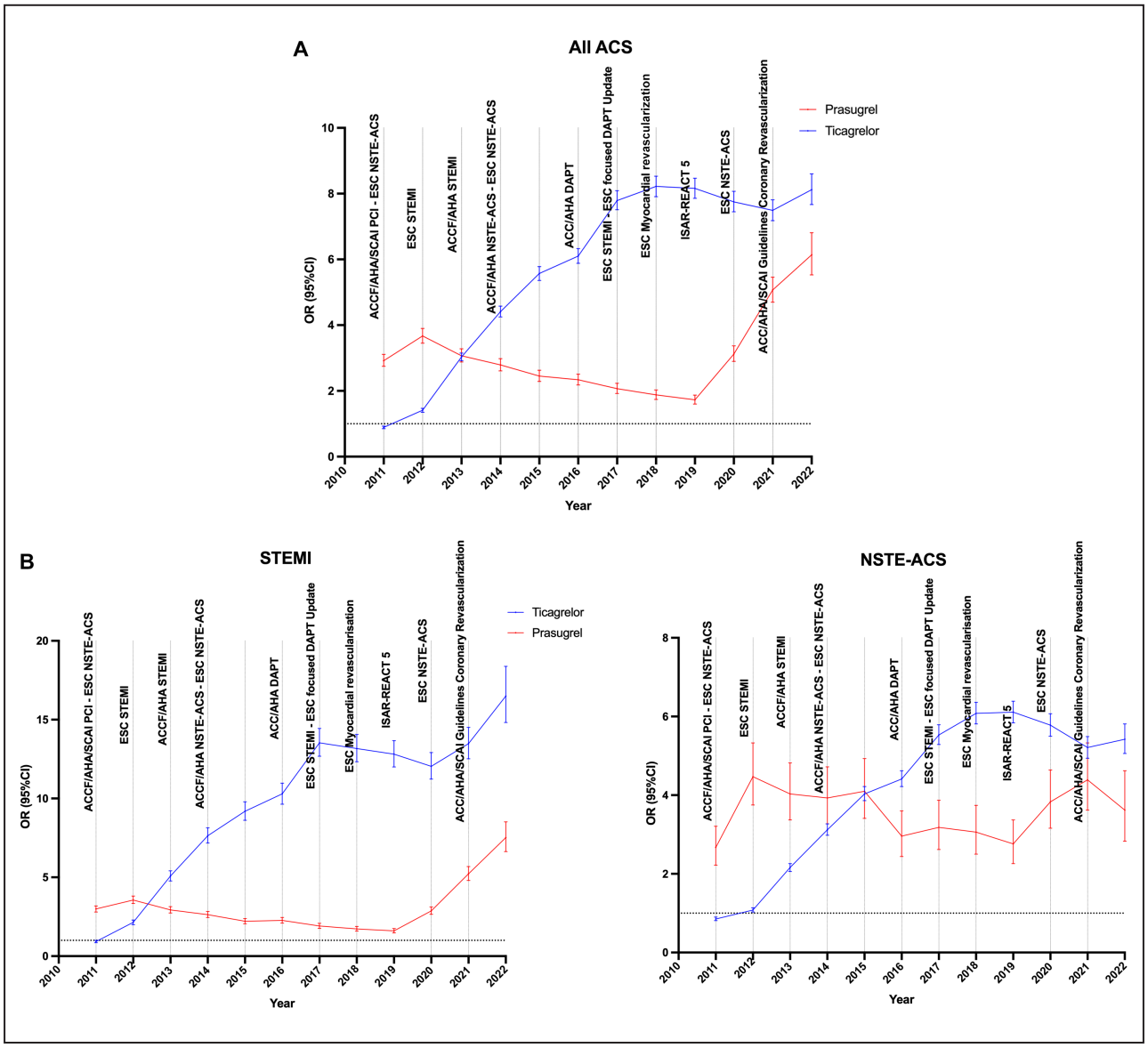

Figure 4. Adjusted odds of receipt of newer $P2Y_{12}$ inhibitors (vs clopidogrel)* over the study period commensurate with society guidelines in (A) the overall cohort and (B) stratified by clinical syndrome.
ACCF indicates American College of Cardiology Foundation; ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; OR, odds ratio; AHA, American Heart Association; ISAR-REACT 5, Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndrome; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SCAI, Society for Cardiovascular Angiography and Interventions; and STEMI, ST-segment–elevation myocardial infarction. *Reference is 2010.

guidelines for antiplatelet strategy can be a cumbersome process involving many stakeholders. Fourth, a proportion of patients will have an indication for anticoagulation (eg, atrial fibrillation or venous thromboembolism) and, therefore, may be offered clopidogrel only as part of a triple-therapy regime. Although our data set did not capture direct oral anticoagulants, we do not expect the proportion of patients with an indication for anticoagulation to have substantially changed over the years. Therefore, this would not have substantially modified the trend of uptake of newer $P2Y_{12}$ inhibitors seen in our temporal analysis. Finally, sometimes clinicians may take time to see "which way the wind is blowing" among fellow clinicians and opinion leaders. These factors may delay change of any therapy, and particularly those with a nuanced risk/benefit calculation where harm can occur, as well as benefit.

Our analysis highlighted several factors associated with increased odds of receipt of newer $P2Y_{12}$ inhibitors as previously discussed. Some factors were surrogates of lower bleeding risk such as younger age, absence of renal failure, or previous stroke, thereby

explaining the preference for newer $P2Y_{12}$ inhibitors among clinicians. Similarly, factors such as prior PCI, stent thrombosis PCI indication, greater number of lesions/stents, and LMS or graft PCI cases were associated with increased odds of receipt of newer $P2Y_{12}$ inhibitors given the higher ischemic risk of these patient groups. We observe that Black and South Asian patients were independently associated with increased odds of receipt of newer $P2Y_{12}$ inhibitors, which may reflect clinicians' concerns around their increased risk of stent thrombosis due to variations in bioavailability of clopidogrel and on-treatment platelet reactivity in these patient groups.[4,19] Wang et al examined determinants of receipts of newer $P2Y_{12}$ inhibitors (versus clopidogrel) in their study of 62 423 patients with ACS undergoing PCI in the United States and reported similar predictors of receipt of newer $P2Y_{12}$ inhibitors, although advanced age and severe chronic kidney disease did not appear to be associated with a lower incidence of ticagrelor or prasugrel use.[16] However, this analysis included a smaller cohort of patients and did not capture procedural information such as type of vessel (eg, LMS or graft), number of vessels treated, and stents implanted, as well as stent type and haemodynamic stability (eg, presence of cardiogenic shock or need for mechanical circulatory support), all of which are predictive markers of repeat revascularization and stent thrombosis.

Limitations

There are several limitations to the present study. First, while the BCIS data set captures a wide range of patient and procedural characteristics prospectively, there is limited information on concomitant direct oral anticoagulant use and certain components of the CRUSADE score, which may influence the choice of antiplatelet therapy. Second, our data set does not capture individual patient preference choice of $P2Y_{12}$ inhibitor. Third, registries cannot capture clinical frailty, which is independently associated with increased bleeding risk and may have an impact on the choice

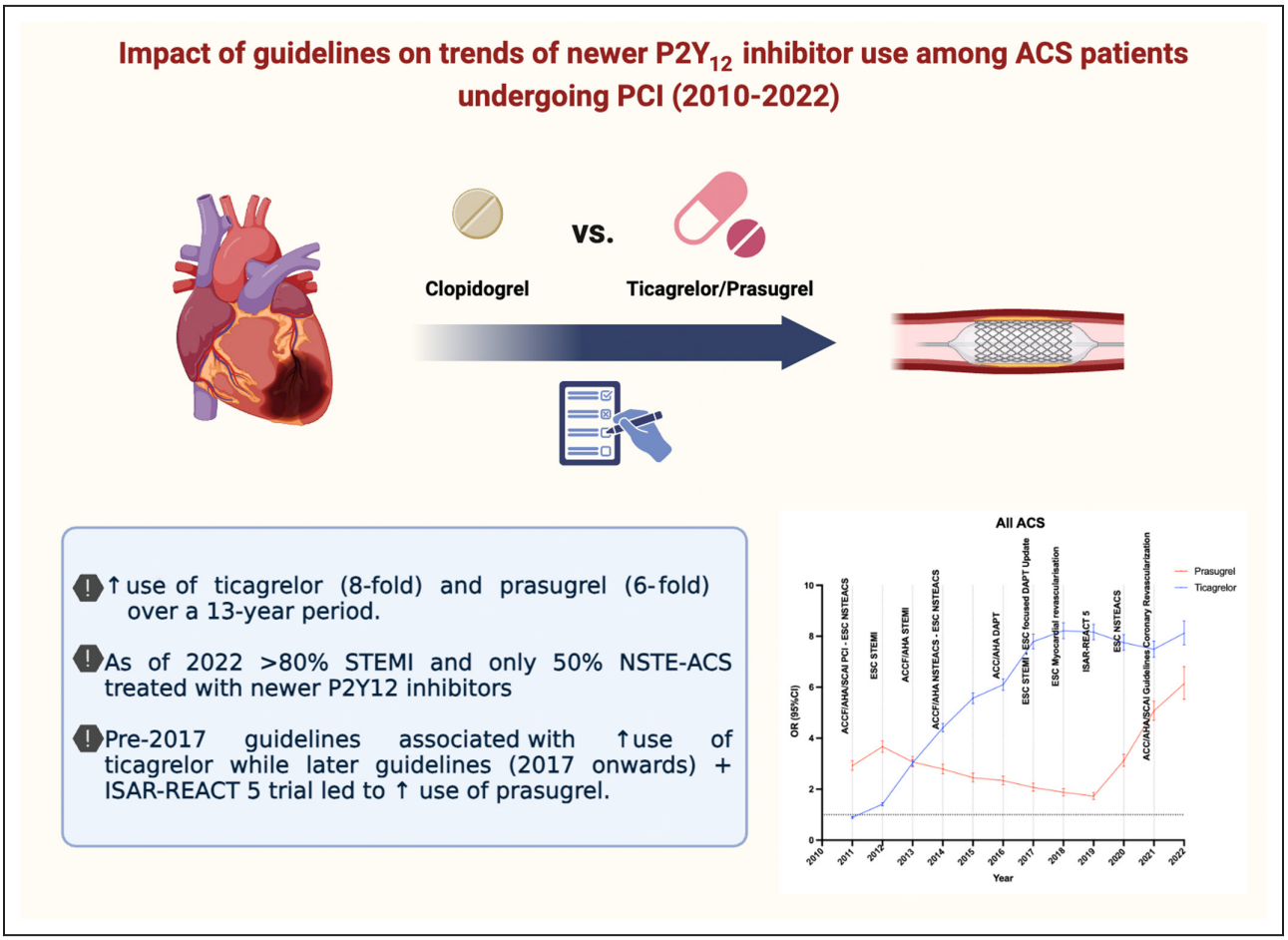

Figure 5. Summary of study findings.
ISAR-REACT 5 indicates Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndrome; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; and STEMI, ST-segment–elevation myocardial infarction.

of $P2Y_{12}$ inhibitor offered to such high-risk patients. Finally, a time lag exists between publication of guidelines and uptake in clinical practice due to specific factors including physician awareness, adoption of new recommendations into local health policies, cost implications, and so on. While the findings reported in our study were based on national data over a 13-year period, the relationship between guideline publication and trends observed does not infer causality.

CONCLUSIONS

In our national analysis of >500 000 patients undergoing PCI for ACS over a 13-year period, we demonstrate a strong shift toward use of newer $P2Y_{12}$ inhibitors compared with clopidogrel, primarily driven by higher rates of ticagrelor use for both NSTE-ACS and STEMI presentations and more recently prasugrel use in patients with STEMI (Figure 5). Earlier society guidelines (up to 2017) had a significant impact on use of ticagrelor but did not influence the uptake of prasugrel, while the ISAR-REACT 5 trial and later society guidelines including the 2020 ESC guidelines for NSTE-ACS and beyond correlated with a significant increase in the use of prasugrel. Notwithstanding this, the rate of use of newer $P2Y_{12}$ inhibitors remains lower than expected, with more than half of patients with NSTE-ACS in receipt of clopidogrel as of 2022. Several factors favored preferential use of newer $P2Y_{12}$ inhibitors over clopidogrel among clinicians, including younger age, non-White race ethnicity, and PCI for stent thrombosis, LMS or graft disease, or extensive disease involving a greater number of vessels and the use of multiple stents.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1

REFERENCES

1. Navarese EP, Khan SU, Kołodziejczak M, Kubica J, Buccheri S, Cannon CP, Gurbel PA, De Servi S, Budaj A, Bartorelli A, et al. Comparative efficacy and safety of oral P2Y12 inhibitors in acute coronary syndrome. *Circulation*. 2020;142:150–160. doi: 10.1161/CIRCULATIONAHA.120.046786
2. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann F-J, Ardissino D, De Servi S, Murphy SA, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015. doi: 10.1056/NEJMoa0706482
3. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057. doi: 10.1056/NEJMoa0904327
4. Yun JE, Kim YJ, Park JJ, Kim S, Park K, Cho MS, Nam GB, Park DW. Safety and effectiveness of contemporary P2Y12 inhibitors in an east Asian population with acute coronary syndrome: a Nationwide population-based cohort study. *J Am Heart Assoc*. 2019;8:e012078. doi: 10.1161/JAHA.119.012078
5. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan G-A, Dweck MR, Galbraith M, et al. ESC guidelines for the management of acute coronary syndromes: developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2023;2023:ehad191. doi: 10.1093/eurheartj/ehad191
6. Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2021;42:1289–1367. doi: 10.1093/eurheartj/ehaa575
7. Lawton Jennifer S, Tamis-Holland Jacqueline E, Bangalore S, Bates Eric R, Beckie Theresa M, Bischoff James M, Bittl John A, Cohen Mauricio G, DiMaio JM, Don Creighton W, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization. *Circulation*. 2022;145:e4–e17. doi: 10.1161/CIR.0000000000001039
8. Ludman PF. British cardiovascular intervention society registry for audit and quality assessment of percutaneous coronary interventions in the United Kingdom. *Heart*. 2011;97:1293–1297. doi: 10.1136/heartjnl-2011-300299
9. Bai J, Perron P. Estimating and testing linear models with multiple structural changes. *Econometrica*. 1998;66:47–78. doi: 10.2307/2998540
10. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. John Wiley & Sons Inc.; 1987. doi: 10.1002/9780470316696
11. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39:213–260. doi: 10.1093/eurheartj/ehx419
12. Authors/Task, Force M, Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Di Mario C, Dickstein K, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *Eur Heart J*. 2012;33:2569–2619. doi: 10.1093/eurheartj/ehs215
13. Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE, Ettinger SM, Fesmire FM, Ganiats TG, Jneid H, Lincoff AM, 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). *Circulation*. 2011;123:2022–2060. doi: 10.1161/CIR.0b013e31820f2f3e
14. Schüpke S, Neumann F-J, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, Richardt G, Liebetrau C, Witzenbichler B, Antoniucci D, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med*. 2019;381:1524–1534. doi: 10.1056/NEJMoa1908973
15. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen 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*. 2018;39:119–177. doi: 10.1093/eurheartj/ehx393
16. Wang Y, Cavallari LH, Brown JD, Thomas CD, Winterstein AG. Assessing the clinical treatment dynamics of antiplatelet therapy following acute coronary syndrome and percutaneous coronary intervention in the US. *JAMA Netw Open*. 2023;6:e238585. doi: 10.1001/jamanetworkopen.2023.8585
17. Excellence NIfHaC. *Acute coronary syndromes (NG185)*. National Institute for Health and Care Excellence; 2020.
18. Excellence NIfHaC. Ticagrelor for the Treatment of Acute Coronary Syndromes (TA236). 2011.
19. Tamargo J, Kaski JC, Kimura T, Barton JC, Yamamoto K, Komiyama M, Drexel H, Lewis BS, Agewall S, Hasegawa K. Racial and ethnic differences in pharmacotherapy to prevent coronary artery disease and thrombotic events. *Eur Heart J Cardiovasc Pharmacother*. 2022;8:738–751. doi: 10.1093/ehjcvp/pvac040