JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 10, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.02.013

Optimal $P2Y_{12}$ Inhibitor in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

A Network Meta-Analysis

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ABSTRACT

OBJECTIVES The study sought to compare the clinical efficacy and safety of $P2Y_{12}$ inhibitors in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous intervention (PPCI).

BACKGROUND Limited data exist regarding the comparative efficacy and safety of $P2Y_{12}$ inhibitors in STEMI patients undergoing PPCI.

METHODS Clinical trials enrolling STEMI patients were identified and relevant data was extracted. Major adverse cardiovascular events (MACE) were defined as the composite of all cause mortality, MI, and target vessel revascularization. Network meta-analysis was performed using Bayesian methods.

RESULTS A total of 37 studies with 88,402 STEMI patients and 5,077 MACE were analyzed. Outcomes at 1 month (22 studies and 60,783 patients) suggest that prasugrel was associated with: lower MACE than clopidogrel (standard dose odds ratio [OR]: 0.59, 95% confidence interval [CI]: 0.50 to 0.69; high-dose OR: 0.60, 95% CI: 0.51 to 0.71; upstream OR: 0.79, 95% CI: 0.66 to 0.94), and ticagrelor (standard dose OR: 0.69, 95% CI: 0.56 to 0.84; upstream OR: 0.72, 95% CI: 0.50 to 1.05); lower mortality and MI than clopidogrel and standard ticagrelor; lower stroke risk than standard clopidogrel and standard or upstream ticagrelor; and lower stent thrombosis than standard or upstream clopidogrel. At 1-year (10 studies, n = 40,333) prasugrel was associated with lower mortality and MACE than other $P2Y_{12}$ inhibitors. MACE was particularly lower with prasugrel in studies where patients received bivalirudin, drug-eluting stents, and but not glycoprotein IIb/IIIa inhibitor.

CONCLUSIONS In STEMI patients undergoing PPCI, prasugrel and ticagrelor are more efficacious than clopidogrel; in addition, prasugrel was superior to ticagrelor particularly in conjunction with bivalirudin and drug-eluting stents. (J Am Coll Cardiol Intv 2016;9:1036–46) © 2016 by the American College of Cardiology Foundation.

Rapid, reliable, and potent inhibition of $P2Y_{12}$ receptors in ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous intervention (PPCI) is critical to reduce ischemic events including stent thrombosis (ST) (1-3). American College of Cardiology Foundation/American Heart Association 2013 STEMI guidelines give a class IB recommendation to clopidogrel,

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Manuscript received November 30, 2015; revised manuscript received January 25, 2016, accepted February 11, 2016.

prasugrel, and ticagrelor (4). European Society of Cardiology 2012 STEMI guidelines recommend ticagrelor and prasugrel as preferred agents (Class I, Level of Evidence: B); and high-dose clopidogrel as an alternative agent (Class I, Level of Evidence: C) (5). Administration of a high loading dose of clopidogrel (600 mg) is associated with improved outcomes, however, delayed onset of action and variable platelet inhibition due to CYP2C19 polymorphisms remain a concern (6,7). Prasugrel and ticagrelor provide more rapid and potent platelet inhibition compared with clopidogrel, which translates into improved clinical efficacy in patients with acute coronary syndromes (ACS) (8,9). Post hoc analysis of STEMI patients in TRITON-TIMI-38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction-38) and PLATO (Platelet Inhibition and Patient Outcomes) demonstrated improved clinical outcomes with prasugrel and ticagrelor compared to clopidogrel. It is clear that $P2Y_{12}$ inhibition is a critical factor in the treatment of STEMI patients, yet there is no large randomized clinical trial comparing clinical outcomes in STEMI patients treated with various $P2Y_{12}$ inhibitors. Therefore, a network meta-analysis was used to compare the outcomes in STEMI patients undergoing PPCI who were treated with $P2Y_{12}$ inhibitors.

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METHODS

Network meta-analysis compares multiple treatments using both direct comparisons of interventions within trials and indirect comparisons across trials based on a common comparator.

OBJECTIVES, DEFINITIONS, AND STUDY DESIGN. The primary objective of this analysis was to compare outcomes of $P2Y_{12}$ inhibitors in STEMI patients undergoing PPCI. Clopidogrel (standard, high, and upstream) and ticagrelor (standard and upstream), and prasugrel administration was evaluated. A clopidogrel loading of 300 mg was considered standard, and 600 mg was considered high dose. Prasugrel 10 mg daily (60 mg loading dose) and ticagrelor 90 mg bid (180 mg loading dose) were considered standard dose. When data regarding loading dose was not specifically described, it was assumed that a standard dose had been administered.

OUTCOMES. Outcomes analyzed included: all cause mortality, cardiovascular mortality, MI, definite/probable ST, target vessel revascularization (TVR), stroke, and major/minor bleed at in-hospital (2 to 10 days), 1-month, and ≥1-year (12 to 36 months) follow-up. Major adverse cardiovascular events (MACE) were defined as all cause mortality, MI, or TVR. Studies were further stratified based on follow-up duration, bivalirudin use, glycoprotein IIb/IIIa inhibitor (GPI) use, transradial access, and bare-metal (BMS) versus drug-eluting (DES) stent use. Definite or probable ST was based on the academic research consortium definition (10). Major bleeding was based on Thrombolysis In Myocardial Infarction (TIMI) definitions (11).

DATA SOURCE AND STUDY SELECTION. A systematic literature review was performed using the following keywords: STEMI, ACS, MI, PPCI, $P2Y_{12}$ inhibitors, thienopyridines, clopidogrel, prasugrel, and ticagrelor. Two investigators (A.M.R., P.N.) independently reviewed the studies. Conflicts were resolved by consensus and discussion with the senior author (T.H). Authors were contacted to obtain missing data where applicable.

DATA EXTRACTION AND QUALITY ASSESSMENT. Data were collected regarding age, sex, hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, smoking status, prior MI, prior PCI, prior coronary artery bypass grafts, anterior MI, left ventricular ejection fraction, % STEMI patients, % patients undergoing PPCI, follow-up interval, $P2Y_{12}$ inhibitor dose and timing (periprocedural or upstream), bivalirudin use, GPI use, radial access, left main disease, stent type, or balloon angioplasty only

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

DES = drug-eluting stent(s)

GPI = glycoprotein IIb/IIIa inhibitors

MACE = major adverse cardiovascular event(s)

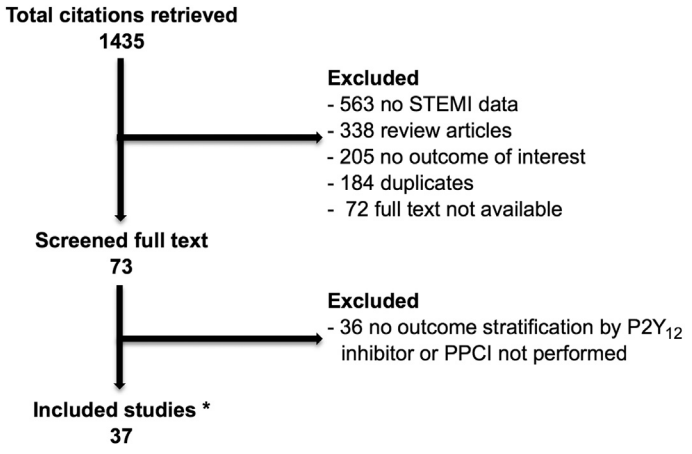
PPCI = primary percutaneous coronary intervention

ST = stent thrombosis

STEMI = ST-segment elevation myocardial infarction

TVR = target vessel revascularization

FIGURE 1 Review Process for Inclusion/Exclusion of Studies



*Included studies are listed in Table 1. PPCI = primary percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

TABLE 1 Baseline Characteristics of Studies Included in Meta-Analysis

Ref. #	First Author/Study; Journal, Year	Enrollment	Study Type	STEMI (%)	Primary Analysis	MACE Endpoints	Available	Bleeding Endpoints	$P2Y_{12}$ Inhibitor	Follow-Up
(1)*	Alexopoulos et al. CCI 2012	2011	RCT	100	Randomization to Pra vs Tic	Death/MI/Stroke/TVR	All	Clinical	Pra/Tic	In-hospital
(2)*	Alexopoulos et al. CDT 2012	2011	RCT	100	Randomization to Clo or Pra if PR >235 2hr post Clo(H)	CV death/MI/Stroke	All	TIMI	Clo(H)/Pra	In-hospital
(3)*	ARMYDA-6 MI; JACC 2011	2011	RCT	100	Randomized to Clo(S) and Clo(H)	Death/MI/TVR/Stroke; Death/MI/TVR	All	TIMI	Clo(S)/Clo(H)	30 days
(4)*	ATACS Zeymer; IJC 2015	2009-2013	Registry	100	Prospective registry of STEMI patients who underwent PCI and received Clo and Pra	Death/MI/Stroke	All	GUSTO	Clo/Pra	In-hospital
(5)*	ATLANTIC;NEJM 2014	2011-2013	RCT	100	Pre-hospital vs. peri-procedure treatment with Tic	Death/MI/TVR/Stroke; ST resolution/Flow <3	Some	PLATO; TIMI; GUSTO; BARC	Tic/Tic(U)	In-hospital; 30 days
(6)*	Austrian Acute PCI; EHJ 2011	2005-2009	Registry	100	Pre-hospital vs. peri-procedure treatment with Clo	Death/MI/Stroke; Death/MI/TVR/Stroke	All	TIMI	Clo/Clo(U)	In-hospital
(7)*	BRAVE 4; EHJ 2014	2009-2013	RCT	100	Pra+Bivalirudin vs. Clo+UFH	Death/MI/TVR/Stroke/Bleed; Death/MI/Stroke/TVR	All	TIMI; HORIZON	Clo(H)/Pra	30 days
(8)*	CHAMPION PCI/STEMI; NEJM 2009	2006-2009	RCT	100	ACS patients randomized to IV cangrelor vs. Clo(H)	Death/MI/TVR	All	GUSTO; TIMI; ACUITY	Clo(H)/Can	2 days; 30 days
(9)*	CHAMPION Phoenix; NEJM 2013	2010-2012	RCT	18	ACS patients randomized to IV cangrelor vs. Clo(S)/Clo(H)	Death/MI/TVR	All	GUSTO	Clo(H)/Clo(S)/Can	2 days; 30 days
(10)*	CIPAMI; Circ 2012	2006-2009	RCT	100	Pre-hospital randomization to Clo(U) 600mg vs. peri-procedure Clo(H) 600mg	Death/MI/TVR	Yes	TIMI	Clo(H)/Clo(U)	In-hospital
(11)*	CRUSADE; AJC 2008	2004-2006	Registry	100	Pre-hospital vs. peri-procedure treatment with Clo and GPI	Death/MI; Death/MI/ADHF	All	TIMI	Clo(S)/Clo(H)/Clo(U)	In-hospital
(12)*	CURRENT OASIS 7 PCI; Lancet 2010	2006-2009	RCT	37	Sub-study of ACS pts randomized to high vs low Clo/Asa	CV death/MI/Stroke	Some	TIMI; CURRENT	Clo(S)/Clo(H)	30 days
(13)*	DeBacker et al. Thrombosis 2015	2009-2014	Obs	100	Pre-hospital administration of $P2Y_{12}$ inhibitors	Death/MI/TVR	All	TIMI; PLATO	Clo/Pra/Tic	In-hospital; 30 days
(14)*	DOUBLE; Thrombosis R 2010	2010	RCT	100	Randomization to 75 vs. 150mg Clo	Death/MI	All	Visible	Clo(S)/Clo(H)	30 days
(15)*	ETAMI; JACC interventions 2015	2014	RCT	92	Randomized comparison of Clo vs Pra	Platelet reactivity	All	TIMI; GUSTO	Clo/Pra	30 days
(16)*	EUROMAX; NEJM 2013	2010-2013	RCT	100	Pre-hosp bivalirudin vs. UFH+GPI	Death/Bleed	Some	TIMI; GUSTO	Clo(H)/Pra/Tic	30 days
(17)*	HEAT PPCI; Lancet 2014	2012-2013	RCT	100	Bivalirudin vs. UFH	Death/MI/TVR/Stroke	Some	BARC	Clo(H)/Pra/Tic	28 days
(18)*	HORIZON AMI; JACC 2009	2005-2007	RCT	100	Bivalirudin vs. UFH+GPI with pre-randomization assignment to Clo(S) vs. Clo(H)	Death/MI/TVR/Stroke	All	TIMI; GUSTO; HORIZON	Clo(S)/Clo(H)	30 days

Continued on the next page

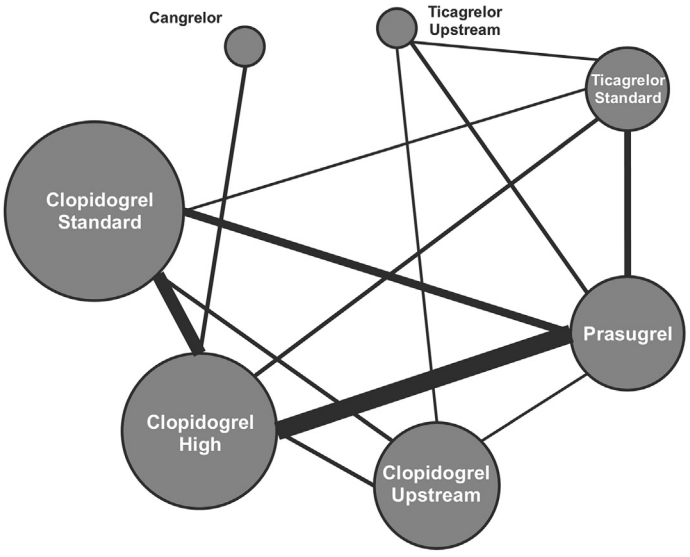
TABLE 1 Continued

Ref. #	First Author/Study; Journal, Year	Enrollment	Study Type	STEMI (%)	Primary Analysis	MACE Endpoints	Available	Bleeding Endpoints	$P2Y_{12}$ Inhibitor	Follow-Up
(19)*	INFUSE AMI; AJC 2014	2009-2011	RCT	100	Treatment with bivalirudin and randomization to IC GPI vs. placebo and +/- aspiration	Death/MI/ADHF; Death/MI/TVR/Stroke	Some	HORIZON	Clo(H)/Pra	30 days; 1 year
(20)*	KAMIR; AHJ 2011	2006-2008	Registry	100	Retrospective evaluation of standard vs. high pre-load Clo	CV Death/MI/TVR; Death/MI/TVR	All	GUSTO	Clo(S)/Clo(H)	In-hospital; 30 days; 1 year
(21)*	Klingenberg et al. Heart 2015	2009-2012	Registry	58	Swiss ACS registry Clo vs. Pra	Death/MI/TVR/Stroke	All	TIMI; GUSTO; BARC	Clo/Pra	1 year
(22)*	Koshy et al. CV Ther. 2014	2008-2011	Obs	100	Retrospective evaluation	Death	Some	Visible	Clo(H)/Pra	In-hospital; 1 year
(23)*	Larson et al. AHJ 2010	2003-2008	Obs	100	Pre-transfer treatment Clo(U) 600mg vs. peri-procedure Clo(H) 600mg	Death/MI; Death/MI/TVR; Death/MI/TVR/Stroke	All	TIMI	Clo(H)/Clo(U)	In-hospital; 30 days; 1 year
(24)*	Lee et al. JCS 2015	2014-2015	RCT	100	Randomization to Pra vs. Tic	Platelet reactivity; CV death/MI/TVR/Stroke	All	-	Pra/Tic	30 days
(25)*	Llera et al. JIC 2013	2007-2012	Obs	100	Retrospective evaluation of STEMI patients undergoing PPCI who received bivalirudin	Death/MI/Stroke	All	TIMI	Clo/Pra	30 days
(26)*	Mangiacapra et al. AJC 2010	2007-2007	Obs	100	Retrospective evaluation of standard vs. high pre-load Clo	Death/MI/TVR	Some	-	Clo(S)/Clo(H)	1 year
(27)*	MULTIPRAC; EHJ 2014	2011-2013	Registry	100	Prospective comparison of Pra vs. Clo	CV death/MI/TVR/Stroke; Death/MI/TVR/Stroke/AKI	All	-	Clo(H)/Clo(S)/Pra	In-hospital
(28)*	PLATO STEMI; Circulation 2010	2008-2008	RCT	100	Sub-study of ACS patients randomized to Pra vs. Tic	CV death/MI/Stroke; CV death/MI/Stroke/Isch.	All	PLATO; TIMI	Clo(S)/Clo(H)/Tic	1 year
(29)*	POBA; JACCi 2013	2013	Registry	30	Evaluation of bleeding predictors	Platelet reactivity	Bleeding	BARC	Clo/Pra	6 months
(30)*	Prometheus; SCAI 2015	2010-2013	Registry	17	Prospective evaluation of patients with ACS undergoing PCI	Death/MI/TVR/Stroke	All	Bleeding req hospitalization	Clo/Pra	30 days; 3 months; 6 months; 1 year
(31)*	RAPID 2; AHJ 2014	2013	RCT	100	Randomization to Pra vs. Tic(H)	Platelet reactivity: Death, CV death, MI	All	TIMI	Pra/Tic	In-hospital
(32)*	RAPID; JACC 2013	2011	RCT	100	Randomization to Pra vs. Tic	Platelet reactivity: Death, CV death, MI	All	TIMI	Pra/Tic	In-hospital
(33)*	Kou et al. EHJ 2011	2003-2008	Registry	100	Pre-hospital vs. peri-procedure treatment with Clo	Death/MI	All	GUSTO	Clo/Clo(U)	30 days; 1 year
(34)*	SCAAR 2010-11; AJC 2014	2010-2011	Registry	35	Retrospective evaluation of ACS registry	Death	All	Visible	Clo/Pra	30 days
(35)*	Song et al. YMJ 2012	2011	Obs	100	Retrospective evaluation of Clo(S) vs. Clo(H)	Death/MI/TVR	All	-	Clo(S)/Clo(H)	30 days; 3 years
(36)*	Translate ACS; AHA 2015	2010-2012	Obs	52	Evaluation of Pra vs. Clo in patients with ACS undergoing PCI	Death/MI/TVR/Stroke; Death/MI/Stroke	All	GUSTO; BARC	Clo/Pra/Tic	1 year
(37)*	TRITON TIMI 38 STEMI; Lancet 2009	2004-2007	RCT	100	Sub-study of ACS patients randomized to Pra vs. Clo	CV death/MI/Stroke; CV death/MI/TVR/Stroke	All	TIMI	Clo(S)/Pra	30 days; 15 months

*Represents references that appear only in the Online Appendix.

ACS = acute coronary syndrome(s); ACUITY = acute catheterization and urgent intervention triage strategy trial; ADHF = acute decompensated heart failure; Asa = aspirin; BARC = bleeding academic research consortium; Clo = clopidogrel; CURRENT = clopidogrel and aspirin optimal dose usage to reduce recurrent events-Seventh organization to assess strategies in ischemic syndromes trial; CV = cardiovascular; GPI = glycoprotein 2b3a inhibitors; GUSTO = global utilization of Streptokinase and Tpa for occluded arteries trial; H = high dose; HORIZON = harmonizing outcomes with revascularization and stents in acute myocardial infarction; IC = intracoronary; IV = intravenous; MI = myocardial infarction; Obs = observational; PCI = percutaneous coronary intervention; PLATO = platelet inhibition and patient outcomes trial; PPCI = primary percutaneous coronary intervention; PR = platelet reactivity; Pra = prasugrel; RCT = randomized controlled trial; S = standard dose; STEMI = ST-segment elevation myocardial infarction; Tic = ticagrelor; TIMI = Thrombolysis In Myocardial Infarction; TVR = target vessel revascularization; U = upstream; UFH = unfractionated heparin.

FIGURE 2 Evidence Network Plot of All Included Studies



and coronary artery bypass grafting, as well as MACE and bleeding outcomes.

INCLUSION/EXCLUSION CRITERIA AND STUDY SELECTION. Randomized and nonrandomized clinical trials enrolling STEMI patients undergoing PPCI with administration of periprocedural $P2Y_{12}$ inhibitor were included. Trials where stratification of outcomes was not available by the type of $P2Y_{12}$ inhibitor were excluded.

STATISTICAL ANALYSIS. WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, and Imperial College School of Medicine, London, United Kingdom) was used for mixed treatment comparison using the Bayesian methods (12). Dichotomous outcomes were compared using posterior median odds ratios and 95% Bayesian confidence intervals. Posterior distributions and network estimates were derived using Gibbs sampling via Markov Chain Monte Carlo simulation. Three chains were fit and checked convergence by assuring Monte Carlo error ≤5% of standard deviation of effect estimates and between-study variance. Convergence and lack of autocorrelation were confirmed after a 50,000 simulation burn-in phase using the Brooks-Gelman-Rubin test. A fixed-effect model was used to minimize the influence on effect size by smaller nonrandomized clinical trials and to reduce the impact of weak informative prior. Forest plots were used to illustrate the median effect estimate and corresponding 95% confidence interval.

RESULTS

EVIDENCE NETWORK. Figure 1 shows the systematic search strategy. A total of 73 full text references were screened and 37 studies were included in the final review (Table 1). The study network plot is shown in Figure 2; further details of the network comparisons are available in Online Table 1.

STUDY CHARACTERISTICS. Major characteristics of the studies including enrollment period (2003 to 2014), primary efficacy endpoints, bleeding definitions (TIMI definition in 19 studies) and follow-up intervals are provided in Table 1. The majority of the trials (n = 29) enrolled only STEMI patients; the other 8 trials reported clinical outcomes in the STEMI cohorts separately.

PATIENT/PROCEDURE CHARACTERISTICS. This analysis included 37 studies with 88,402 STEMI patients and 5,077 MACE events. Baseline demographics across the trials are shown in Online Table 2. The type, dose and timing of antiplatelet agents, and frequency of bivalirudin and GPI use are shown in Online Table 3. Periprocedural characteristics including prevalence of multivessel and left main disease, stent type, radial access and thrombectomy use, pre- and post-PCI TIMI flows are shown in Online Table 4.

IN-HOSPITAL OUTCOMES. In-hospital clinical efficacy end-points analysis included MACE (13 studies with 22,747), mortality (10 studies with 19,438 patients), cardiovascular mortality (3 studies with 1,374 patients), recurrent MI (9 studies with 17,736 patients), probable/definite ST (5 studies with 2,416 patients), and major bleeding (12 studies with 22,215). Prasugrel was associated with lower mortality and MACE than standard or high-dose clopidogrel; lower MACE than upstream clopidogrel and cangrelor but not compared to ticagrelor. Ticagrelor showed a trend to lower MACE than cangrelor. Cangrelor showed a trend to lower in-hospital mortality compared to standard clopidogrel (Online Tables 5 and 6).

ONE-MONTH OUTCOMES. Clinical efficacy end-points analyzed at 1-month included MACE (22 studies with n = 60,783), mortality (21 studies with n = 60,510), cardiovascular mortality (9 studies with n = 17,889), recurrent MI (18 studies with n = 51,629), probable/definite ST (13 studies with n = 29,907), and major bleeding (12 studies with n = 42,084) (Online Table 5). Prasugrel was associated with lower mortality, MI, and MACE than standard, high-dose, or upstream clopidogrel and standard ticagrelor; lower mortality and MACE than upstream ticagrelor; lower stroke risk than standard clopidogrel and standard or upstream ticagrelor; and lower ST than standard or

upstream clopidogrel (**Figures 3A to 3G**). Standard dose ticagrelor showed a trend to lower 1-month mortality and MACE compared to standard dose clopidogrel. There was no significant difference in 1-month rates of cardiac mortality or major bleeding between prasugrel and other $P2Y_{12}$ inhibitors (**Figure 3H**). Limited data was available for cangrelor (2 studies).

ONE-YEAR OUTCOMES. Clinical efficacy endpoints analyzed at 1-year included MACE (10 studies with 40,333 patients), mortality (10 studies with n = 41,766), cardiovascular mortality (3 studies with n = 13,742), recurrent MI (8 studies with n = 39,626), probable/definite ST (6 studies with n = 32,115), and major bleeding (7 studies with n = 23,489) (Online Table 5). Prasugrel was associated with lower mortality, MI, and MACE than standard or high-dose clopidogrel, and lower mortality and MACE than standard ticagrelor, a trend to lower MACE compared to upstream clopidogrel and standard ticagrelor. Prasugrel was associated with lower 1-year MI and TVR rate compared to standard or high dose clopidogrel; and lower ST risk compared to standard and upstream clopidogrel but not compared to ticagrelor (**Figures 4A to 4G**). Standard ticagrelor was also associated with significantly lower 1-year mortality, MI, ST, and MACE compared to standard or high-dose clopidogrel. No long-term follow-up data is available for cangrelor. There was no significant difference in 1-year rates of major bleeding between various $P2Y_{12}$ inhibitors (**Figure 4H**).

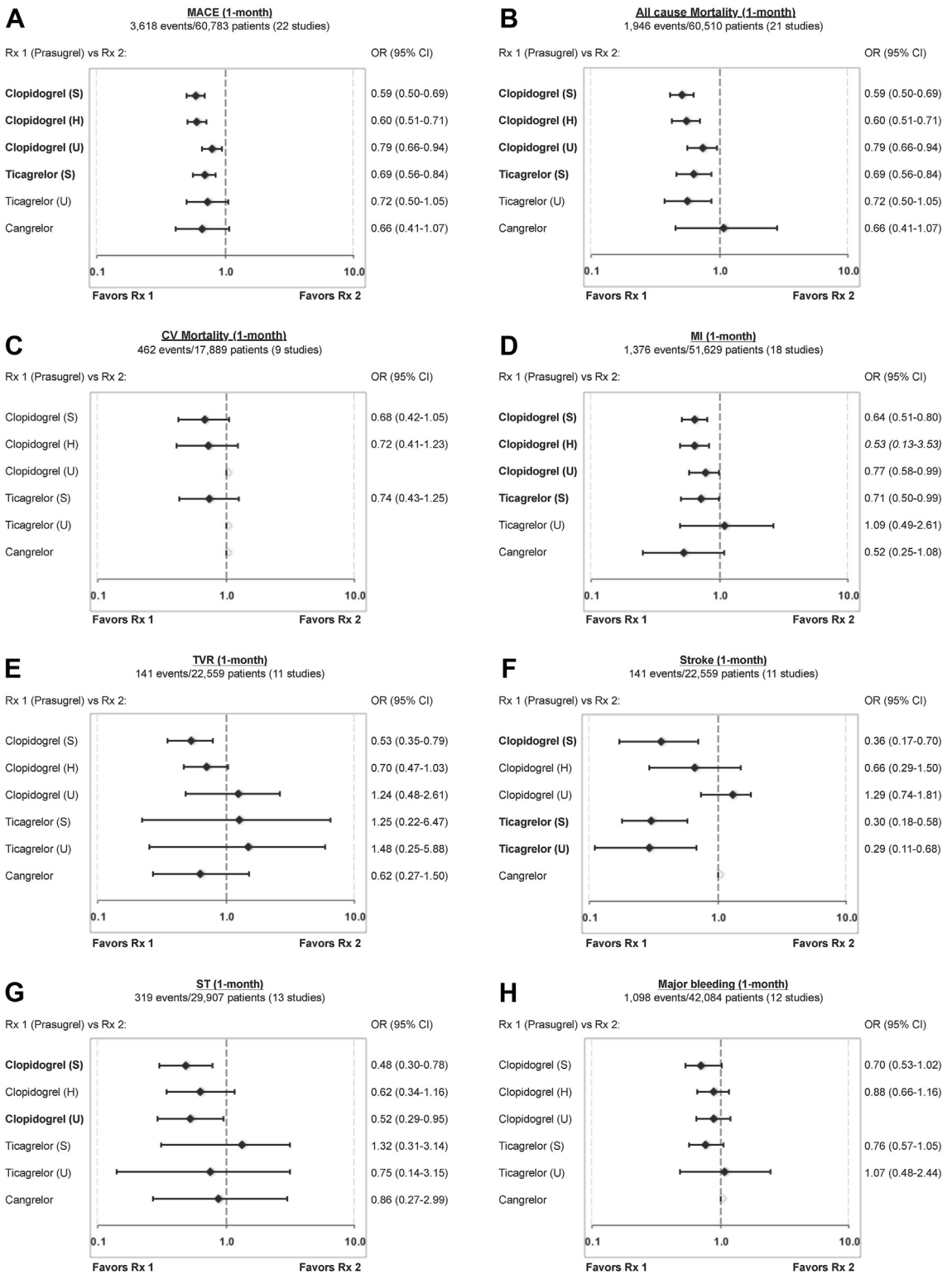
RANDOMIZED TRIALS AND OTHER SUBGROUP ANALYSIS. Analyzing 14 randomized studies, prasugrel was associated with lower 1-month MACE than standard and high-dose clopidogrel, and standard ticagrelor. One-month MACE was further stratified based on: radial access in ≥50% of patients (5 studies), bivalirudin use in ≥50% of patients (10 studies), bivalirudin use in <50% of patients (12 studies), GPI use in ≥50% of patients (7 studies), GPI use in <50% of patients (15 studies), DES use in ≥50% of patients (11 studies), and bare-metal stent use in ≥50% of patients (11 studies). Prasugrel was associated with lower 1-month MACE than standard clopidogrel across all groups; and lower 1-month MACE than high-dose clopidogrel and standard ticagrelor in studies where ≥50% patients: received bivalirudin, did not receive GPIs, and received DES (**Figures 5A to 5H**).

DISCUSSION

This network meta-analysis is the largest study comparing the relative efficacy and safety profile of various $P2Y_{12}$ inhibitors in STEMI patients undergoing PPCI. Despite the clinical importance and abundant observational data, there is a paucity of data from RCTs comparing $P2Y_{12}$ inhibitors exclusively in STEMI patients. The principle findings of our network analysis are that at 1-month and 1-year follow-up, prasugrel was associated with a lower mortality, MI, and MACE rate than standard or high-dose clopidogrel; lower mortality and MACE than ticagrelor; and lower ST than standard or upstream clopidogrel. Ticagrelor was also associated with significantly lower 1-year mortality, MI, ST, and MACE than standard or high-dose clopidogrel. In patients receiving bivalirudin, DES, but not GP IIb/IIIa inhibitors; prasugrel was associated with lower 1-month MACE than clopidogrel and ticagrelor. There was no significant difference in major bleeding rates between various $P2Y_{12}$ inhibitors in STEMI patients.

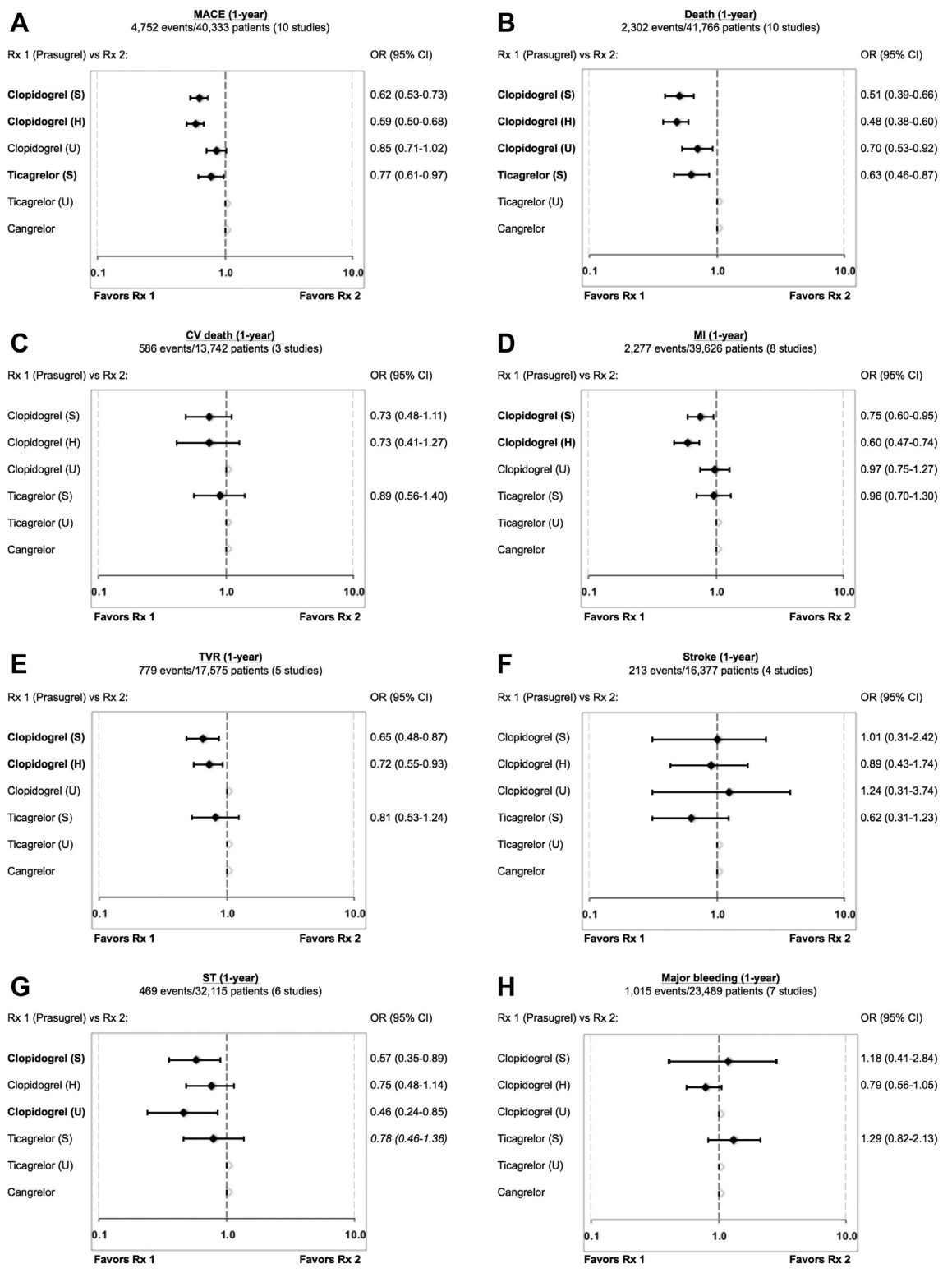
Higher platelet reactivity after clopidogrel loading is associated with larger intracoronary thrombus burden, worse post-PCI myocardial flow and perfusion (13). Genetic polymorphisms in *CYP2C19,* specifically *2 and *3 alleles result in reduced clopidogrel induced platelet inhibition (14). Slower onset can be partially overcome by higher dose or upstream administration of clopidogrel (15). In the TRITON-38 trial all patients received only a "standard" 300 mg loading dose of clopidogrel; in the PLATO trial, 36% of patients received a "high dose" 600 mg loading dose of clopidogrel. In the GRAVITAS (Gauging Responsiveness with a VerifyNow Assay—Impact on Thrombosis and Safety) trial high-dose clopidogrel did not reduce MACE in patients with high on-treatment reactivity (16). Upstream administration of a $P2Y_{12}$ inhibitor may not be feasible for all STEMI patients. Prasugrel and ticagrelor achieve more rapid and greater platelet inhibition than clopidogrel (17–20). Following a 60-mg loading dose of prasugrel, 90% of ACS patients achieved 50% platelet inhibition at 1 h independent of CYP2C19 genotype (21). However, in STEMI patients, residual platelet reactivity after a loading dose of these new $P2Y_{12}$ inhibitors is higher than in patients with stable coronary artery disease (22–24) likely due to poor drug absorption. In STEMI patients 2 h after loading dose ticagrelor achieved 12% platelet inhibition compared to 48% with prasugrel; and mean time to achieve PR <240 units was 3 ± 2 h with prasugrel compared to 5 ± 4 h in the ticagrelor group (25). A double loading dose of ticagrelor (360 mg) failed to achieve faster and more intense platelet inhibition (26). Therefore, a several-hour vulnerable window of suboptimal antithrombotic therapy exists in which STEMI patients are at risk of having ST. Cangrelor offers instant onset of

FIGURE 3 1-Month Outcomes



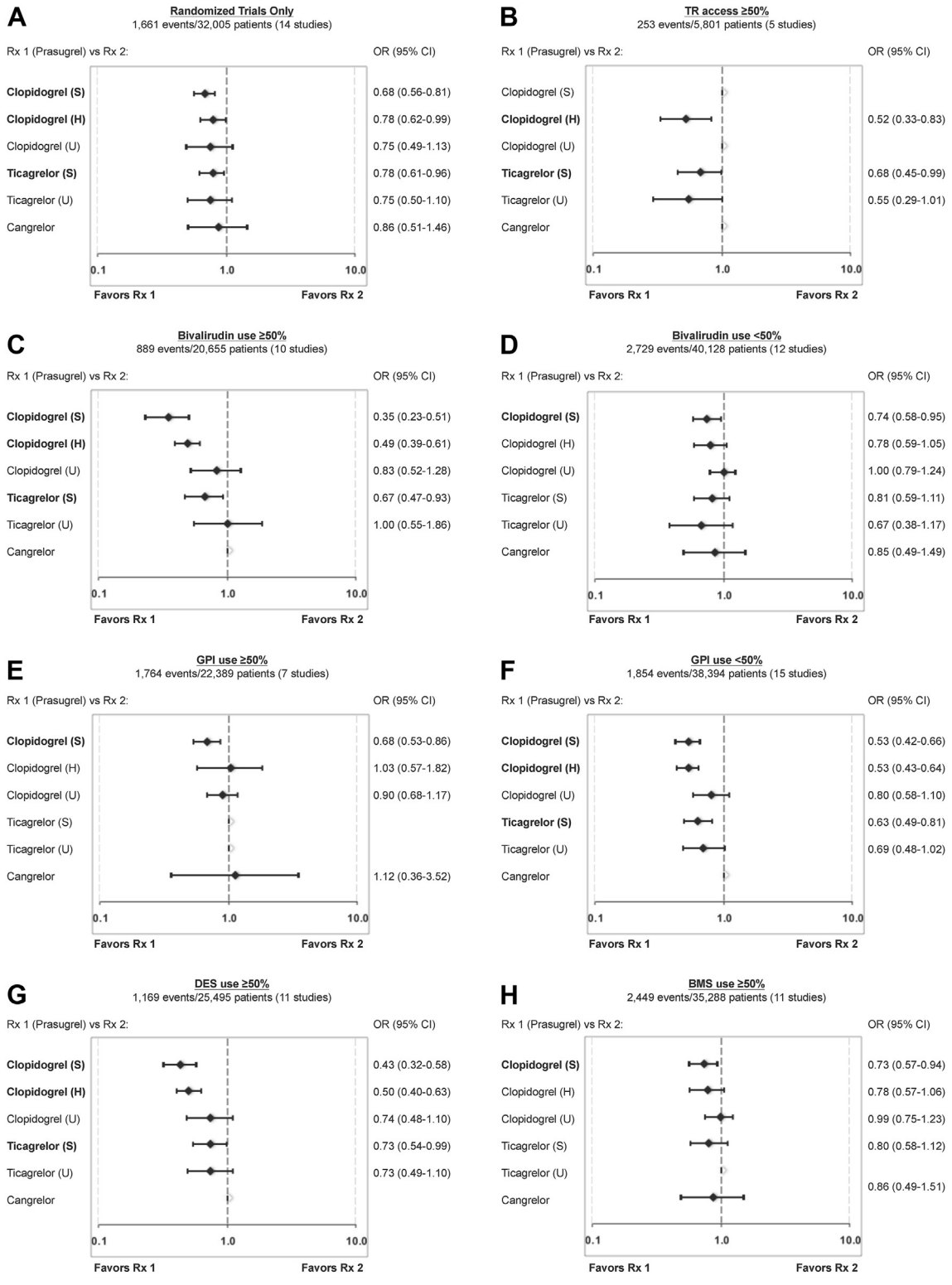
One-month pooled odds ratios (OR) and 95% confidence interval intervals (CI) comparing prasugrel with other $P2Y_{12}$ inhibitor for **(A)** major adverse cardiovascular events (MACE), **(B)** mortality, **(C)** cardiovascular (CV) mortality, **(D)** myocardial infarction, **(E)** target vessel revascularization (TVR), **(F)** stroke, **(G)** definite/probable stent thrombosis (ST), and **(H)** major bleeding. H = high dose; S = standard dose; U = upstream.

FIGURE 4 1-Year Outcomes



One-year pooled OR and 95% CI comparing prasugrel with other P2Y$_{12}$ inhibitor for **(A)** MACE, **(B)** mortality, **(C)** CV mortality, **(D)** myocardial infarction; **(E)** TVR; **(F)** stroke; **(G)** definite/probable ST, and **(H)** major bleeding. Abbreviations as in Figure 3.

FIGURE 5 Subgroup Analysis of Outcomes



Pooled OR and 95% CI comparing 1-month MACE between prasugrel with other $P2Y_{12}$ inhibitors stratifying studies by: **(A)** randomized trials only, **(B)** transradial (TR) access used ≥50%, **(C)** bivalirudin use ≥50%, **(D)** bivalirudin use <50%, **(E)** glycoprotein IIb/IIIa inhibitors **(GPI)** use ≥50%, **(F)** GPI use <50%, **(G)** drug-eluting stent (DES) use ≥50%, and **(H)** bare-metal stent (BMS) use ≥50% patients. Other abbreviations as in Figure 3.

action after intravenous administration; however, data is limited to 2 clinical trials and there are no studies comparing it to newer $P2Y_{12}$ inhibitors.

Despite the limitations, these results point to better outcomes with prasugrel without significant increase in major bleeding. Bleeding is less frequent in STEMI patients due to younger age (on average 3 years) and fewer comorbidities. Lower bleeding rates with prasugrel may be related to selection bias due to Food and Drug Administration black box warning. In the PLATO trial mortality was higher than expected in the placebo arm, there was significant regional heterogeneity in clinical outcomes (46% MACE from 2 countries enrolling 21% patients) and outcomes were worse for U.S. patients, which was attributed to higher aspirin dose (27,28). A recent study reported that prasugrel but not ticagrelor was associated with lower 1-month mortality than clopidogrel in STEMI patients (29).

A randomized comparison of ticagrelor vs. prasugrel in patients with ACS and a planned invasive strategy (ISAR-REACT 5 [Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment]) trial is underway. However, the relative merits of ticagrelor versus prasugrel in the treatment of ACS patients cannot necessarily be extended to STEMI patients. Our study highlights the need for a randomized clinical trial to compare various $P2Y_{12}$ inhibitors in STEMI patients.

STUDY LIMITATIONS. Our study includes the limitations of the original studies analyzed. Network meta-analysis assumes that patients enrolled in the various studies were sampled from the same theoretical population and that various drugs would have a consistent risk-benefit ratio across trials. Sources of heterogeneity include varying use of bivalirudin, GPI, DES, radial access, operator experience, door to balloon time, timing, loading dose and duration of $P2Y_{12}$ inhibitor therapy, variable follow-up duration, and different definitions of clinical events across trials including MACE, bleeding, and recurrent MI. Outcomes with fewer events such as stroke, ST, and major bleeding may not be reliably estimated.

CONCLUSIONS

This network meta-analysis suggests that in STEMI patients undergoing PPCI, prasugrel is associated with better clinical outcomes than standard or high-dose clopidogrel at both 1-month and 1-year follow-up; ticagrelor is associated with better outcomes than standard or high-dose clopidogrel at 1-year; and prasugrel appears superior to standard ticagrelor at both 1 month and 1 year. Prasugrel is particularly more effective in patients receiving bivalirudin and DES.

ACKNOWLEDGMENTS The authors are thankful to the investigators of various clinical for sharing and clarifying the data, including Dr. Shahzad Adeel (United Kingdom), Dr. David J. Kurz (Switzerland), and Dr. Leonardo De Luca (Italy).

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PERSPECTIVES

WHAT IS KNOWN? $P2Y_{12}$ receptor inhibition is critical to reduce ischemic events in patients undergoing PPCI. Despite this clinical relevance, there are no randomized trials comparing various $P2Y_{12}$ inhibitors exclusively in STEMI patients.

WHAT IS NEW? In STEMI patients undergoing PPCI, prasugrel is associated with better clinical outcomes than standard or high-dose clopidogrel; ticagrelor is associated with better outcomes than standard or high-dose clopidogrel; and prasugrel appears superior to standard ticagrelor. The risk of major bleeding was not significantly different between various $P2Y_{12}$ inhibitors.

WHAT IS NEXT? This study highlights the need for a randomized clinical trial to compare the clinical efficacy and safety of various $P2Y_{12}$ inhibitors in STEMI patients.

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KEY WORDS angioplasty, clopidogrel, $P2Y_{12}$ inhibitors, percutaneous coronary intervention, prasugrel, ST-segment elevation myocardial infarction, thienopyridines, ticagrelor

APPENDIX For supplemental tables, please see the online version of this article.