Meta-Analysis Comparing the Safety and Efficacy of Prasugrel and Ticagrelor in Acute Coronary Syndrome

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Prasugrel and ticagrelor are preferred over clopidogrel for patients with acute coronary syndrome who underwent percutaneous coronary intervention. We sought to determine the relative merits of 1 agent over the other. Multiple databases were queried to identify relevant randomized control trials (RCTs) and observational cohort studies. Random-effects model was used to calculate an unadjusted odds ratio (OR) for major adverse cardiovascular and cerbrovascular events (MACCE) and its components. A total of 27 (7 RCTs, 20 observational cohort studies) studies comprising 118,266 (prasugrel 62,716, ticagrelor 51,196) patients were included. At 30 days, prasugrel was associated with a significantly lower odds of MACCE (OR 0.75, 95% confidence interval [CI] 0.67 to 0.85, p ≤0.0001) and mortality (OR 0.65, 95% CI 0.59 to 0.71, p ≤0.0001). At 1 year, the overall odds of mortality favored prasugrel (OR 0.79, 95% CI 0.68 to 0.92, p = 0.002), but no significant interdrug difference was seen in terms of MACCE (OR 0.89, 95% CI 0.76 to 1.05, p = 0.16). There was no significant difference in the odds of overall myocardial infarction, revascularization, stent thrombosis, stroke, and major bleeding events between the 2 groups on both 30-day and 1-year follow-up. A subgroup analysis of RCTs data showed no significant difference between prasugrel and ticagrelor in terms of any end point at all time points. In conclusion, prasugrel might have lower odds of MACCE and mortality at 30 days. However, there was no difference in the safety and efficacy end points of 2 drugs at 1 year. The observed transient prasugrel-related mortality benefits were subject to the bias of nonrandomized assignment. **(Am J Cardiol 2020;132:22−28)**

According to the American Heart Association, approximately 720,000 individuals in the United States had a primary acute coronary syndrome (ACS) and 335,000 a recurrent ACS event in 2019.[1] The standard of care for these patients includes the administration of dual-antiplatelet therapy which includes aspirin and the adenosine diphosphate receptor antagonist, clopidogrel.[2] Recently ticagrelor and prasugrel which provide a more rapid and sustained platelet inhibition have been shown to be more efficacious than the conventionally used P2Y12 inhibitor clopidogrel.[3,4] The updated guidelines by the American College of Cardiology (2017) and the European Society of Cardiology have recommended prasugrel or ticagrelor as a class I recommendation for patients with ACS; however, there have been no clear preference recommendations. The ISAR-REACT5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) trial recently favored prasugrel over ticagrelor due to a significantly lower risk of the primary composite end point, whereas the trial by Motovska et al showed no significant difference between the 2 regimens.[5,6] The aim of this meta-analysis is to systematically pool the results of all previously published trials, to provide clarity on the relative merits of the 2 medications.

Methods

Electronic databases (PubMed, Embase, clinicaltrials.gov, and Cochrane) were searched up to February 2020 using a combination of keywords and medical subject headings (MeSH) (Supplementary Appendix). All randomized control trials (RCT), retrospective, and prospective cohort studies reporting the use of prasugrel and ticagrelor in post-percutaneous coronary intervention (PCI) patients were evaluated. The primary efficacy outcome was defined as a major adverse cardiovascular event (MACE), including death, nonfatal myocardial infarction (MI) and nonfatal stroke. Secondary end points included stroke, revascularization, stent thrombosis, or all-cause mortality. The primary safety end point was defined as major bleeding.

Statistical analysis was performed using the DerSimonian and Laird tool under the random-effects model to calculate pooled unadjusted odds ratio (OR) for the efficacy and safety end points. The probability value of $p < 0.05$ was considered statistically significant. Subgroup analysis stratified by the study design, type of MI, and history of diabetes mellitus (DM) was also performed. Higgins I-squared (I^2) statistic model was used to assess variations in outcomes of included studies. Publication bias was illustrated graphically using a funnel plot asymmetry and quantitatively using Egger's tests. The methodological quality of the included articles

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See page 27 for disclosure information.

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was performed using the risk of bias-2 (RoB-2) tool. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was applied for literature search. All statistical analyses were performed using the Cochrane Review Manager (RevMan) version 5.3.

The overall quality of the included RCTs was high. Due to adequate randomization and allocation concealment in most studies, the risk of selection bias in RCTs was low. The risk of selection bias across retrospective studies was high. However, this risk was minimized by a few studies using propensity-matched scoring for both study groups. The fact that most RCTs used an intention to treat model or had a minimal loss to follow-up of its participants, the risk of attrition bias was low (Supplementary Figures 1 and 2).

Results

Our initial search identified 1,111 articles. Following removal of irrelevant (369) and duplicate items (613), 129 articles were deemed relevant for full-text review. We further excluded 102 articles based on our selection criteria; 27 articles qualified for final analysis. The PRISMA flow diagram is shown in Figure 1.

The selected studies comprised 7 RCTs and 20 retrospective studies, recruiting 118,226 patients (prasugrel 62,716 and ticagrelor 51,196[5-11] (Supplementary References 1 to 19). The main indication for dual-antiplatelet therapy was secondary prevention of ACS after PCI. The loading dose

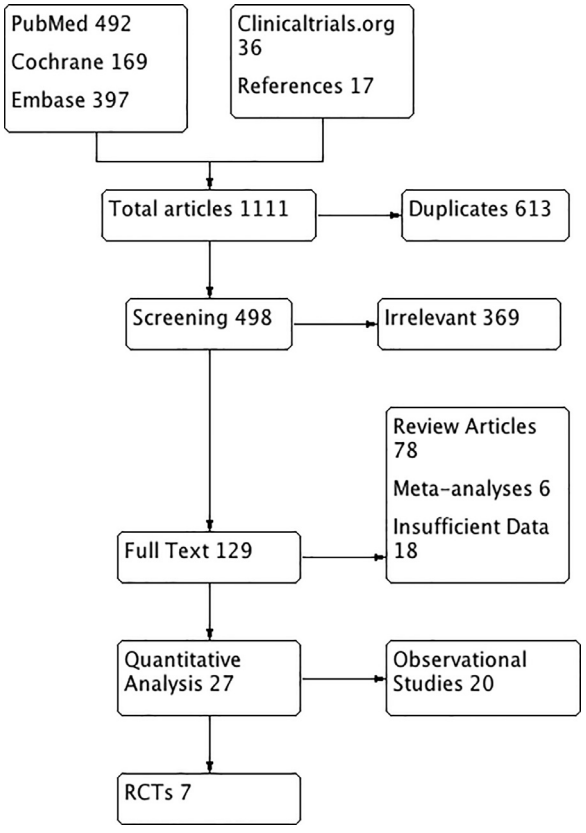

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the included studies.

used was 180 mg for ticagrelor and 60 mg for prasugrel across all studies. The maintenance dose was 90 mg twice daily (ticagrelor) or 10 mg daily (prasugrel). Baseline characteristics of prasugrel versus ticagrelor included hypertension (47.7% vs 51.4%, p=0.57), DM (27.4% vs 19.0%, p = 0.85), hyperlipidemia (38.2% vs 39.3%, p = 0.88), and history of smoking (39.0% vs 37.0%, p = 0.77), respectively. The major bleeding criteria varied among the included studies. The ISAR REACT-5 and the study by Bonello et al used the Bleeding Academic Research Consortium scale. The remaining clinical trials used the Thrombolysis in Myocardial Infarction bleeding criteria. The overall mean follow-up period ranged from 30 days to 1 year. Detailed characteristics of the included RCTs and OCS are shown in Table 1 and Supplementary Table 1, respectively.

At 30 days, patients on prasugrel had significantly lower odds of MACCE (OR 0.75, 95% confidence interval [CI] 0.67 to 0.85, p ≤0.0001) and mortality (OR 0.65, 95% CI 0.59 to 0.71, p ≤0.0001) compared with ticagrelor (Figure 2). There was no significant difference in the odds of MI (OR 0.80, 95% CI 0.60 to 10.7, p = 0.13), revascularization (OR 0.81, 95% CI 0.60 to 1.08, p = 0.15), stent thrombosis (OR 0.54, 95% CI 0.28 to 1.02, p = 0.06), stroke (OR 1.03, 95% CI 0.59 to 1.79, p = 0.92), or major bleeding (OR 0.86, 95% CI 0.69 to 1.07, p = 0.17) between the 2 groups (Figure 3). At 1 year, the relative odds of mortality (OR 0.79, 95% CI 0.68 to 0.92, p = 0.002) favored prasugrel. There was no significant difference in the odds of MACCE (OR 0.89, 95% CI 0.76 to 1.05, p = 0.16), MI (OR 0.78, 95% CI 0.54 to 0.1.13, p = 0.19), revascularization (OR 0.83, 95% CI 0.46 to 1.48, p = 0.53), stent thrombosis (OR 1.02, 95% CI 0.64 to 1.63, p = 0.93), stroke (OR 1.20, 95% CI 0.83 to 1.73, p = 0.32), or major bleeding (OR 0.78, 95% CI 0.54 to 1.13, p = 0.19) between the 2 groups (Figures 4 and 5).

Subgroup analyses in most measured variables closely mirrored the trends of the overall results with few exceptions. In contrast to the pooled results, the odds of MACCE in both drugs across the RCTs at 30 days were identical, whereas prasugrel had significantly lower odds of MACE across OCS at 1 year. Similarly, the pooled odds of a mortality benefit were also found to be driven by observational studies. However, a stratified analysis of MACE based on the history of DM and type of MI showed no significant difference between the 2 regimens. The risk of bleeding was also identical on a stratified analysis based on the criteria of major bleeding (Thrombolysis in Myocardial Infarction vs Bleeding Academic Research Consortium), type of study (OCS vs. RCT), history of DM (DM vs. no-DM), type of index MI [ST-segment elevation myocardial infarction (STEMI) vs. Non-STEMI (NSTEMI)] and follow-up duration (30 days vs 1 year). There was no significant difference in prasugrel or ticagrelor with respect to all other end points (stroke, stent thrombosis, major bleeding, and need for revascularization) irrespective of the study design at all time points. The outcomes of the included studies showed variable amounts of heterogeneity ranging from minimal to severe ($I^2 = 0\%$ to 72%; Supplementary Figures 3 to 14, Supplementary Table 2).

On visual assessment, our funnel plot was symmetrical, indicating no publication bias. The Sterne and Egger's regression test was also nonsignificant (2-tailed p = 0.35; Figure 6, Supplementary Figures 15 and 16).

Table 1
Baseline characteristics of the included randomized controlled trials

Author	Country	Total	Prasugrel/ticagrelor	Hypertension	Diabetes mellitus	Hyperlipidemia	Smoker	Loading dose protocol	Follow-up (months)
Shupke (ISAR-REACT 5)-2019-5	Germany	4018	2006(50%)/2012 (50%)	1384(69%)/1429 (71%)	421(21%)/463(23%)	1163(58%)/1187 (59%)	662(33%)/684(34%)	T180 before PCI, P60 before PCI in STEMI after Angiography in NSTEMI	12
Motovska (PRAGUE 18)-2018-6	Czech republic	1230	634(52%)/596(48%)	323(51%)/304(51%)	127(20%)/125(21%)	209(33%)/209(35%)	406(64%)/393(66%)	T180 and P60 after PCI	12
Welsh (TOTAL)-7	Canada	3432	1244(36%)/2188 (64%)	560(45%)/963(44%)	249(20%)/328(15%)	-	597(48%)/940(43%)	-	12
Bonello-2015-8	Czech republic	213	107(50%)/106(50%)	62(58%)/56(53%)	44(41%)/31(29%)	48(45%)/56(53%)	40(37%)/51(48%)	T180 B4 PCI, P60 after PCI	1
Perl-2014-9	Israel	114	62(54%)/52(46%)	27(43%)/34(65%)	17(27%)/19(36%)	37(59%)/33(63%)	32(51%)/18(34%)	P60 T180 before or after PCI	1
Parodi (RAPID)-2013-10	Italy	50	25(50%)/25(50%)	15(60%)/18(72%)	6(24%)/3(12%)	5(20%)/10(40%)	9(36%)/9(36%)	P60 T180 before PCI	In-Hospital
Laine-2014-11	France	100	50(50%)/50(50%)	35(70%)/40(80%)	50(100%)/50(100%)	31(62%)/28(56%)	14(28%)/14(28%)	P60 T180 before PCI	4

P60 = prasugrel 60 mg; PCI = percutaneous coronary intervention; s/p = status post; T180 = ticagrelor 180 mg.

Discussion

Our study revealed no significant long-term difference between prasugrel and ticagrelor in terms of ischemic end points or major bleeding. However, at 30 days, patients on prasugrel were seen to have significantly lower odds of MACE and mortality by 25% and 35%, respectively. These results were mostly driven by observational studies, as illustrated by our subgroup analysis. A stratified comparison across a subset of RCTs showed a 13% lower incidence in MACE between prasugrel and ticagrelor, which was not statistically different. Similarly, the overall efficacy benefits of prasugrel in terms of lower primary composite end point were attenuated (from 31% to 11%), when the follow-up period was extended to 1 year. The safety end point of bleeding remained identical between the 2 groups, irrespective of the bleeding criteria, history of DM, type of MI, and follow-up duration. Similarly, there was no significant difference in the odds of stroke, stent thrombosis, MI, and the need for revascularization between the 2 groups at both follow-up durations.

On review of the included studies, a significant amount of heterogeneity was found in both the included populations and outcomes.[5–11] Bonello et al were the first to study the effects of ticagrelor or prasugrel before PCI.[8] Unfortunately, due to the small sample size (213 patients), this study was vastly underpowered to compare hard clinical end points. Additionally, only the effects of loading dose were studied with no assessment of long-term benefits. Furthermore, this study included NSTEMI patients; it is unclear whether these findings can be extrapolated to patients with STEMI.[8] By contrast, the PRAGUE-18 trial randomized patients with STEMI after PCI to receive maintenance doses of trial regimens. This trial found no significant difference in the rate of MI, stent thrombosis, stroke, major bleeding, cardiovascular mortality, or all-cause mortality among patients treated with prasugrel or ticagrelor at 1 year.[6] However, about 34% of the prasugrel and 44% of the ticagrelor group were financially motivated to switch to clopidogrel. This substantial amount of crossover precluded a reliable comparison of the 2 drugs in this trial.[6] Moreover, the higher discontinuation rate for ticagrelor was attributed to the selective economic discrimination in favor of prasugrel (some recruitment centers provided reimbursements for prasugrel only).[6] Together, these limitations rendered this trial underpowered to draw definitive conclusions.

The recently published larger scale REACT-ISAR-5 trial randomized 4,018 STEMI and NSTEMI patients.[5] Surprisingly, in contrast to previous trials, prasugrel was superior to ticagrelor in terms of MACE (6.9% vs 9.3%, $p = 0.006$) with an identical risk of major bleeding (4.8% vs 5.4%, $p = 0.46$), respectively. REACT-ISAR-5, however, also reported a significant amount of noncompliance to the trial medications (15% ticagrelor and 12% prasugrel). Additionally, the interpretation of the results was complicated by the trial protocol; that involved delaying the loading dose of prasugrel in NSTEMI patients until after a diagnostic angiography, without a similar delay for patients randomized to the ticagrelor

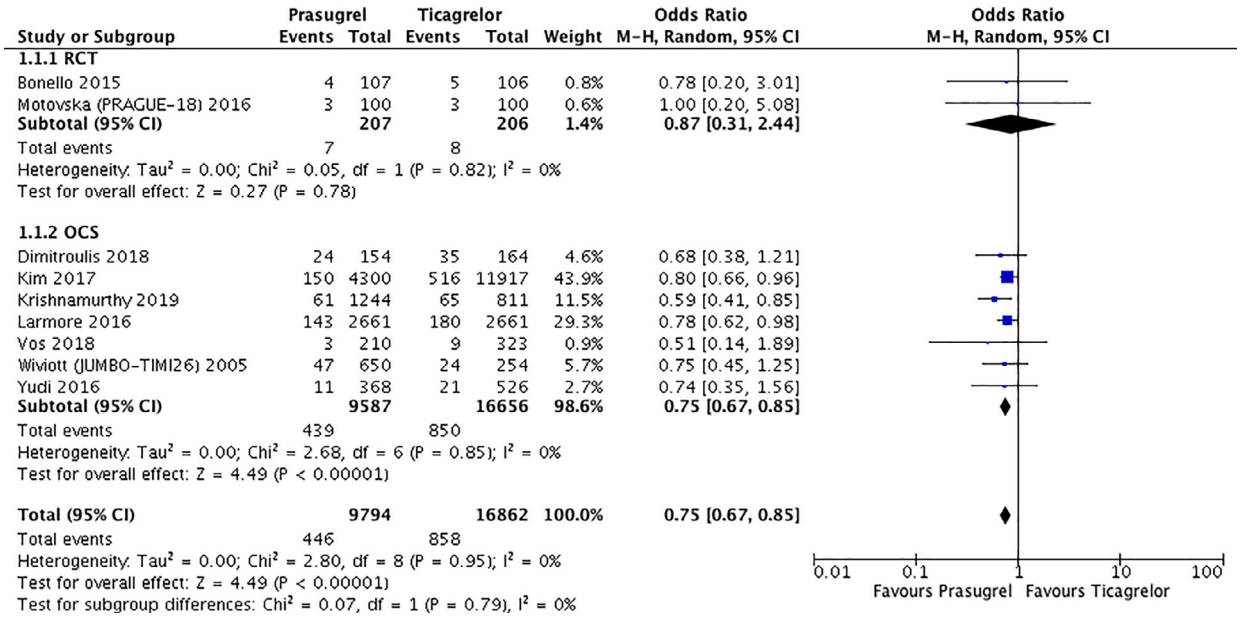

Figure 2. Forest plot for MACE showing study-design subgroups and pooled OR for studies comparing prasugrel to ticagrelor at a follow-up duration of 30 days. The pooled ORs with 95% CI were calculated using random-effects models. Weight refers to the contribution of each study to the overall pooled estimate of treatment effect. Each square and horizontal line denotes the point estimate and 95% CI for each trial's OR, respectively. The diamonds signify the pooled OR; the diamond's center denotes the point estimate and width denotes the 95% CI.

arm.[5] Interestingly, a stratified analysis based on the ACS type (NSTEMI and STEMI) shows no significant difference between the two trial regimens. This contrasts with the combined results which seem to favor the prasugrel-based regimen.

Previous meta-analyses attempted to determine the relative safety and efficacy of these agents. However, given the inherent methodological biases of these studies and now with new emerging evidence, the results cannot be relied upon to inform clinical decision-making. All previous

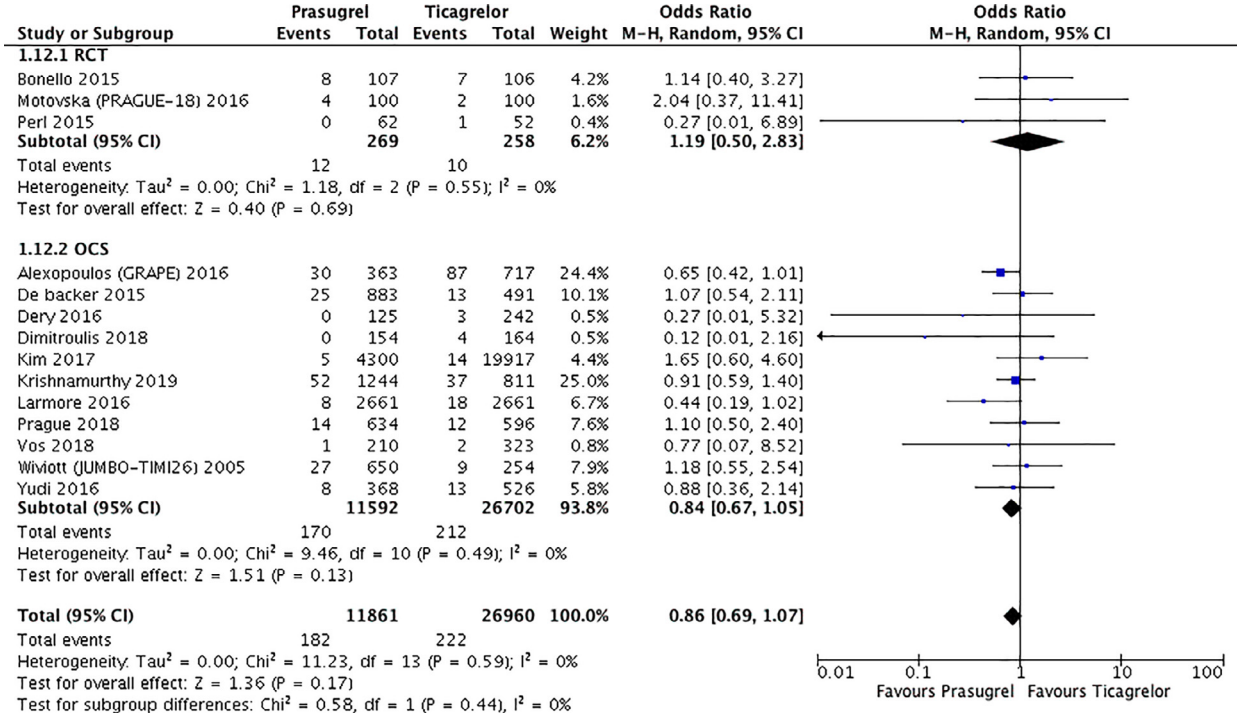

Figure 3. Forest plot for bleeding showing an individual and pooled OR for studies comparing prasugrel to ticagrelor at a follow-up duration of 30 days.

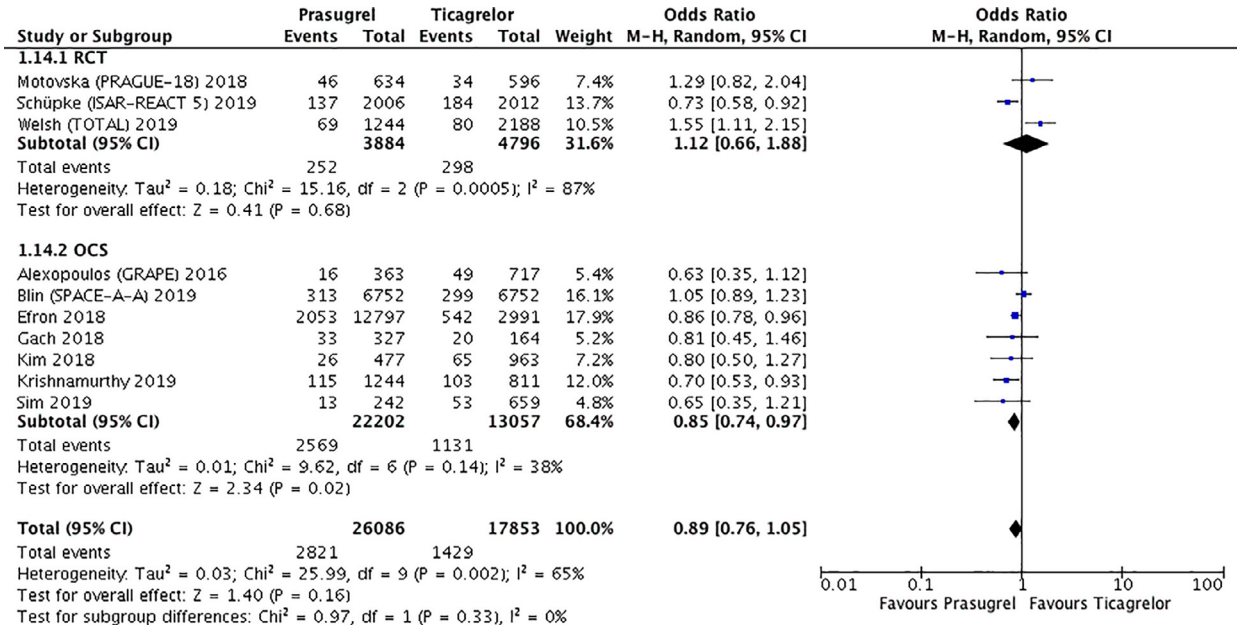

Figure 4. Forest plot for MACE showing subgroups based on study design and pooled OR for studies comparing prasugrel to ticagrelor at a follow-up duration of 1 year.

meta-analyses were published prior to the ISAR-REACT-5, the largest and most contemporary RCT on the subject. The detailed limitations of previous meta-analyses are given in Supplementary Table 3.

The present study represents the most comprehensive and updated evidence, incorporating 27 studies (including the ISAR-REACT-5). We have determined that the early transient benefits of prasugrel over ticagrelor gradually diminish over time and that there is no overall difference in the safety and efficacy of the 2 drugs. These findings contrast with the recent ISAR-REACT-5 trial and all previous meta-analyses, which have tended to favor prasugrel or ticagrelor. Furthermore, this meta-analysis suggests that the apparent short-term benefit of prasugrel might be attributed to low-quality evidence based on nonrandomized data, until more evidence is available.

Our study is constrained by the limitations of the included studies. Due to scarce randomized data, there were several subgroup analyses that were not feasible,

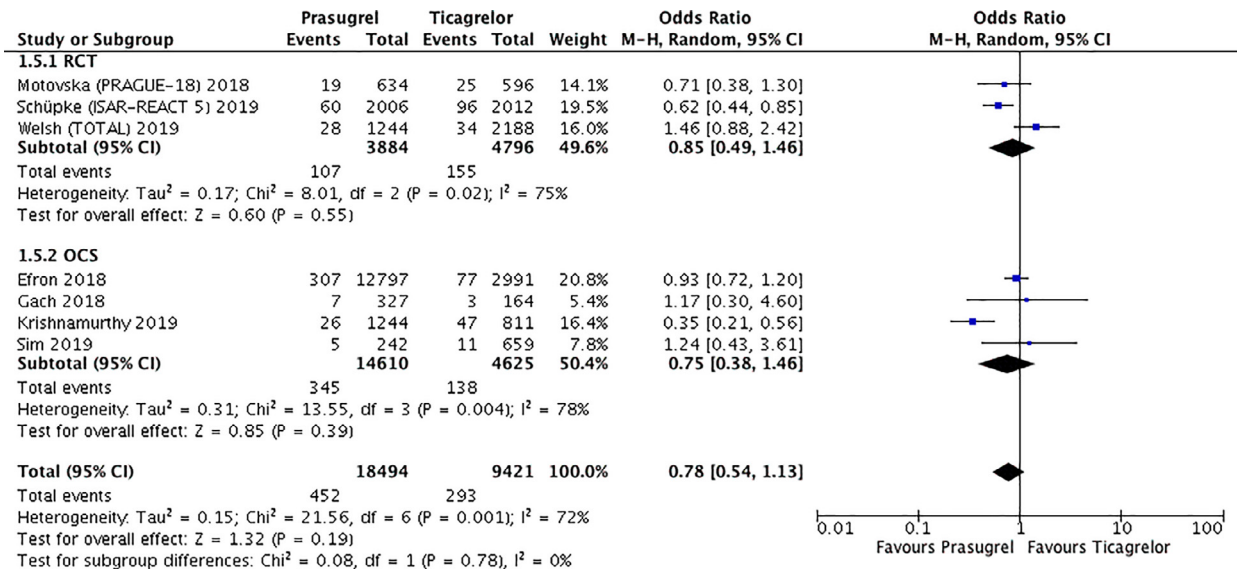

Figure 5. Forest plot for major bleeding showing subgroups based on study design and pooled OR for studies comparing prasugrel to ticagrelor at a follow-up duration of 1 year.

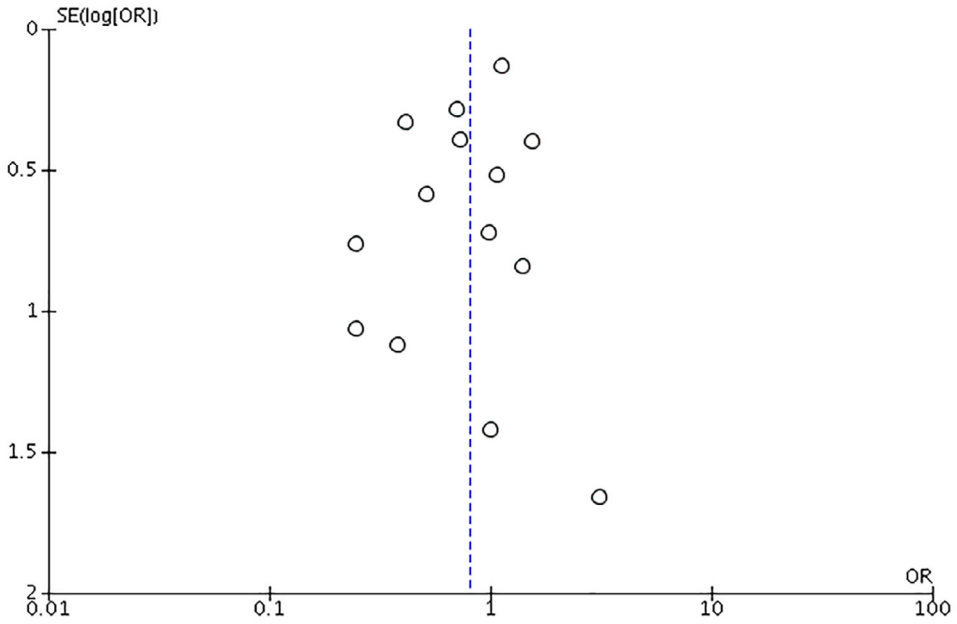

Figure 6. Funnel plot showing minimal publication bias across the studies comparing MACCE at 1 year.

including a comparison based on the varying protocols (loading dose administration before vs after PCI), clinical outcomes such as MI (STEMI vs NSTEMI), and stent designs (bare-metal stent vs drug-eluting stent). The long-term clinical outcomes of patients beyond 1 year could also not be assessed. The study was not designed to perform a cost-benefit analysis or to rationalize the short-term differential efficacy of the trial drugs in terms of their mechanisms.

In conclusion, ACS (STEMI and NSTEMI) patients on prasugrel have an identical long-term risk of the composite end point (death, myocardial infarction, and stroke), major bleeding, revascularization, and stent thrombosis compared with patients receiving ticagrelor.

Author Contribution

Waqas Ullah, MD: Conceptualization; Roles/Writing - original draft; Formal analysis
Zain Ali, MD: Data curation
Usama Sadiq: Investigation; Methodology
Ali Rafiq: Roles/Writing - original draft
Salman Hoti MBBS: Data Collection
Pierre Sabouret, MD: Validation; Critical Review
Mamas A. Mamas, FRCP: Validation; Visualization
David Fischman, FACC: Supervision; Critical Review

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.07.017.

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