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Systematic Review

P2Y12 Inhibitors for Non–ST-Segment Elevation Acute Coronary Syndrome: A Systematic Review and Network Meta-Analysis

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Abstract

Background: For patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS), prasugrel was recommended over ticagrelor in a recent randomized controlled trial, although more data are needed on the rationale. Here, the effects of P2Y12 inhibitors on ischemic and bleeding events in patients with NSTE-ACS were investigated.

Methods: Clinical trials that enrolled patients with NSTE-ACS were included, relevant data were extracted, and a network meta-analysis was performed.

Results: This study included 37,268 patients with NSTE-ACS from 11 studies. There was no significant difference between prasugrel and ticagrelor for any end point, although prasugrel had a higher likelihood of event reduction than ticagrelor for all end points except cardiovascular death. Compared with clopidogrel, prasugrel was associated with decreased risks of major adverse cardiovascular events (MACE) (hazard ratio [HR], 0.84; 95% CI, 0.71-0.99) and myocardial infarction (HR, 0.82; 95% CI, 0.68-0.99) but not an increased risk of major bleeding (HR, 1.30; 95% CI, 0.97-1.74). Similarly, compared with clopidogrel, ticagrelor was associated with a reduced risk of cardiovascular death (HR, 0.79; 95% CI, 0.66-0.94) and an increased risk of major bleeding (HR, 1.33; 95% CI, 1.00-1.77; $P = .049$). For the primary efficacy end point (MACE), prasugrel showed the highest likelihood of event reduction ($P = .97$) and was superior to ticagrelor ($P = .29$) and clopidogrel ($P = .24$).

Conclusion: Prasugrel and ticagrelor had comparable risks for every end point, although prasugrel had the highest probability of being the best treatment for reducing the primary efficacy end point. This study highlights the need for further studies to investigate optimal P2Y12 inhibitor selection in patients with NSTE-ACS.

Keywords: Non-ST elevated myocardial infarction; acute coronary syndrome; ticagrelor; prasugrel hydrochloride; purinergic P2Y receptor antagonists

Introduction

Dual antiplatelet therapy (DAPT), consisting of aspirin in combination with a P2Y12 inhibitor, is a crucial treatment for the prevention of thrombotic events. Current guidelines recommend DAPT in patients with acute coronary syndrome (ACS).[1-4] Non–ST-segment elevation myocardial infarction (NSTEMI)

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and unstable angina are collectively referred to as non–ST-segment elevation ACS (NSTE-ACS).[5,6] Previous landmark studies recommended a more potent P2Y12 inhibitor (prasugrel or ticagrelor) over clopidogrel for patients with STEMI or NSTE-ACS.[1,2,6-10] A recent randomized control trial (RCT) of a head-to-head comparison of prasugrel and ticagrelor demonstrated that the former significantly reduced the composite outcome of death, MI, or stroke among patients with NSTE-ACS.[11,12] Based on that single RCT, the current European Society of Cardiology guidelines, updated in 2020, give a class IIA recommendation for prasugrel as the preferred agent over ticagrelor for patients with NSTE-ACS who require percutaneous coronary intervention (PCI).[13] The level of evidence is limited, however, and a recent large-scale retrospective study demonstrated that prasugrel and ticagrelor had similar efficacy and safety in real-world patients with ACS.[14] The current systematic review and meta-analysis investigated the effect of P2Y12 inhibitors on ischemic and bleeding events in patients with NSTE-ACS.

Abbreviations and Acronyms

ACS	acute coronary syndrome
CV	cardiovascular
DAPT	dual antiplatelet therapy
HR	hazard ratio
MACE	major adverse cardiovascular events
NSTE-ACS	non–ST-segment elevation acute coronary syndrome
NSTEMI	non–ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction

Methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement standards.[15] The study protocol was registered in International Prospective Register of Systematic Reviews (registration No. CRD42021235922). No patient or public entity was involved in the study.

Eligibility Criteria

The eligibility criteria were as follows: (1) the study was published in a peer-reviewed journal, (2) the study was an RCT or subgroup analysis of an RCT of patients with NSTE-ACS that examined at least 2 different P2Y12 inhibitors, and (3) the study reported outcomes of interest.

Information Sources and Search

All studies investigating the effect of P2Y12 inhibitors in patients with NSTE-ACS were searched using the following strategy. First, the PubMed, Embase, and CENTRAL databases were searched on November 26, 2020. The search terms included PCI; acute coronary syndrome; antiplatelet OR aspirin OR prasugrel OR clopidogrel OR ticagrelor OR p2y12; and randomized OR randomly OR random. The authors did not apply any language restrictions.

Study Selection and Data-Collection Process

Relevant studies were identified through a manual search of secondary sources, including references to the initially identified articles, reviews, and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analysis. Two independent, blinded authors (T.F. and T.K.[16]) reviewed the search results and selected studies based on the inclusion and exclusion criteria. If these 2 authors could not reach consensus, a third author (H.T.[17]) was consulted to reach a decision. Any disagreements were resolved by consensus.

Data were collected according to the PICOS framework:

- **P (Population):** Patients with NSTE-ACS
- **I (Intervention):** Potent P2Y12 inhibitors (prasugrel and ticagrelor)
- **C (Comparison):** Other P2Y12 inhibitors
- **O (Outcome):** Major adverse cardiovascular events (MACE), all-cause mortality, cardiovascular (CV) death, MI, stroke, or major bleeding
- **S (Study type):** RCT

Risk-of-Bias Assessment

Study quality was assessed by using version 2 of the Cochrane risk-of-bias tool for randomized trials.[18] Two investigators (T.F. and T.K.) reviewed the studies and judged the selection, comparability, and outcomes independently.

Outcomes

The primary end point was the occurrence of MACE. Trial-defined MACE included any of the following: composite of CV death, MI, and stroke; composite of death, MI, and stroke; or composite of death, MI, stroke, and rehospitalization for CV causes or bleeding. Secondary end points included all-cause mortality, CV death, MI, stroke, and trial-defined major bleeding. Major bleeding events were defined in various ways in included studies as Thrombolysis in Myocardial Infarction (TIMI) major bleeding; non–coronary artery bypass graft–related TIMI major bleeding; and Bleeding Academic Research Consortium grade 3, 4, or 5 bleeding. The hazard ratios (HRs) and risk ratios were calculated for each study. If the HR or risk ratio was not described in a study, only the risk ratio was calculated from the event and patient numbers.

Statistical Analysis

A network meta-analysis was performed using the netmeta 3.6.2 package (R Foundation for Statistical Computing) to calculate the pooled HRs with 95% CIs for all outcomes comparing each P2Y12 inhibitor.[19] Statistical significance was defined as $P < .05$. If a specific P2Y12 inhibitor was used in more than 90% of the patients in a group, the group was classified into a specific P2Y12 inhibitor group. Within the framework, I^2 and Q statistics, which represent the proportion of total variation in study estimates resulting from heterogeneity, were used to quantify heterogeneity.[20,21] The Q statistic is the sum of a statistic for heterogeneity and a statistic for inconsistency and represents the variability of treatment effect between direct and indirect comparisons at the meta-analytical level.[22] The P-score metric was used to rank the treatments' comparative hierarchy of efficacy and safety; P-scores ranged from 0 to 1, with a higher value indicating a higher likelihood of a treatment being more effective or safe and a lower value indicating that the treatment was ineffective.

For the sensitivity analysis, ReviewManager, version 5.4 (The Cochrane Collaboration) was used to calculate the pooled HRs with 95% CIs for all outcomes by comparing the potent P2Y12 inhibitors with clopidogrel. A random-effects model was used regardless of interstudy heterogeneity because it allows a more conservative assessment of the pooled effect size. Significant heterogeneity was considered to be present when the I^2 index was greater than 50% or $P < .05$ for heterogeneity. Publication bias was assessed by using funnel plots.

Results

This study identified 11 eligible RCTs (Fig. 1), for a total of 37,268 patients from analyses of the DISPERSE-2,[23]

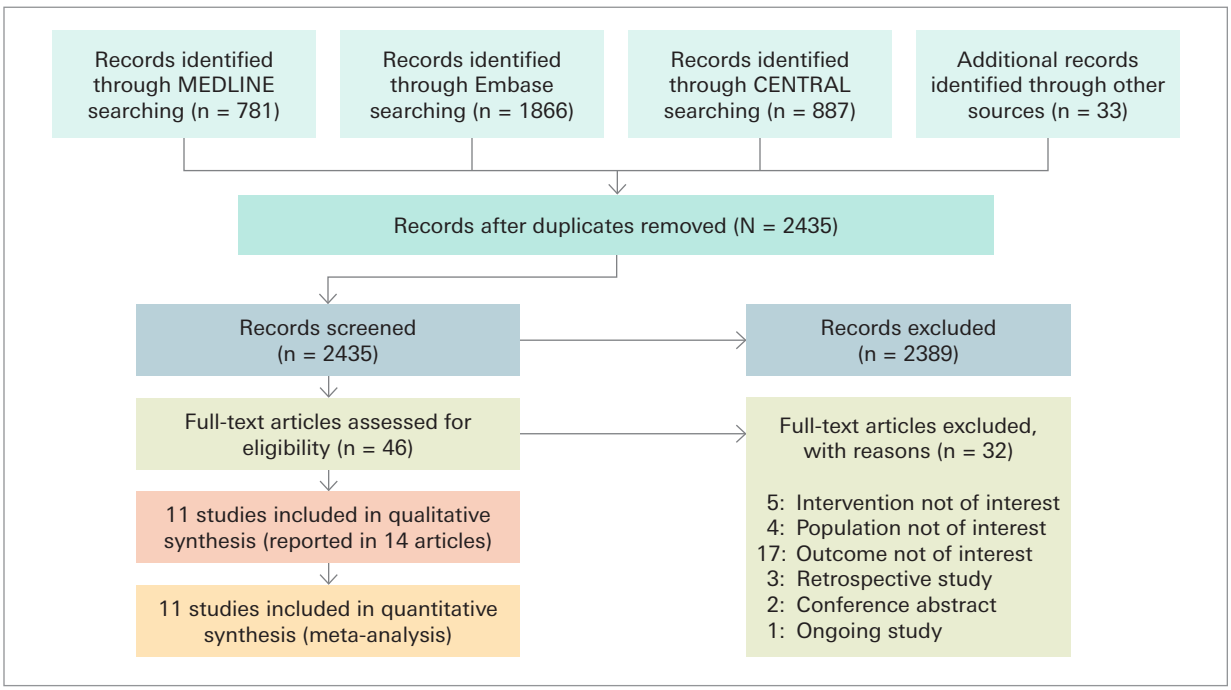

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study selection process.

TRITON-TIMI 38,[9,24] PLATO,[10,25] TRILOGY ACS,[26] PRASFIT-ACS,[27] PHILO,[28] PRAGUE-18,[29] Elderly ACS II,[30] ISAR-REACT 5,[11,12] TICAKOREA,[31] and POPular AGE trials.[32] Four trials compared prasugrel and clopidogrel, 4 trials compared ticagrelor and clopidogrel, 2 trials compared prasugrel and ticagrelor, and 1 trial compared clopidogrel with other potent P2Y12 inhibitors (prasugrel, 5%; ticagrelor, 95%). The median follow-up period of the included studies ranged from 3 to 30 months.

Patients' Baseline Characteristics

The demographics of the patients with NSTE-ACS in each trial are summarized in Table I.[9-12,23-32] The median age ranged from 61 to 77 years, and the percentage of men ranged from 60% to 75%. A reduced maintenance dose of prasugrel (3.75-5 mg daily) was administered to patients who were 75 years of age or older or weighed less than 60 kg in the TRILOGY ACS, PRAGUE-18, ISAR-REACT 5, and POPular AGE trials. Details of the baseline demographics of patients with NSTE-ACS in the PRASFIT ACS, PHILO, PRAGUE-18, and TICAKOREA trials were not available. The baseline characteristics of all patients, including patients with STEMI and not limited to the NSTE-ACS population, in each trial are summarized in Supplemental Table I. The Elderly ACS II and POPular AGE trials mainly included older patients (ie, patients whose mean age was greater than that in other studies). Most patients underwent invasive management for their index events, except for those in the TRILOGY ACS trial, which excluded patients who underwent PCI. Approximately half of the patients received bare-metal stents in 4 trials (DISPERSE-2, TRITON-TIMI 38, PLATO, and PRASFIT ACS). All studies defined MACE as a composite of CV death, MI, and stroke, except for the ISAR-REACT 5 trial (which defined it as a composite of death, MI, and stroke) and Elderly ACS II (which defined it as a composite of death, MI, disabling stroke, and rehospitalization for CV causes or bleeding) (Supplemental Table II). All the studies were considered to have a low risk of bias (Supplemental Fig. 1).

Network Meta-Analysis

MACE

Compared with ticagrelor, prasugrel was not associated with a reduced risk of MACE (HR, 0.83; 95% CI, 0.66-1.04). Prasugrel was associated with a decreased risk of MACE (HR, 0.84; 95% CI, 0.71-0.99; $P = .04$) compared with clopidogrel. Significant heterogeneity ($I^2 = 51.4\%$; $P = .07$) and inconsistencies ($P = .02$) were noted (Fig. 2). The P-score analysis confirmed that prasugrel was most likely the best treatment for the primary end point because it had a significantly higher P-score (0.97) than did ticagrelor (P-score = 0.29) or clopidogrel (P-score = 0.24).

All-Cause Death

There was no significant difference among any P2Y12 inhibitors for the risk of all-cause mortality. Considerable heterogeneity ($I^2 = 56.7\%$; $P = .33$) and inconsistencies ($P = .03$) were observed (Supplemental Fig. 2). The P-scores were 0.78, 0.47, and 0.25 for prasugrel, ticagrelor, and clopidogrel, respectively.

Cardiovascular Death

There was no significant difference in CV death between the prasugrel and ticagrelor groups. Ticagrelor was associated with a reduced risk of CV death compared with clopidogrel (HR, 0.79; 95% CI, 0.66-0.94; $P < .01$), without significant heterogeneity ($I^2 = 0\%$; $P = .70$) (Supplemental Fig. 3). Ticagrelor was most likely the best treatment (P-score = 0.97), followed by prasugrel (P-score = 0.44) and clopidogrel (P-score = 0.09).

Myocardial Infarction

There was no significant difference in MI between prasugrel and ticagrelor. Prasugrel was associated with a decreased risk of MI (HR, 0.82; 95% CI, 0.68-0.99; $P = .04$) compared with clopidogrel. There was significant heterogeneity ($I^2 = 52.4\%$; $P = .10$) without significant inconsistency ($P = .13$) (Supplemental Fig. 4). The P-scores were 0.89, 0.50, and 0.11 for prasugrel, ticagrelor, and clopidogrel, respectively.

Stroke

There was no significant difference among the P2Y12 inhibitors in the risk of stroke, and there was no significant heterogeneity ($I^2 = 0\%$; $P = .54$) or inconsistency ($P = .95$) (Supplemental Fig. 5). The P-scores were 0.60, 0.45, and 0.44 for prasugrel, ticagrelor, and clopidogrel, respectively.

Major Bleeding

There was no significant difference in major bleeding between the prasugrel and ticagrelor groups. Ticagrelor was associated with an increased risk of major bleed-

TABLE I. Characteristics of Patients With NSTE-ACS in Each Trial

	DISPERSE-2[23]		TRITON-TIMI 38[9,24]				PLATO[10,25]		TRILOGY ACS[26]		PRASFIT-ACS[27]		PHILO[28]		PRAGUE-18[29]		Elderly ACS II[30]		ISAR-REACT 5[11,12]		TICAKOREA[31]		POPular AGE[32]	
ACS type	NSTE-ACS		Unstable angina		NSTEMI		NSTE-ACS		NSTE-ACS		NSTE-ACS		NSTE-ACS		NSTEMI		NSTEMI		NSTE-ACS		NSTE-ACS		NSTE-ACS	
Medication	T	C	P	C	P	C	T	C	P	C	P	C	T	C	P	T	P	C	T	P	T	C	C	T or P
Loading dose, mg	0 or 270	300	60	300	60	300	180	300	30	300	20	300	180	300	60	180	30	300 or 600	180	60	180	600	300 or 600	P: 60 T: 180
Maintenance dose, mg	90 or 180 2×/d	75 1×/d	10 1×/d	75 1×/d	10 1×/d	75 1×/d	90 2×/d	75 1×/d	5/10 1×/d[a]	75 1×/d	3.75 1×/d	75 1×/d	90 2×/d	75 1×/d	5/10 1×/d[a]	90 2×/d	5 1×/d	75 1×/d		5/10 1×/d[a]	90 2×/d	75 1×/d	75 1×/d	P: 5/10 1×/d[a] T: 90 2×/d
DAPT duration, mo	1-3		6-15				12		≤30		6-12		6-12		12		12		12		12		12	
DAPT duration, median (IQR), mo	1.9		NA				NA		14.8 (8.2-23.6)		NA		NA		12		NA		NA		NA		12	10.7
Patients, No.	657	327	1,271	1,257	3,771	3,770	5,581	5,499	4,663	4,663	343	337	185	183	36	36	415	433	1,179	1,186	230	244	500	502
Age, mean (SD) or mean (IQR), y	64 (12), 63 (11)	62 (11.0)	62 (11)	62 (11)	61 (11)	61 (11)	64 (56-72)	64 (56-72)	66 (58-74)	66 (59-73)	NA		NA		NA		NA		66.0 (11.7)	65.6 (12.0)	NA		77 (73-81)	77 (73-82)
BMI, mean (SD) or mean (IQR)	28 (5.4), or 29 (5.1)	29 (5.0)	NA				27.5 (24.8-30.8)	27.4 (24.8-30.5)	NA		NA		NA		NA		NA		27.9 (4.73)	27.9 (4.52)	NA		26.7 (4.0)	26.9 (4.2)
Weight <60 kg, %	NA		NA				7.2	7.1	15.2	14.9	NA		NA		NA		NA		5.71	4.75	NA		7	6
Male, %	63.2	66.4	71.0	68.9	74.7	73.3	68.7	68.2	60.8	60.9	NA		NA		NA		NA		75.7	74.5	NA		63	65
HTN, %	NA		73.4	74.2	67.9	67.8	70.2	69.8	81.9	82.0	NA		NA		NA		NA		77.7	75.0	NA		73	73
HLD, %	NA		NA				51.8	51.9	59.0	59.3	NA		NA		NA		NA		64.5	64.7	NA		65	65
Diabetes, %	24.4	24.8	26.8	24.6	24.0	24.3	28.9	27.7	37.7	38.3	NA		NA		NA		NA		25.2	23.9	NA		29	30
Smoker, %	NA	NA	NA	NA	NA	NA	29.4	29.9	19.7	20.2	NA		NA		NA		NA		28.7	28.2	NA		14	13
Previous MI, %	24.2	27.8	25.9	26.1	19.2	18.5	25.1	25.7	42.9	43.3	NA		NA		NA		NA		18.0	19.5	NA		24	27
Previous PCI, %	14.3	17.1	20.7	21.1	14.0	14.4	16.9	16.7	25.6	26.7	NA		NA		NA		NA		28.1	28.9	NA		20	24
Previous CABG, %	8.2	11.0	11.6	10.9	9.3	8.5	7.1	7.8	15.2	16.1	NA		NA		NA		NA		7.46	9.11	NA		17	17

Continued

TABLE I. Characteristics of Patients With NSTE-ACS in Each Trial (continued)

	DISPERSE-2[23]	TRITON-TIMI 38[9,24]		PLATO[10,25]		TRILOGY ACS[26]		PRASFIT-ACS[27]	PHILO[28]	PRAGUE-18[29]	Elderly ACS II[30]	ISAR-REACT 5[11,12]		TICAKOREA[31]	POPular AGE[32]	
Diagnosis																
STEMI, %	0	0	0	8.1	8.0	0	0	NA	NA	NA	NA	0	0	NA	0	0
NSTEMI, %	62	0	100	64.8	64.3	70.4	69.4	NA	NA	NA	NA	78.9	78.0	NA	86	86
Unstable angina, %	38	100	0	27.1	27.8	29.6	30.6	NA	NA	NA	NA	21.1	22.0	NA	11	11
Procedure																
Coronary angiography, %	67	NA	NA	74.5	74.2	41.2	41.4	NA	NA	NA	NA	99.3	99.6	100 100	88	90
PCI, %	42	99.1		46.4	46.4	0	0	NA	NA	NA	NA	76.3	77.0	NA	46	48
DES, %	19.2	NA		NA		0	0	NA	NA	NA	NA	66.9	69.1	NA	94	93
BMS, %	20.2	NA		NA		0	0	NA	NA	NA	NA	0.2	0.3	NA	1	3
CABG, %	9	0.3		5.3	5.5	NA		NA	NA	NA	NA	3.59	2.78	NA	16	17

ACS, acute coronary syndrome; BMI, body mass index; BMS, bare-metal stent; C, clopidogrel; CABG, coronary artery bypass graft; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; HLD, hyperlipidemia; HTN, hypertension; MI, myocardial infarction; NA, not available; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; NSTEMI, non–ST-segment elevation myocardial infarction; P, prasugrel; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; T, ticagrelor.

[a] Prasugrel was continued at a maintenance dose of 10 mg once per day, which was adjusted to 5 mg for patients who were 75 years of age or older or weighed less than 60 kg.

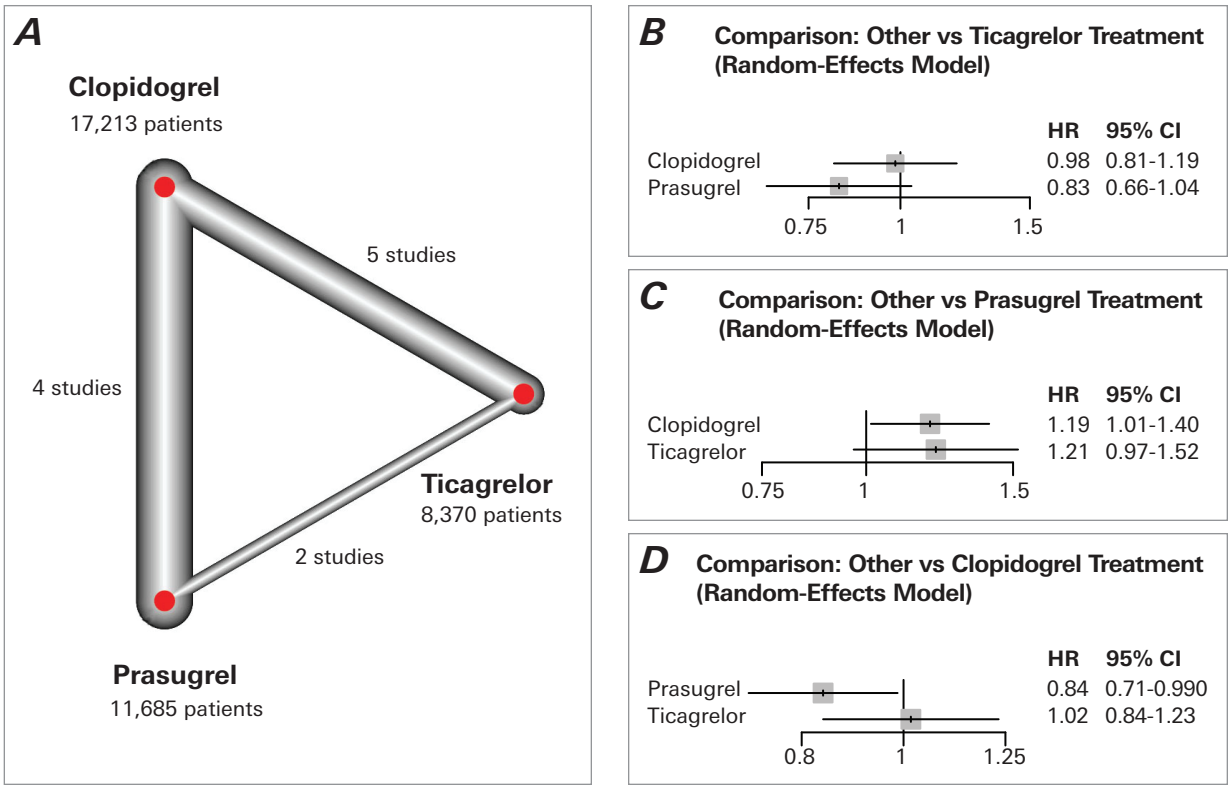

Fig. 2 Network meta-analysis of MACE (random-effects model). The figure presents each treatment arm's hazard ratio and 95% CI. **A**) Network plot of P2Y12 inhibitor regimens. **B**) Forest plot comparing other inhibitors with ticagrelor, showing no significant difference between other inhibitors and ticagrelor. **C**) Forest plot comparing other inhibitors and prasugrel. **D**) Forest plot comparing other inhibitors with clopidogrel, showing that prasugrel is associated with a decreased risk of MACE vs clopidogrel.

HR, hazard ratio; MACE, major adverse cardiac events.

ing compared with clopidogrel (HR, 1.33; 95% CI, 1.00-1.77; $P=.049$). Prasugrel was not associated with an increased risk of major bleeding compared with clopidogrel (HR, 1.30; 95% CI, 0.97-1.74; $P=.08$). No significant heterogeneity ($I^2=41.1\%$; $P=.09$) or inconsistency ($P=.68$) was noted (Fig. 3). The P-scores were 0.97, 0.30, and 0.23 for clopidogrel, prasugrel, and ticagrelor, respectively.

Sensitivity Analysis

The use of potent P2Y12 inhibitors was associated with decreased risks of MACE (HR, 0.90; 95% CI, 0.81-1.00; $P=.04$), CV death (HR, 0.88; 95% CI, 0.79-0.98; $P=.02$), and MI (HR, 0.86; 95% CI, 0.76-0.96; $P<.01$) vs clopidogrel. The use of potent P2Y12 inhibitors was associated with an increased risk of major bleeding (HR, 1.31; 95% CI, 1.05-1.65; $P=.02$). There were no significant differences in the risks of all-cause mortality (HR, 0.87; 95% CI, 0.74-1.03; $P=.10$) or stroke (HR, 0.98; 95% CI, 0.80-1.20; $P=.85$) between the potent P2Y12 inhibitors and clopidogrel. There was also no significant heterogeneity in these outcomes among the studies (Supplemental Fig. 6). Funnel plots were used to evaluate publication bias; no significant publication bias was observed for any of the outcomes assessed (Supplemental Fig. 7).

Discussion

The key findings of this meta-analysis of the efficacy and safety of various P2Y12 inhibitors in patients with NSTE-ACS are as follows: (1) There was no significant difference between prasugrel and ticagrelor in any end point, although the P-score analysis demonstrated that prasugrel had a higher probability of being a better treatment than ticagrelor for all end points, except CV death; (2) prasugrel was associated with a reduced risk of MACE and MI vs clopidogrel; and (3) ticagrelor

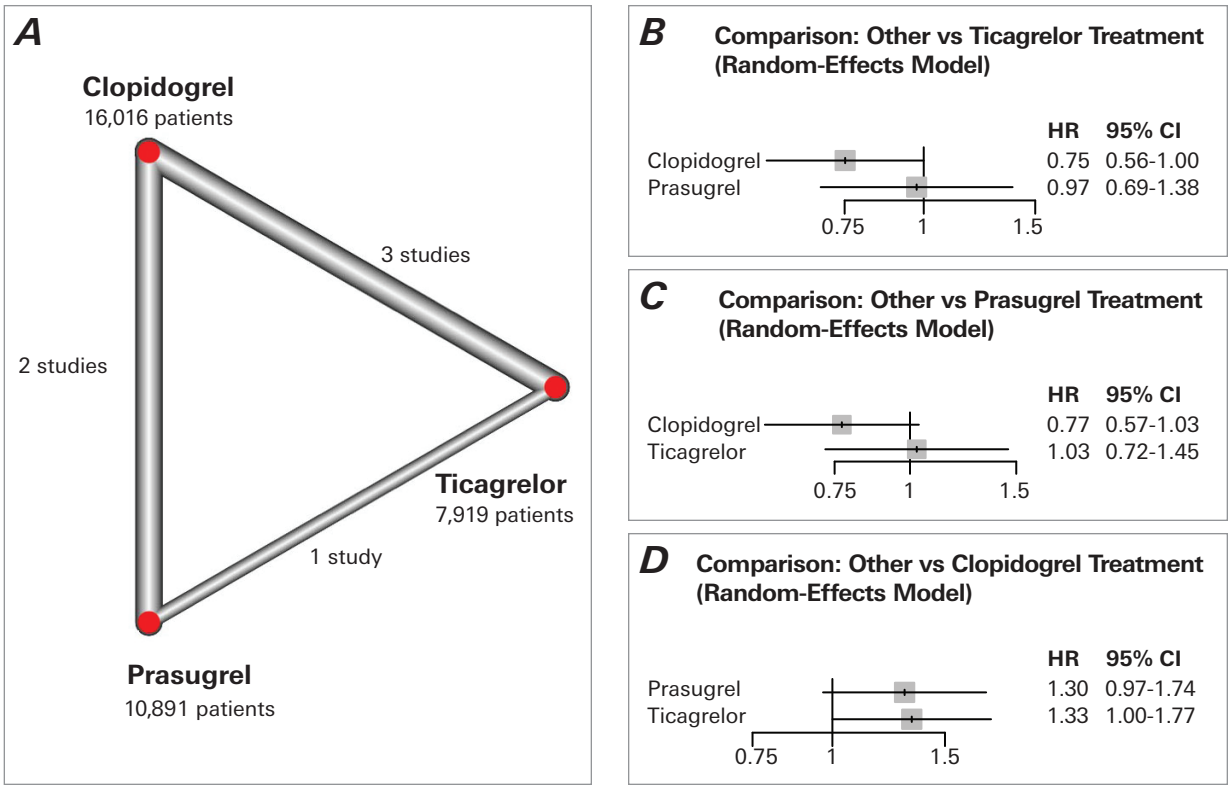

Fig. 3 Network meta-analysis of major bleeding (random-effects model). The figure presents each treatment arm's HR and 95% CI. **A**) Network plot of P2Y12 inhibitor regimens. Forest plots comparing **B**) other inhibitor with ticagrelor, **C**) other inhibitor with prasugrel, and **D**) other inhibitor with clopidogrel show that ticagrelor is associated with an increased risk of major bleeding compared with clopidogrel ($P = .049$).

HR, hazard ratio.

was associated with a reduced risk of CV death and an increased risk of major bleeding vs clopidogrel.

The ISAR-REACT 5 trial compared prasugrel and ticagrelor in 4,018 patients with ACS (NSTE-ACS and STEMI) for whom invasive management was planned; it demonstrated that prasugrel was superior to ticagrelor at reducing the combined 1-year risk of death, MI, and stroke without increasing the risk of bleeding.[12] Fewer MI events in the prasugrel group primarily drove this result. A post hoc subgroup analysis of the ISAR-REACT 5 trial showed the same results in patients with NSTE-ACS.[11] In contrast, a small subgroup analysis of 72 patients with NSTEMI in the PRAGUE-18 trial showed no significant differences between prasugrel and ticagrelor for MACE—a composite of CV death, MI, and stroke—and bleeding outcomes during the first year after MI.[29] In real-world patients with ACS, a retrospective study using the SWEDEHEART registry demonstrated that prasugrel and ticagrelor had similar efficacy and safety.[14] Although studies are limited, the current European Society of Cardiology guidelines recommend prasugrel over ticagrelor for patients with NSTE-ACS who require PCI based on the ISAR-REACT 5 trial findings.[13] The current large-scale network meta-analysis provided essential insight into the limited evidence of selecting P2Y12 inhibitors among patients with NSTE-ACS.

This study demonstrates that patients with NSTE-ACS have better outcomes after treatment with potent P2Y12 inhibitors for ischemic events. The rationale for this finding is clear: novel, potent P2Y12 inhibitors have more reliable pharmacologic properties.[2] Despite the absence of a statistically significant difference between prasugrel and ticagrelor for each end point, P-score analysis suggested that prasugrel has a greater chance of being the best treatment for all ischemic outcomes, except CV death. Recent studies demonstrated that prasugrel was associated with improved endothelial function and better platelet inhibition than ticagrelor in patients with ACS undergoing PCI.[33,34] Furthermore, prasugrel

featured irreversible P2Y12 inhibition and better compliance with once-daily dosing. These differences between the 2 potent P2Y12 inhibitors might explain the further reduction in ischemic end points by prasugrel.

Large registries show that STEMI is less common than NSTE-ACS in older adults (≥75 years of age)[35,36] and that older age and multiple comorbidities are associated with bleeding events.[37] In addition, major bleeding is associated with an increased risk of mortality in patients with NSTE-ACS, similar to ischemic events.[38] The previous meta-analysis of patients with STEMI showed no significant difference in 1-year rates of major bleeding among various P2Y12 inhibitors,[39] whereas the current meta-analysis of patients with NSTE-ACS demonstrated that the use of potent P2Y12 inhibitors increased major bleeding compared with clopidogrel. Bavishi et al[40] previously performed a conventional meta-analysis in patients with NSTE-ACS and reported that bleeding events increased with prasugrel compared with clopidogrel. The current network meta-analysis showed, however, that ticagrelor and prasugrel similarly increased bleeding compared with clopidogrel, although only the ticagrelor vs clopidogrel result showed statistical significance. This discordance may be explained by the inclusion of recent dedicated trials in the current network meta-analysis.

Distinguishing the timing of DAPT administration between NSTE-ACS and STEMI is vital. In patients with STEMI, the use of a potent P2Y12 inhibitor is recommended as early as possible, or at least at the time of primary PCI,[7,8] because patients with STEMI have transmural myocardial ischemia with cell damage caused by a greater thrombus burden than patients with NSTE-ACS, in whom the pathophysiology at the myocardial level is limited to subendocardial ischemia with or without cell damage. In patients with NSTE-ACS, based on the findings of landmark trials such as PLATO[10] and ACCOAST,[41] it has become common practice to perform early loading with ticagrelor at the time of diagnosis or prasugrel administration in catheterization laboratories when the coronary anatomy is known. A large-scale observational study of 64,857 patients with NSTE-ACS, however, demonstrated that pretreatment with P2Y12 antagonists was associated with an increased risk of bleeding without improved efficacy outcomes,[42] whereas the ISAR-REACT 5 trial showed the superiority of prasugrel over ticagrelor treatment with a pretreatment strategy.[12] The current European Society of Cardiology guidelines recommend against pretreatment with P2Y12 inhibitors for patients with NSTE-ACS in whom the coronary anatomy is unknown and early invasive management is planned.[13] In our analysis, the bleeding risks associated with pretreatment may explain the increased risk of major bleeding in the ticagrelor group.

In addition, the dose arrangement available for prasugrel may partially explain the absence of a statistically significant difference in the risk of major bleeding between the prasugrel and clopidogrel groups in our analysis. The TRITON-TIMI 38 trial[9,24] showed no net clinical benefit of prasugrel vs clopidogrel in patients 75 years of age or older or those with a lower body weight (<60 kg) because of high rates of bleeding events; therefore, a reduced dosage of prasugrel is recommended for these patients. In contrast, in the PLATO trial,[10,25] bleeding complications occurred more frequently with ticagrelor than with clopidogrel in patients 75 years of age or older, but the superiority of ticagrelor in terms of ischemic end points was not age dependent; therefore, dose reduction of ticagrelor is not recommended.

This study has several limitations. First, it was a meta-analysis of trial-level data; thus, differences in trial designs, compared treatment regimens, and individual patient data were not fully accounted for. Second, there were insufficient data to evaluate differences within the P2Y12 inhibitor group. Third, the medication dose used or compliance with each treatment strategy was not considered. Fourth, the definitions of end points (MACE and bleeding events) varied across studies. Finally, despite the high-quality designs of the RCTs included in this analysis, significant heterogeneity and inconsistencies were noted in several end points. This heterogeneity could be the result of interstudy differences in designs, patient populations, and treatment strategies. Therefore, these results should be interpreted with caution. A P-score analysis was used to rank the P2Y12 inhibitors.

Conclusion

The present network meta-analysis demonstrated that prasugrel and ticagrelor had comparable effects in terms of efficacy end points. Nevertheless, prasugrel showed the highest probability of being the best treatment for reducing the primary end point, and no significant difference in bleeding was observed between prasugrel and ticagrelor. These findings align with the current guidelines' rationale but suggest a more neutral stance regarding the preferential use of prasugrel over ticagre-

lor. This study highlights the need for further studies to investigate optimal P2Y12 inhibitor selection in patients with NSTE-ACS. For instance, more large-scale multiethnic studies and novel trials assessing the efficacy of new DAPT strategies (ie, short DAPT, precision medicine–guided DAPT, P2Y12 inhibitor monotherapy, and P2Y12 inhibitor deescalation) are warranted.

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References

1. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2016;68(10):1082-1115. doi:10.1016/j.jacc.2016.03.513
2. Valgimigli M, Bueno H, Byrne RA, et al; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 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(3):213-260. doi:10.1093/eurheartj/ehx419
3. Mangieri A, Gallo F, Sticchi A, et al. Dual antiplatelet therapy in coronary artery disease: from the past to the future prospective. *Cardiovasc Interv Ther.* 2020;35(2):117-129. doi:10.1007/s12928-020-00642-w
4. Saito Y, Kobayashi Y, Tanabe K, Ikari Y. Antithrombotic therapy after percutaneous coronary intervention from the Japanese perspective. *Cardiovasc Interv Ther.* 2020;35(1):19-29. doi:10.1007/s12928-019-00633-6
5. Puymirat E, Simon T, Cayla G, et al; USIK, USIC 2000, and FAST-MI investigators. Acute myocardial infarction: changes in patient characteristics, management, and 6-month outcomes over a period of 20 years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. *Circulation.* 2017;136(20):1908-1919. doi:10.1161/CIRCULATIONAHA.117.030798
6. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;64(24):e139-e228. doi:10.1016/j.jacc.2014.09.017
7. Ibanez B, James S, Agewall S, et al; ESC Scientific Document Group. 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.* 2017;39(2):119-177. doi:10.1093/eurheartj/ehx393
8. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;61(4):e78-e140. doi:10.1016/j.jacc.2012.11.019
9. Wiviott SD, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357(20):2001-2015. doi:10.1056/NEJMoa0706482
10. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361(11):1045-1057. doi:10.1056/NEJMoa0904327
11. Valina C, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol.* 2020;76(21):2436-2446. doi:10.1016/j.jacc.2020.09.584
12. Schüpke S, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med.* 2019;381(16):1524-1534. doi:10.1056/NEJMoa1908973
13. Collet JP, Thiele H, Barbato E, et al; ESC Scientific Document Group. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021;42(14):1289-1367. doi:10.1093/eurheartj/ehaa575
14. Venetsanos D, Träff E, Erlinge D, et al. Prasugrel versus ticagrelor in patients with myocardial infarction undergoing percutaneous coronary intervention. *Heart.* 2021;107(14):1145-1151. doi:10.1136/heartjnl-2020-318694
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.* 2009;151(4):W65-W94. doi:10.7326/0003-4819-151-4-200908180-00136
16. Kuno T, Takagi H, Ando T, et al. Oral anticoagulation for patients with atrial fibrillation on long-term hemodialysis. *J Am Coll Cardiol.* 2020;75(3):273-285. doi:10.1016/j.jacc.2019.10.059
17. Takagi H, Hari Y, Nakashima K, Kuno T, Ando T; ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. Meta-analysis for impact of statin on mortality after transcatheter aortic valve implantation. *Am J Cardiol.* 2019;124(6):920-925. doi:10.1016/j.amjcard.2019.05.069
18. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898. doi:10.1136/bmj.l4898
19. Neupane B, Richer D, Bonner AJ, Kibret T, Beyene J. Network meta-analysis using R: a review of currently available automated packages. *PLoS One.* 2014;9(12):e115065. doi:10.1371/journal.pone.0115065

20. Rücker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods.* 2012;3(4):312-324. doi:10.1002/jrsm.1058
21. You R, Cao YS, Huang PY, et al. The changing therapeutic role of chemo-radiotherapy for loco-regionally advanced nasopharyngeal carcinoma from two/three-dimensional radiotherapy to intensity-modulated radiotherapy: a network meta-analysis. *Theranostics.* 2017;7(19):4825-4835. doi:10.7150/thno.21815
22. Ribassin-Majed L, Marguet S, Lee AWM, et al. What is the best treatment of locally advanced nasopharyngeal carcinoma? An individual patient data network meta-analysis. *J Clin Oncol.* 2017;35(5):498-505. doi:10.1200/JCO.2016.67.4119
23. Cannon CP, Husted S, Harrington RA, et al; DISPERSE-2 Investigators. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol.* 2007;50(19):1844-1851. doi:10.1016/j.jacc.2007.07.053
24. De Servi S, Goedicke J, Schirmer A, Widimsky P. Clinical outcomes for prasugrel versus clopidogrel in patients with unstable angina or non-ST-elevation myocardial infarction: an analysis from the TRITON-TIMI 38 trial. *Eur Heart J Acute Cardiovasc Care.* 2014;3(4):363-372. doi:10.1177/2048872614534078
25. Lindholm D, Varenhorst C, Cannon CP, et al. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. *Eur Heart J.* 2014;35(31):2083-2093. doi:10.1093/eurheartj/ehu160
26. Roe MT, Armstrong PW, Fox KA, et al; TRILOGY ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med.* 2012;367(14):1297-1309. doi:10.1056/NEJMoa1205512
27. Saito S, Isshiki T, Kimura T, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: the PRASFIT-ACS study. *Circ J.* 2014;78(7):1684-1692. doi:10.1253/circj.cj-13-1482
28. Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome—randomized, double-blind, phase III PHILO study. *Circ J.* 2015;79(11):2452-2460. doi:10.1253/circj.CJ-15-0112
29. Motovska Z, Hlinomaz O, Kala P, et al; PRAGUE-18 Study Group. 1-year outcomes of patients undergoing primary angioplasty for myocardial infarction treated with prasugrel versus ticagrelor. *J Am Coll Cardiol.* 2018;71(4):371-381. doi:10.1016/j.jacc.2017.11.008
30. Savonitto S, Ferri LA, Piatti L, et al; Elderly ACS 2 Investigators. Comparison of reduced-dose prasugrel and standard-dose clopidogrel in elderly patients with acute coronary syndromes undergoing early percutaneous revascularization. *Circulation.* 2018;137(23):2435-2445. doi:10.1161/CIRCULATIONAHA.117.032180
31. Park DW, Kwon O, Jang JS, et al; TICAKOREA Investigators. Clinically significant bleeding with ticagrelor versus clopidogrel in Korean patients with acute coronary syndromes intended for invasive management: a randomized clinical trial. *Circulation.* 2019;140(23):1865-1877. doi:10.1161/CIRCULATIONAHA.119.041766
32. Gimbel M, Qaderdan K, Willemsen L, et al. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. *Lancet.* 2020;395(10233):1374-1381. doi:10.1016/S0140-6736(20)30325-1
33. Schnorbus B, Daiber A, Jurk K, et al. Effects of clopidogrel vs. prasugrel vs. ticagrelor on endothelial function, inflammatory parameters, and platelet function in patients with acute coronary syndrome undergoing coronary artery stenting: a randomized, blinded, parallel study. *Eur Heart J.* 2020;41(33):3144-3152. doi:10.1093/eurheartj/ehz917
34. Mayer K, Bongiovanni D, Karschin V, et al. Ticagrelor or prasugrel for platelet inhibition in acute coronary syndrome patients: the ISAR-REACT 5 trial. *J Am Coll Cardiol.* 2020;76(21):2569-2571. doi:10.1016/j.jacc.2020.09.586
35. Alexander KP, Newby LK, Armstrong PW, et al; American Heart Association Council on Clinical Cardiology; Society of Geriatric Cardiology. Acute coronary care in the elderly, part II: ST-segment-elevation myocardial infarction: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation.* 2007;115(19):2570-2589. doi:10.1161/CIRCULATIONAHA.107.182616
36. Alexander KP, Newby LK, Cannon CP, et al; American Heart Association Council on Clinical Cardiology; Society of Geriatric Cardiology. Acute coronary care in the elderly, part I: non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation.* 2007;115(19):2549-2569. doi:10.1161/CIRCULATIONAHA.107.182615
37. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. *Circulation.* 2019;140(3):240-261. doi:10.1161/CIRCULATIONAHA.119.040167
38. Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *Eur Heart J.* 2017;38(11):804-810. doi:10.1093/eurheartj/ehw525
39. Rafique AM, Nayyar P, Wang TY, et al. Optimal P2Y12 inhibitor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a network meta-analysis. *JACC Cardiovasc Interv.* 2016;9(10):1036-1046. doi:10.1016/j.jcin.2016.02.013
40. Bavishi C, Panwar S, Messerli FH, Bangalore S. Meta-analysis of comparison of the newer oral P2Y12 inhibitors (prasugrel or ticagrelor) to clopidogrel in patients with non-ST-elevation acute coronary syndrome. *Am J Cardiol.* 2015;116(5):809-817. doi:10.1016/j.amjcard.2015.05.058
41. Montalescot G, Bolognese L, Dudek D, et al; ACCOAST Investigators. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med.* 2013;369(11):999-1010. doi:10.1056/NEJMoa1308075
42. Dworeck C, Redfors B, Angerås O, et al. Association of pretreatment with P2Y12 receptor antagonists preceding percutaneous coronary intervention in non-ST-segment elevation acute coronary syndromes with outcomes. *JAMA Netw Open.* 2020;3(10):e2018735. doi:10.1001/jamanetworkopen.2020.18735