



Effectiveness and Safety of Prasugrel versus Ticagrelor in PCI-treated ACS/AMI Patients: Meta-analysis

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ABSTRACT

Introduction: As per international guidelines the P2Y12 receptor inhibitor, ticagrelor or prasugrel is recommended over clopidogrel for patients with acute coronary syndrome (ACS).

Aims: To determine the effectiveness and safety of Prasugrel versus ticagrelor in patients with ACS/AMI (acute myocardial infarction) who underwent percutaneous coronary intervention (PCI) through meta-analysis of clinical trials.

Methods: We performed a meta-analysis of randomized and non-randomized trials [with search results up to April 2023 in the following databases: PubMed (MEDLINE) and Google Scholar comparing prasugrel and ticagrelor in PCI-treated acute ACS/AMI patients for the following: Composite of 1-year all-cause death, non-fatal MI, or stroke; Composite of 1-year cardiovascular death, non-fatal MI, or stroke; and individual parameters (all-cause death, cardiovascular death, non-fatal MI and stroke) and major bleeding as Bleeding Academic Research Consortium (BARC) type 3 to 5 bleeding (more severe bleeding) at 1-year. 4 studies met the metanalysis inclusion criteria. It was conducted on the data of a total of 10479 patients (5079 in the prasugrel group and 5400 ticagrelor group).

Results: Prasugrel and ticagrelor have insignificant differences for the pooled relative risks of the following: composite of 1-year all-cause death, non-fatal myocardial infarction (MI), or stroke 0.921 (95% CI, 0.719 to 1.181; $p=0.518$); composite of 1-year cardiovascular death, non-fatal MI, or stroke 0.830 (95% CI, 0.598 to 1.152; $p=0.265$); BARC type 3 to 5 bleeding (more severe bleeding) at 1-year was 0.988 (95% CI, 0.774 to 1.262; $p=0.924$); individual parameters (all-cause death, cardiovascular death, non-fatal myocardial infarction (MI) and stroke). There was either inconsistency/heterogeneity and minimal or no inconsistency/heterogeneity for different parameters in the data. There was no publication bias for all trials.

Conclusion: Prasugrel and ticagrelor have similar effects for their relative risks of the following; composite of 1-year all-cause death, non-fatal MI, or stroke; composite of 1-year cardiovascular death, non-fatal MI, or stroke; and individual parameters and BARC type 3 to 5 bleeding at 1 year in patients with ACS/AMI undergoing PCI.

Key Words: Prasugrel, Ticagrelor, Meta-analysis, ACS, AMI, PCI, BARC

INTRODUCTION

Oral P2Y12 receptor inhibitor is recommended along with aspirin as an antiplatelet strategy after acute coronary syndrome (ACS).^{1,2} As per international guidelines the P2Y12 inhibitor, ticagrelor or prasugrel is recommended over clopidogrel for patients with ACS³⁻⁵ due to their faster onset of action, higher potency, and lesser interindividual variability; all these aspects of ticagrelor or prasugrel lead to improved clinical outcomes in the ACS-related setting⁶⁻¹⁰

A multicenter, randomized, open-label trial, comparing prasugrel and ticagrelor reported better efficacy of prasugrel over

ticagrelor without any apparent difference in bleeding risk in (percutaneous coronary intervention (PCI) treated ACS patients.¹¹ However, these results are contradictory to some studies because prasugrel and ticagrelor were found to be similarly effective and safe during the first year in PCI-treated ACS/acute myocardial infarction (AMI).^{12,13,14} Not many meta-analyses are done on this subject (Prasugrel vs. Ticagrelor) as far as all appropriate relevant clinical outcomes are concerned.

Considering contradictory results with prasugrel and ticagrelor in comparative studies, our aim is to carry out a meta-analysis of comparative randomized and non-randomized

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clinical trials to determine the effectiveness and safety of prasugrel versus ticagrelor in patients with Acute Coronary Syndrome/AMI who underwent PCI through meta-analysis.

MATERIALS AND METHODS

We performed a meta-analysis of randomized and non-randomized trials (with search results up to April 2023) comparing prasugrel and ticagrelor in PCI-treated acute ACS/AMI patients with respect to the Composite of 1-year all-cause death, non-fatal MI, or stroke; Composite of 1-year cardiovascular death, non-fatal MI, or stroke; and individual parameters (all-cause death, cardiovascular death, non-fatal MI and stroke) and major bleeding as Bleeding Academic Research Consortium (BARC) type 3 to 5 bleeding (more severe bleeding) at 1-year.

Objective

To determine the effectiveness and safety of Prasugrel versus ticagrelor in patients with ACS/AMI who underwent percutaneous coronary intervention (PCI) through meta-analysis of comparative randomized and non-randomized clinical trials.

Inclusion criteria

The inclusion criteria were as follows:

- Comparative (randomized trials and non-randomized/observational) studies investigating oral prasugrel or ticagrelor
- PCI-treated acute coronary syndrome patients
- All of the following clinical outcomes: 1-year rate of Composite of all-cause death, non-fatal MI, or stroke; Composite of 1-year cardiovascular death, non-fatal MI, or stroke; and 1-year rate of individual parameters (all-cause death, cardiovascular death, nonfatal MI, or stroke and BARC type 3 to 5 bleeding (more severe bleeding) in patients with ACS/AMI undergoing PCI (percutaneous coronary intervention). BARC was considered as it is considered standard for evaluation of the safety of oral P2Y12 inhibitors
- Publications for which full-text articles are available
- Studies published in all languages (with English translations)
- Full-text articles were reviewed after studies satisfied the inclusion criteria

Exclusion criteria

The Exclusion criteria were as follows:

- Small randomized controlled trials (RCTs) whose analyses were not on clinical events
- Small RCTs that reported and compared clinical outcomes were of lower follow-up duration (<12 months) and small sample size (under 100)

- Studies that evaluated incidences of the following: Thrombolysis in Myocardial Infarction (TIMI) defined minor bleeding; TIMI-defined major bleeding; total bleeding events, BARC type <3 bleeding

Primary endpoints and secondary endpoints:

The primary (efficacy) endpoint was the composite of 1-year rate of all-cause death, non-fatal myocardial infarction, or stroke.

The secondary (efficacy) endpoints were composite of the 1-year rate of cardiovascular death, non-fatal MI, or stroke and the 1-year rate of individual parameters (all-cause death; cardiovascular death; non-fatal myocardial infarction; stroke).

The secondary (safety) endpoint was the 1-year rate of Bleeding Academic Research Consortium type 3 to 5 bleeding.

Literature search

The following databases were used: PubMed (MEDLINE) and Google Scholar.

The search strategy included the following key terms: Prasugrel, ticagrelor, Acute Coronary Syndrome, death, myocardial infarction, stroke, Bleeding Academic Research Consortium type 3 to 5 bleeding, one year- clinical trial, randomized, observational studies. Figure 1. shows the PRISMA statement flowchart on the literature search and study selection process.

Statistical analyses

Software used: MedCalc Statistical Software version 19.0.6 (MedCalc Software bvba, Ostend, Belgium; <https://www.medcalc.org>; 2019)

Procedure: A meta-analysis integrated the quantitative findings from separate but similar studies and provides a numerical estimate of the overall effect of interest (Petrie et al., 2003). The fixed effects model assumes that all studies come from a common population and that the effect size (the proportions) is not significantly different among the different trials. The random effects model may be more appropriate where studies come from different populations, in which both the random variation within the studies and the variation between the different studies are incorporated.

Weight calculation: Freeman-Tukey transformation (arc-sine square root transformation; Freeman and Tukey, 1950) is used to calculate the weighted summary Proportion under the fixed and random effects model (Der Simonian and Laird, 1986).

Heterogeneity test: Failed heterogeneity was detected in the data, and therefore we used the random effect model for further analysis. I^2 statistic: I^2 (inconsistency) is the percentage of observed total variation across studies that is due

to real heterogeneity rather than chance. It is calculated as $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df is the degrees of freedom. Negative values of I^2 are put equal to zero so that I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity and larger values show increasing heterogeneity (Higgins et al., 2003). Forest plots were also used for visual inspection.

Bias analysis

Egger's and Begg's tests and funnel plots were used to identify whether the publication bias existed. Funnel plots of effect estimates against the standard error were examined to assess publication bias.

Characteristics of studies included for meta-analysis:

Table 1 demonstrates the Characteristics of studies included in the meta-analysis.

RESULTS

Efficacy

Meta-analysis: relative risk of Composite of 1-year all-cause death, non-fatal MI, or stroke

As shown in Table 2 and Figure 2 A, the pooled relative risk of the composite of 1-year all-cause death, non-fatal myocardial infarction (MI), or stroke for Prasugrel versus Ticagrelor was 0.921 (95% CI, 0.719 to 1.181; $p = 0.518$). Thus, due to insignificant differences, prasugrel and ticagrelor have similar effects with respect to the relative risk of the composite of 1-year all-cause death, non-fatal myocardial infarction (MI), or stroke. Also, there was inconsistency/heterogeneity in the data ($I^2 = 61.86\%$; 95% CI: 0.00 to 89.12; $p = 0.0727$). The funnel plot (Figure 2B) shows that there was no publication bias.

Meta-analysis: relative risk of the composite of 1-year cardiovascular death, non-fatal MI, or stroke

As shown in Table 3, the pooled relative risk of the composite of 1-year cardiovascular death, non-fatal MI, or stroke for Prasugrel versus Ticagrelor was 0.830 (95% CI, 0.598 to 1.152; $p = 0.265$). Thus, due to insignificant differences, prasugrel and ticagrelor have similar effects with respect to the relative risk of the composite of 1-year cardiovascular death, non-fatal MI, or stroke. Also, there was inconsistency/heterogeneity in the data ($I^2 = 46.94\%$; 95% CI: 0.00 to 84.42; $p = 0.1519$).

Meta-analysis: relative risk of BARC type 3 to 5 bleeding at 1 year

As shown in Table 4, the pooled relative risk of BARC type 3 to 5 bleeding (more severe bleeding) at 1-year for

Prasugrel versus Ticagrelor was 0.988 (95% CI, 0.774 to 1.262; $p = 0.924$). Thus, due to insignificant differences, prasugrel and ticagrelor have similar effects with respect to the relative risk of BARC type 3 to 5 bleeding at 1-year. Also, there was minimal or no inconsistency/heterogeneity in the data ($I^2 = 0.00\%$; 95% CI: 0.00 to 96.29; $p = 0.4045$).

Meta-analysis: relative risk of 1-year all-cause death

As shown in Table 5, the pooled relative risk of all-cause death at 1 year for Prasugrel versus Ticagrelor was 0.859 (95% CI, 0.693 to 1.065; $p = 0.166$). Thus, due to insignificant differences, prasugrel and ticagrelor have similar effects with respect to the relative risk of all-cause death at 1 year. Also, there was minimal or no inconsistency/heterogeneity in the data ($I^2 = 0.00\%$; 95% CI: 0.00 to 94.43; $p = 0.5478$).

Meta-analysis: relative risk of 1-year cardiovascular death

As shown in Table 6, the pooled relative risk of cardiovascular death at 1 year for Prasugrel versus Ticagrelor was 0.951 (95% CI, 0.716 to 1.262; $p = 0.727$). Thus, due to insignificant differences, prasugrel and ticagrelor have similar effects with respect to the relative risk of cardiovascular death at 1 year. Also, there was minimal or no inconsistency/heterogeneity in the data ($I^2 = 0.00\%$; 95% CI: 0.00 to 82.71; $p = 0.8236$).

Meta-analysis: relative risk of 1-year Non-fatal MI

As shown in Table 7, the pooled relative risk of non-fatal MI at 1 year for Prasugrel versus Ticagrelor was 0.898 (95% CI, 0.531 to 1.517; $p = 0.687$). Thus, due to insignificant differences, prasugrel and ticagrelor have similar effects with respect to the relative risk of non-fatal MI at 1 year. Also, there was large inconsistency/heterogeneity in the data ($I^2 = 75.32\%$; 95% CI: 31.71 to 91.08; $p = 0.0069$).

Meta-analysis: relative risk: 1-year stroke

As shown in Table 8, the pooled relative risk of stroke at 1 year for Prasugrel versus Ticagrelor was 0.935 (95% CI, 0.620 to 1.412; $p = 0.750$). Thus, due to insignificant differences, prasugrel and ticagrelor have similar effects with respect to the relative risk of stroke at 1 year. Also, there was minimal or no inconsistency/heterogeneity in the data ($I^2 = 0.00\%$; 95% CI: 0.00 to 83.68; $p = 0.4986$).

Thus, prasugrel and ticagrelor have similar effects with respect to their relative risks of the following: Composite of 1-year all-cause death, non-fatal MI, or stroke; Composite of 1-year cardiovascular death, non-fatal MI, or stroke; and individual parameters and BARC type 3 to 5 bleeding at 1 year.

The literature quality

We found all trials included in the meta-analysis were of high quality and publication bias was not identified. The funnel

plots for all parameters (provided in Annexures) showed potential symmetry, but Egger's and Begg's tests were insignificant.

DISCUSSION

The current meta-analysis from 4 studies (2 randomized controlled and two observational) evaluated the efficacy and safety profile of Prasugrel versus Ticagrelor in ACS/AMI patients undergoing PCI. The main findings are as follows: no significant difference with respect to their relative risks of the following: Composite of 1-year all-cause death, non-fatal MI, or stroke; Composite of 1-year cardiovascular death, non-fatal MI, or stroke; and individual parameters and BARC type 3 to 5 bleeding at 1 year. Thus, prasugrel and ticagrelor have similar profiles with respect to efficacy and safety.

These results are in line with the previous meta-analysis done by Fong LCW et al. for most parameters except MI.¹⁵ A network meta-analysis by Navarese EP et al. supports the results of the current metanalysis with respect to almost all parameters. But, major bleeding events were classified variably in those trials.¹⁶ Similarly, as per previous meta-analyses of some randomized trials, there were no clear differences in efficacy and safety parameters between prasugrel and ticagrelor though there were some differentiations in parameters compared to the current metanalysis.¹⁶⁻¹⁹

As per the study (ISAR-REACT 5 trial) conducted by Schupke et al., the incidence of death, myocardial infarction, or stroke was significantly lesser among patients who received prasugrel than those who received ticagrelor; this difference was mainly due to more incidence of MI in the ticagrelor group.^{11,14}

As per a review by Venetsanos D et al., ISAR-REACT5 trial was an evaluation between two treatment strategies with, in addition to differences in drug treatment, loading dose strategies (preloading more often in ticagrelor-treated patients); nearly 20% of the enrolled patients in the study were discharged with no study treatment and at 1-year follow-up additional 15.2% of patients assigned to ticagrelor and 12.5% of patients allotted to prasugrel had stopped study treatment earlier.^{11,14}

Though Schupke et al. study outcomes were in favour of prasugrel. Studies conducted by Motovska et al., Venetsanos et al. and Alexopoulos et al. seem to have contributed to outcomes as no significant difference between prasugrel and ticagrelor in the current meta-analysis.¹²⁻¹⁴

How might this impact on clinical practice?

In patients with ACS/AMI treated with PCI, prasugrel and ticagrelor appear to be associated with similar efficacy and

safety during 1-year follow-up. Thus, clinicians can choose any one of both prasugrel and ticagrelor. This study may allow clinicians to decide the line of treatment between both prasugrel and ticagrelor probably based on the patient's compliance could be relevant to a dose of administration per day (prasugrel; once a day and ticagrelor; twice a day) and the cost of the treatment.

Our analysis may provide an opportunity for further consideration of the assessment of comparative results for stent thrombosis and various grades of bleeding with prasugrel and ticagrelor.

Limitations

There was heterogeneity among the data. This meta-analysis included four studies. There is a scarcity of randomized clinical studies for all shortlisted parameters from the present meta-analysis. The results of two observational studies were included in the meta-analysis considering that data as important real-world/ real-life data outside the setting of randomized trials. More RCTs on a larger scale with long-term follow-up are desirable to confirm these findings further. The long-term (>1 year) efficacy and safety of prasugrel and ticagrelor need to be evaluated in the future if sufficient data are available.

The use of other antiplatelet and other cardiac medications was ignored in the present analysis. However, aspirin was used at a dosage of 100 mg per day by patients in all included studies.

Despite adequate statistical methods to adjust for differences in patients' characteristics, residual confounders cannot be excluded. The relatively small prasugrel-treated population in the present analysis especially because of Venetsanos D, et al. study (2073 in the prasugrel group and 35 917 in the ticagrelor group), increases the risk for a type II error. However, the point estimates and confidence interval (CI) do not indicate any large differences between the groups. Venetsanos D, et al. mentioned that propensity matching through IPTW (inverse probability of treatment weighting) weighting led to a total population of 4142 patients, 2071 in each group, well balanced in all covariates included in the PS calculation.¹⁴

The results were analyzed based on trial/study-level data and not based on specific patients' data. Moreover, the component trials/studies of meta-analyses might not be powered for some endpoints or lacked various adjustments in a statistical hierarchy. However, there was consistency between direct and indirect estimates-related analyses, and the sensitivity analyses performed showed comparable results, signifying that the overall effect is robust and justified.

Strengths of the present study

This data provides important evidence regarding the benefits and risks of oral P2Y₁₂ receptor antagonists and may help to

improve the clinical care of PCI-treated ACS/AMI patients. Not many meta-analyses are done on this subject considering all appropriate relevant parameters including major bleeding. This meta-analysis includes a relatively good number of the population. The follow-up time period was also equivalent in all studies included in this analysis. Most of the parameters assessed were common in most of the included studies. This meta-analysis includes data from randomized controlled studies and real-life data from observational studies.

CONCLUSION

The current meta-analysis of 4 studies showed that prasugrel and ticagrelor have similar effects with respect to their relative risks of the following: Composite of 1-year all-cause death, non-fatal MI, or stroke; Composite of 1-year cardiovascular death, non-fatal MI, or stroke; and individual parameters and BARC type 3 to 5 bleeding at 1 year in patients with ACS/AMI undergoing PCI.

Therefore, any of both prasugrel and ticagrelor might be used without any preference with respect to their efficacy and safety in patients with ACS/AMI following coronary intervention. However, head-to-head comparison of prasugrel and ticagrelor still remains a major challenge which should be resolved in more randomized clinical trials considering all relevant confounding factors.

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Individual Authors Contribution

Dr. Chinniah Karthikeyan was involved in concept building, protocol development, parameters assessment, and manuscript writing. Dr. Shahabdeen Shuib Mohammed was involved in literature search, data analysis and statistics.

REFERENCES

1. Tantry US, Navarese EP, Myat A, Chaudhary R, Gurbel PA. Combination oral antithrombotic therapy for the treatment of myocardial infarction: recent developments. *Expert Opin Pharmacother*. 2018;19(7):653-665.
2. Navarese EP, Khan SU, Kołodziejczak M, Kubica J, Buccheri S, Cannon CP, et al. Comparative Efficacy and Safety of Oral P2Y₁₂ Inhibitors in Acute Coronary Syndrome: Network Meta-Analysis of 52816 Patients From 12 Randomized Trials. *Circulation*. 2020;142(2):150-160.
3. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, 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(2):119-177.
4. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: 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*. 2016;37(3):267-315.
5. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 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.
6. Storey RF, Angiolillo DJ, Patil SB, Desai B, Ecob R, Husted S, et al. Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes: the PLATO (PLATElet inhibition and patient Outcomes) PLATELET substudy. *J Am Coll Cardiol*. 2010;56(18):1456-1462.
7. Antman EM, Wiviott SD, Murphy SA, Voitek J, Hasin Y, Widimsky P, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. *J Am Coll Cardiol*. 2008;51(21):2028-2033.
8. James S, Akerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, et al. Comparison of ticagrelor, the first reversible oral P2Y₁₂ receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATElet inhibition and patient Outcomes (PLATO) trial. *Am Heart J*. 2009;157(4):599-605.
9. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057.
10. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-2015.
11. Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med*. 2019;381(16):1524-1534.
12. Motovska Z, Hlinomaz O, Kala P, Hromadka M, Knot J, Varvarovsky I, 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.
13. Alexopoulos D, Xanthopoulou I, Devereux S, Hamilos M, Sitafidis G, Kanakakis I, et al., Contemporary antiplatelet treatment in acute coronary syndrome patients undergoing percutaneous coronary intervention: 1-year outcomes from the Greek AntiPlatelet (GRAPE) Registry. *J Thromb Haemost*. 2016;14(6):1146-1154.
14. Venetsanos D, Träff E, Erlinge D, Hagström E, Nilsson J, Desta L, et al. Prasugrel versus ticagrelor in patients with myocardial infarction undergoing percutaneous coronary intervention. *Heart*. 2021;107(14):1145-1151.

15. Fong LCW, Lee NHC, Yan AT, Ng MY. Comparison of prasugrel and ticagrelor for patients with acute coronary syndrome: a systematic review and meta-analysis. *Cardiology*. 2022;147(1):1-13.
16. Navarese EP, Khan SU, Kołodziejczak M, Kubica J, Buccheri S, Cannon CP, et al. Comparative efficacy and safety of oral p2y12 inhibitors in acute coronary syndrome: network meta-analysis of 52816 patients from 12 randomized trials. *Circulation*. 2020;142(2):150-160.
17. 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.
18. Steiner S, Moertl D, Chen L, Coyle D, Wells GA. Network meta-analysis of prasugrel, ticagrelor, high- and standard-dose clopidogrel in patients scheduled for percutaneous coronary interventions. *Thromb Haemost*. 2012;108(2):318-327.
19. Chatterjee S, Ghose A, Sharma A, Guha G, Mukherjee D, Frankel R. Comparing newer oral anti-platelets prasugrel and ticagrelor in reduction of ischemic events-evidence from a network meta-analysis. *J Thromb Thrombolysis*. 2013;36(3):223-232.

Table 1: Characteristics of studies included for meta-analysis

Study - First Author	Year	Study design	Total population (Prasugrel)	Total population (Ticagrelor)	Study setting summary
Schüpke S et al.	2019	Multicenter, randomized, controlled, open-label	2006	2012	PCI-treated ACS patients
Motovska Z et al.	2018	Multicenter, randomized, controlled, open-label	639	600	
Alexopoulos D et al.	2016	Prospective, observational, multicenter cohort	363	717	PCI-treated AMI patients
Venetsanos D et al.	2021	Real-world observational study	2071*	2071*	
All studies			5079	5400	

The follow-up period was 1-year for all studies. ACS - acute coronary syndrome; PCI - percutaneous coronary intervention; AMI - acute myocardial infarction. PSM cohort* *Propensity matching resulted in a population of 4142 patients (PSM cohort), 2071 in each group. PSM -propensity score matched

Table 2: The relative risk of the composite of 1-year all-cause death, non-fatal MI, or stroke

Study	Prasugrel (cases/n)	Ticagrelor (cases/n)	Relative risk	95% CI	z	P-Value	Weight (%)	
							Fixed	Random
Schüpke S et al.	137/2006	184/2012	0.747	0.604 to 0.923			47.34	39.03
Motovska Z et al.	56/639	49/600	1.073	0.744 to 1.549			15.86	24.90
Venetsanos D, et al.	127/2071	122/2071	1.041	0.818 to 1.325			36.79	36.07
Total (fixed effects)	320/4716	355/4683	0.894	0.773 to 1.034	-1.511	0.131	100.00	100.00
Total (random effects)	320/4716	355/4683	0.921	0.719 to 1.181	-0.647	0.518	100.00	100.00

Overall Heterogeneity I² 61.86%

n= Total number of cases; CI: confidence intervals; Random: random-effects model; MI, Myocardial infarction

Table 3: The relative risk of the composite of 1-year cardiovascular death, non-fatal MI, or stroke

Study	Prasugrel (cases/n)	Ticagrelor (cases/n)	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
Motovska Z et al.	42/637	34/597	1.158	0.747 to 1.794			19.36	30.92
Schüpke S et al.	124/2006	161/2012	0.772	0.616 to 0.968			72.86	52.13
Alexopoulos D et al.	10/363	35/717	0.564	0.283 to 1.127			7.78	16.94
Total (fixed effects)	176/3006	230/3326	0.812	0.670 to 0.984	-2.127	0.033	100.00	100.00
Total (random effects)	176/3006	230/3326	0.830	0.598 to 1.152	-1.115	0.265	100.00	100.00

Overall Heterogeneity I^2 46.94%; N= Total number of cases; CI: confidence intervals; Random: random-effects model; MI - myocardial infarction.

Table 4: The relative risk of BARC type 3 to 5 bleeding at 1 year

Study	Prasugrel (cases/n)	Ticagrelor (cases/n)	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
Schüpke S et al.	80/1773	95/1989	0.945	0.707 to 1.263			70.73	70.73
Alexopoulos D et al.	18/363	39/717	0.912	0.529 to 1.571			20.16	20.16
Motovska Z et al.	16/637	9/600	1.675	0.746 to 3.760			9.12	9.12
Total (fixed effects)	114/2773	143/3306	0.992	0.778 to 1.265	-0.0657	0.948	100.00	100.00
Total (random effects)	114/2773	143/3306	0.988	0.774 to 1.262	-0.0954	0.924	100.00	100.00

Overall Heterogeneity I^2 0.00%. N= Total number of cases; CI: confidence intervals; Random: random-effects model

Table 5: The relative risk of 1-year all-cause death

Study	Prasugrel (cases/n)	Ticagrelor (cases/n)	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
Schüpke S et al.	73/2006	90/2012	0.814	0.601 to 1.101			50.34	50.34
Motovska Z et al.	30/639	25/596	1.119	0.666 to 1.881			17.10	17.10
Venetsanos D, et al.	48/2071	59/2071	0.814	0.559 to 1.185			32.56	32.56
Total (fixed effects)	151/4716	174/4679	0.859	0.693 to 1.064	-1.393	0.164	100.00	100.00
Total (random effects)	151/4716	174/4679	0.859	0.693 to 1.065	-1.386	0.166	100.00	100.00

Overall Heterogeneity I^2 0.00%; N= Total number of cases; CI: confidence intervals; Random: random-effects model

Table 6: The relative risk of 1-year cardiovascular death

Study	Prasugrel (cases/n)	Ticagrelor (cases/n)	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
Motovska Z et al.	21/637	18/600	1.099	0.591 to 2.042			20.85	20.85
Schüpke S et al.	59/2006	63/2012	0.939	0.662 to 1.332			65.48	65.48
Alexopoulos D et al.	9/363	22/717	0.808	0.376 to 1.737			13.67	13.67
Total (fixed effects)	89/3006	103/3329	0.950	0.716 to 1.260	-0.357	0.721	100.00	100.00
Total (random effects)	89/3006	103/3329	0.951	0.716 to 1.262	-0.350	0.727	100.00	100.00

Overall Heterogeneity I^2 0.00%; N= Total number of cases; CI: confidence intervals; Random: random-effects model

Table 7: The relative risk of 1-year Non-fatal MI

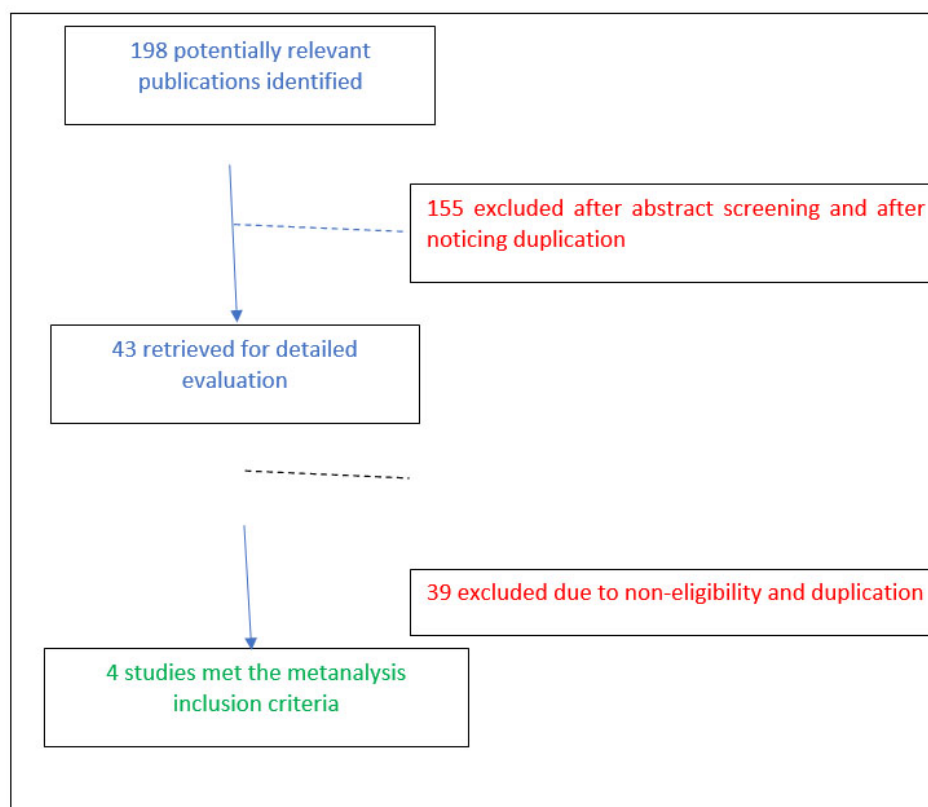
Study	Prasugrel (cases/n)	Ticagrelor (cases/n)	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
Schüpke S et al.	60/2006	96/2012	0.627	0.457 to 0.860			44.38	35.06
Motovska Z et al.	19/634	15/600	1.199	0.615 to 2.337			9.98	24.35
Alexopoulos D et al.	1/363	8/717	0.247	0.0310 to 1.967			1.03	5.52
Venetsanos D, et al.	85/2071	66/2071	1.288	0.939 to 1.766			44.61	35.08
Total (fixed effects)	165/5074	185/5400	0.903	0.734 to 1.111	-0.967	0.334	100.00	100.00
Total (random effects)	165/5074	185/5400	0.898	0.531 to 1.517	-0.403	0.687	100.00	100.00

Overall Heterogeneity I^2 75.32%; N= Total number of cases; CI: confidence intervals; Random: random-effects model; MI - myocardial infarction.

Table 8: The relative risk of 1-year stroke

Study	Prasugrel (cases/n)	Ticagrelor (cases/n)	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
Schüpke S et al.	19/2006	22/2012	0.866	0.470 to 1.595			45.41	45.41
Motovska Z et al.	7/637	9/600	0.733	0.275 to 1.955			17.58	17.58
Alexopoulos D et al.	0/363	5/717	0.179	0.00994 to 3.234			2.02	2.02
Venetsanos D, et al.	18/2071	14/2071	1.286	0.641 to 2.578			34.98	34.98
Total (fixed effects)	44/5077	50/5400	0.909	0.606 to 1.364	-0.461	0.645	100.00	100.00
Total (random effects)	44/5077	50/5400	0.935	0.620 to 1.412	-0.318	0.750	100.00	100.00

Overall Heterogeneity I^2 0.00%; N= Total number of cases; CI: confidence intervals; Random: random-effects model

**Figure 1:** Flowchart on the literature search and study selection process for Meta-Analyses.

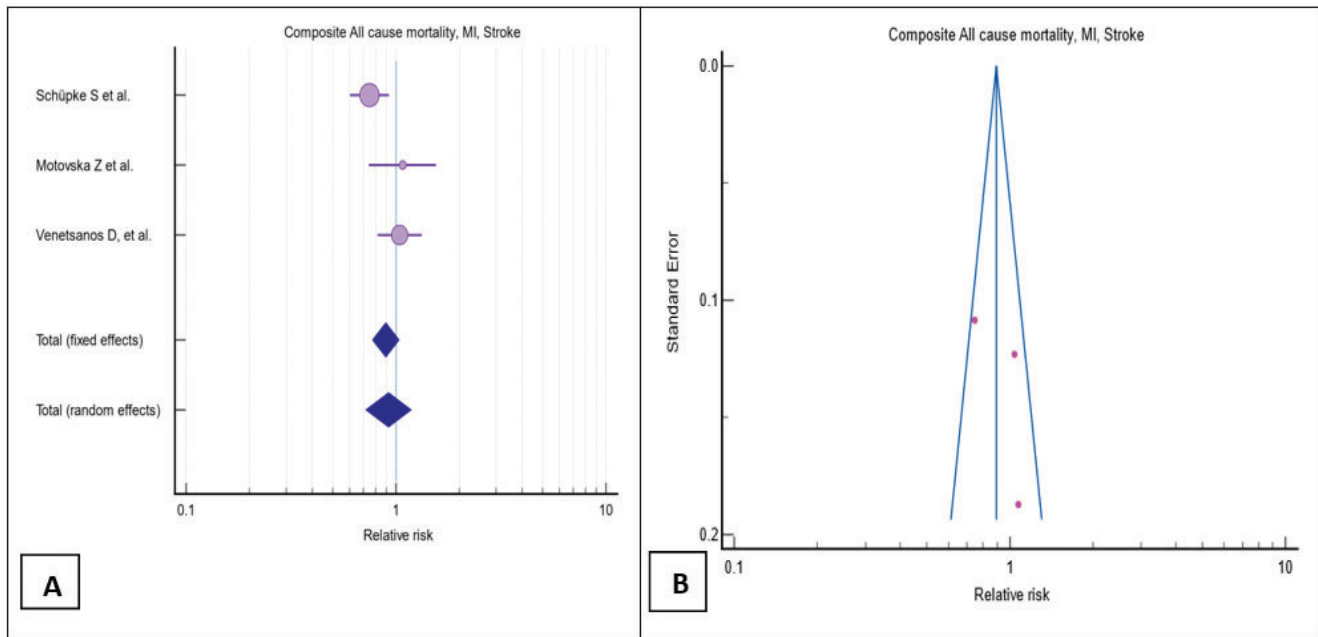


Figure 2: A. Forest plot showing the relative risk of the composite of 1-year all-cause death/mortality, MI (non-fatal MI), or stroke for Prasugrel and Ticagrelor groups. A forest plot is an effective measure of relative risk. The bubble size indicates the extent of relative risk; the error bars represent 95% CIs
B. Funnel plot showing the relative risk of the composite of 1-year all-cause death/mortality, MI (non-fatal MI), or stroke