Comparative efficacy and safety of oral P2Y₁₂ inhibitors after non-ST-elevation acute coronary syndromes: a network meta-analysis

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ABSTRACT

Background Currently, potent P2Y₁₂ inhibition with the use of prasugrel or ticagrelor is the mainstay of treatment after an acute coronary syndrome (ACS). The 2020 European Society of Cardiology (ESC) Guidelines recommend the use of prasugrel over ticagrelor in patients with non-ST-elevation ACS (NSTEMI-ACS) intended to receive invasive management (class IIa recommendation), however there are contradictory views regarding this recommendation.

Aim To compare oral P2Y₁₂ inhibitors in NSTEMI-ACS in terms of efficacy and safety with a focus on patients intended to proceed to invasive management.

Methods We systematically searched PubMed, Cochrane Central Register of Controlled Trials and Web of Science to identify studies that compared different oral P2Y₁₂ inhibitors (clopidogrel, prasugrel and ticagrelor) in patients with NSTEMI-ACS. Efficacy outcomes included the major adverse cardiovascular events outcome and safety outcomes included minor and major bleedings. We performed a frequentist network meta-analysis.

Results Nine studies (n=35,441 patients) were included in the systematic review. There was no difference between prasugrel and ticagrelor in the composite cardiovascular end point (prasugrel vs ticagrelor HR=0.80, 95% CI=0.61 to 1.06) in all patients with NSTEMI-ACS. In patients intended to receive invasive management, prasugrel resulted in a reduction of the composite cardiovascular end point both versus clopidogrel (HR=0.76, 95% CI=0.61 to 0.95) and ticagrelor (HR=0.74, 95% CI=0.56 to 0.98). Inconsistency was moderate and non-significant (I²=27%, total Q p=0.2). Prasugrel ranked as the most efficient treatment in the composite cardiovascular efficacy outcome, all-cause death, myocardial infarction and definite stent thrombosis, while clopidogrel ranked as safest in the bleeding outcomes.

Conclusion In patients with NSTEMI-ACS intended to receive invasive management, an antiplatelet strategy based on prasugrel is more efficient than a similar strategy based on ticagrelor on a moderate level of evidence. This analysis supports the current recommendations by the ESC guidelines.

Key questions

What is already known about this subject?

- The initiation of dual antiplatelet therapy constituted by aspirin and a P2Y₁₂ inhibitor, in the absence of indication for an oral anticoagulant, is the mainstay of antithrombotic therapy after an acute coronary syndrome (ACS).

What does this study add?

- In patients with NSTEMI-ACS intended to receive invasive management, an antiplatelet strategy based on prasugrel is more efficient than a similar strategy based on ticagrelor on a moderate level of evidence.

How might this impact on clinical practice?

- This analysis supports the current recommendations by the European Society of Cardiology guidelines.

INTRODUCTION

The management of antithrombotic therapy after an acute coronary syndrome (ACS) is getting increasingly complicated.1 Large outcome trials that test different strategies of antithrombotic therapies during the acute phase, in the immediate period after and long-term following an ACS are constantly being published altering the landscape of recommendations. However, to date, the initiation of dual antiplatelet therapy constituted by aspirin and a P2Y₁₂ inhibitor, in the absence of indication for an oral anticoagulant, is the mainstay of antithrombotic therapy after an ACS.

Following the landmark Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 and Study of Platelet Inhibition and Patient Outcomes (PLATO)3 studies, the use of potent P2Y₁₂ inhibitors (ie,
prasugrel and ticagrelor) is recommended over clopidogrel as an integral part of antithrombotic therapy after an ACS, whether a revascularisation or a conservative management strategy is followed. The 2020 European Society of Cardiology (ESC) guidelines for the management of patients with non-ST-elevation ACS (NSTE-ACS) suggest that prasugrel should be considered in preference to ticagrelor for patients with NSTE-ACS who proceed to percutaneous coronary intervention (PCI) (class of recommendation IIa, level of evidence B). This recommendation is mainly based on the results of the 2019 Intra-coronary Stenting and Antithrombolytic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial, an open-label, investigator-initiated randomised controlled trial (RCT), which showed that prasugrel had superior efficacy in the prevention of cardiovascular events over ticagrelor, without significantly increased rates of bleeding. However, given its design and methodological limitations, the study’s results and the subsequent guideline recommendation have received criticism.

We aimed to synthesise the evidence across the literature regarding the use of oral P2Y12 inhibitors in patients with NSTE-ACS concentrating on their comparative efficacy and safety in this population and focusing in the subgroup of patients intended to receive invasive management. Because of the lack of numerous large trials that compare prasugrel and ticagrelor head-to-head, we aimed to incorporate direct and indirect evidence by conducting a network meta-analysis.

METHODS
This systematic review and network meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for Network Meta-analyses (online supplemental PRISMA Checklist). The protocol of this study is published in the PROSPERO registry (CRD42020211123).

Search strategy
We used terms related to ‘P2Y12 inhibitors’, ‘acute coronary syndrome’ and an RCT search filter to search MEDLINE (via PubMed), the Cochrane Central Register of Controlled Trials and the Web of Science for RCTs that compared different oral P2Y12 inhibitors in patients with NSTE-ACS. For PubMed, a search string was created and modified accordingly to search in other databases. According to the snowball effect, all references from selected studies were retrieved and carefully examined. In addition, we looked for relevant abstracts from major cardiology conferences and combed through Clinical-Trials.gov for active research. There were no language limitations. Online supplemental material 1 contains the search string and search syntax.

Eligibility criteria
We included full-text RCTs that compared the different oral P2Y12 inhibitors (clopidogrel vs ticagrelor, clopidogrel vs prasugrel, ticagrelor vs prasugrel) in the setting of ACS and reported serious adverse cardiovascular events and/or bleeding events within the NSTE-ACS subgroup. We included RCTs which were designed to study the efficacy and safety of P2Y12 inhibitors in the entire ACS population and that reported outcomes on the NSTE-ACS population in a subgroup analysis. The efficacy composite end point of cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke was used as a primary end point, and the individual components of the primary efficacy composite end point, all-cause mortality and stent thrombosis were used as secondary efficacy end points. Major bleeding (as defined by each trial) and major or minor bleeding combined were the safety end points.

Studies with a primary pharmacokinetic/pharmacodynamic outcome, studies randomising patients based on genotype guidance or any other guidance, studies switching, by protocol definition, to an antiplatelet regimen at some point after ACS and studies with fewer than 100 patients in total were all excluded. Studies investigating short-acting intravenous P2Y12 inhibitors (such as cangrelor) were ruled out. When numerous texts with possibly overlapping populations were identified, we included the most current study.

Study selection, data extraction and quality assessment
All of the results of the search were entered into a reference management programme (Mendeley 1.19.3). All duplicates were deleted, and three reviewers (ID, AP and SZ) independently reviewed titles, abstracts and full texts for papers that were eligible. To resolve any discrepancies regarding research eligibility, a fourth review author (ITF) was consulted. We recorded all reasons for exclusion at the stage of full-text eligibility screening.

On a structured spreadsheet, two reviewers (AP, ITF) independently retrieved data on research design, efficacy and safety results. Before beginning, a pilot test was conducted to ensure coherence between authors, and any disagreements were settled through consensus. All data were extracted using standard procedures provided by the Cochrane Collaboration from full-texts, summary tables and figures or online supplemental information. Substudies related to the parent trials included in the analysis were retrieved to extract data from the NSTE-ACS and the invasively managed population (online supplemental material 13). Any missing data relevant to the analysis were obtained by contacting the authors.

Eligible studies were assessed for risk of bias (RoB) by two review authors (ITF, SZ) using the Cochrane collaboration RoB tool for RCTs (RoB 2). A sensitivity analysis was carried out to eliminate studies of poor quality. When relevant, the Egger’s test and visual assessment of funnel plot asymmetry were used to assess publication bias in the systematic review.

Strategy for data synthesis
To combine direct and indirect evidence across trials, we used a frequentist network meta-analysis with a random-effects model. To account for the time-to-event parameter,
the effect estimate was the HR with the appropriate 95% CIs. Both global approaches, such as the Cochran’s Q and the $I^2$ statistic (25% low, 25%–50% moderate and >50% high heterogeneity), and local ones, such as analysing consistency across direct and indirect comparisons with the node-splitting method, were used to measure consistency. The p-score was used to categorise interventions in a hierarchical order. This statistic has a range of 0–1, with values closer to 1 indicating better outcomes with the relevant intervention and values closer to 0 indicating worse outcomes. We used rankograms to visualise the probability of each treatment being at each possible rank.9 We explored the importance of each study to each comparison in the network by estimating the relative loss of precision if this study was left out of the network.10 An importance value of 1 means that the variance of the network effect becomes infinite if the study is removed from the network and, therefore, the study is an essential link to the specific comparison. We conducted a sensitivity analysis excluding patients that were treated conservatively (ie, without revascularisation).

All analyses were considered statistically significant if the p value was <0.05. The ‘netmeta’ package in the R Project for Statistical Computing was used for all analyses (V.3.6.3).11

**Grading of evidence**

We used the Confidence in Network Meta-analysis (CINeMA) framework, which was implemented in a web application available at http://cinema.ispm.ch, to assess the confidence in the network meta-analysis results. CINeMA is a network meta-analysis version of the Grading of Recommendations Assessment, Development, and Evaluation method.12

**Patient and public involvement**

There was no patient or public involvement during the completion of this paper.

**RESULTS**

**Search results, study characteristics and quality assessment**

The search strategy yielded 6406 results after duplicates removal. Following the initial screening phase, 86 full-text studies were screened for eligibility and 77 studies were excluded with reasons. Ultimately, nine studies (n=35,441 patients) were included in our analysis. The study selection process can be seen in figure 1. Study characteristics for each individual study are presented in online supplemental material 2. The median percentage of patients with NSTE-ACS in the RCTs was 59%. The median follow-up period ranged from 9.2 to 17 months. Three studies compared prasugrel with clopidogrel.2 13 14

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**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of the study selection process.
four studies compared ticagrelor with clopidogrel\textsuperscript{3, 15-17} and two studies compared prasugrel with ticagrelor.\textsuperscript{18, 19}

Employing the RoB.2 tool, the RoB was assessed as low in five studies, with some concerns in three studies and high in one study (online supplemental material 3). After visual assessment of the funnel plots for each outcome, there was no evidence of publication bias.

**Network meta-analysis**

**Primary efficacy outcome**

Eight studies (n=34,433 patients) contributed to the analysis.\textsuperscript{2, 3, 13-16, 18, 19} The network graph of interventions is presented in figure 2. With clopidogrel set as reference group, prasugrel showed a significant reduction of the primary efficacy end point (prasugrel vs clopidogrel HR=0.81, 95\% CI=0.67 to 0.99), whereas ticagrelor did not (ticagrelor vs clopidogrel HR=1.01, 95\% CI=0.79 to 1.29) (figure 3). In the prasugrel versus ticagrelor comparison the effect estimate favoured prasugrel, although the difference between the two treatments was not statistically significant (prasugrel vs ticagrelor HR=0.80, 95\% CI=0.61 to 1.06). Prasugrel ranked best (p-score=0.96), followed by clopidogrel (p-score=0.28) and ticagrelor (p-score=0.26). The inconsistency was high in the model (I\(^2\)=60\%, total Q p=0.01). No disagreement was detected between direct and indirect evidence with the node-splitting method. Further details on inconsistency, the funnel plot and individual studies’ impact in the network of the primary outcome are presented in online supplemental material 4.

In the analysis of patients managed invasively (seven studies, n=19,049 patients), prasugrel resulted in a significant reduction in the primary end point versus clopidogrel (HR=0.76, 95\% CI=0.61 to 0.95), as well as versus ticagrelor (HR=0.74, 95\% CI=0.56 to 0.98). Inconsistency was moderate and non-significant (I\(^2\)=27\%, total Q p=0.2). The importance of ISAR-REACT 5 study to the prasugrel versus ticagrelor comparison (0.45) was slightly greater than PLATO (0.31) and TRITON-TIMI 38 (0.28). However, a sensitivity analysis excluding ISAR-REACT 5 resulted in an unchanged p-score ranking (prasugrel=0.96, clopidogrel=0.35, ticagrelor=0.19).

**Secondary efficacy outcomes**

Five studies (n=33,841) contributed to the network for the outcome of cardiovascular death (online supplemental material 5).\textsuperscript{2, 3, 13-17, 19} Ticagrelor significantly reduced cardiovascular death compared with clopidogrel (HR=0.81, 95\% CI=0.69 to 0.96), whereas prasugrel did not (HR=0.91, 95\% CI=0.80 to 1.04), with no difference between prasugrel versus ticagrelor (HR=1.12, 95\% CI=0.91 to 1.38) (I\(^2\)=0\%). However, in the sensitivity analysis of invasively managed patients none of the potent P2Y\(_{12}\) inhibitors resulted in significant reduction of the end point (online supplemental material 5). Four studies (n=25,773 patients) contributed to the network for the outcome of all-cause death (online supplemental material 6).\textsuperscript{3, 13-17, 19} None of the potent P2Y\(_{12}\) inhibitors resulted in significant reduction of the end point (I\(^2\)=64\%, total Q p=0.06), whereas in the sensitivity analysis both potent P2Y\(_{12}\) inhibitors led to reduction of all-cause mortality (HR=0.54 and 0.78, respectively, I\(^2\)=0\%).

Five studies (n=33,841) contributed to the network for the MI outcome (online supplemental material 7).\textsuperscript{2, 3, 13-17, 19} There was no difference between the interventions in the main analysis (I\(^2\)=60\%, total Q p=0.05), however, in patients managed invasively prasugrel led to better outcomes when compared with clopidogrel (HR=0.75, 95\% CI=0.66 to 0.86) and also, when compared with
ticagrelor (HR=0.78, 95% CI=0.62 to 0.99) (I²=0%). Five studies (n=33,841 patients) contributed to the network for the stroke outcome (online supplemental material 8).\textsuperscript{2,3,13,17,19} There was no difference between the interventions both in the main and the sensitivity analysis (I²=0%).

Three studies (n=23,513) contributed to the network for the stent thrombosis outcome (online supplemental material 9).\textsuperscript{2,3,19} Prasugrel resulted in reduced rates of stent thrombosis compared with clopidogrel (HR=0.43, 95% CI=0.29 to 0.62), but not compared with ticagrelor (HR=0.60, 95% CI=0.34 to 1.05) (I²=0%).

The results of the main efficacy analysis are collectively shown in figure 3 and the results of the sensitivity analysis of invasive management is shown in figure 4.

Safety outcomes
Six studies (n=33,702) contributed to the network for the major bleeding outcome (online supplemental material 10).\textsuperscript{2,3,13,16,17} The definition of major bleeding was not consistent across studies and it was defined by different criteria in each study (online supplemental material 2, column 7). Major bleeding did not differ between the interventions (prasugrel vs clopidogrel HR=1.15, 95% CI=0.75 to 1.75, ticagrelor vs clopidogrel HR=1.36, 95% CI=0.90 to 2.06, prasugrel vs ticagrelor HR=0.84, 95% CI=0.52 to 1.37) (figure 5). Inconsistency was high in the model (I²=73%) and significant (total Q p=0.005). The sensitivity analysis excluding patients with conservative management did not show any significant difference between the interventions (figure 5).

Five studies (n=31,870) contributed to the network for the major or minor bleeding outcome (online supplemental material 10).\textsuperscript{2,3,13,16,17} Both prasugrel and ticagrelor resulted in more major or minor bleeding than clopidogrel (HR=1.37, 95% CI=1.07 to 1.75 and HR=1.28, 95% CI=1.04 to 1.58, respectively) (figure 5). No difference was observed between prasugrel versus ticagrelor (HR=1.07, 95% CI=0.77 to 1.47). Inconsistency was moderate in the model (I²=46%) and non-significant (total Q p=0.14). Excluding conservative management patients, there was no longer difference in the prasugrel versus clopidogrel comparison (figure 5).

Treatment rankings
Rankograms of probabilities for each treatment to lie at each possible rank concerning the main analysis can be seen in online supplemental material 11. The corresponding rankograms for the patients managed invasively can be seen in figure 6. Prasugrel ranked with great probability as the most efficient treatment in the composite efficacy outcome, all-cause death, MI and definite stent thrombosis, while ticagrelor ranked as the most efficient treatment in cardiovascular death outcome, although with modest probability. Concerning the bleeding outcomes, clopidogrel ranked as the safest treatment with great probability.

Grading of evidence
Details for the grading of evidence for all outcomes can be seen in online supplemental material 12. Grading of evidence in patients managed invasively (sensitivity analysis) can also be seen in online supplemental material 12.

DISCUSSION
In this study, we generated a network meta-analysis to assess the comparative efficacy and safety of P2Y12 inhibitors in patients with NSTE-ACS, focusing on patients receiving an invasive course of management. Our results suggest that, in patients with invasive management, prasugrel was associated with lower rates of the composite cardiovascular efficacy end point by 26% compared with ticagrelor on a moderate level of evidence. Prasugrel ranked as the most effective treatment in the composite efficacy outcome, all-cause death, MI and definite stent
thrombosis, without an excessive risk of major bleeding compared with clopidogrel.

The sole largest RCT powered for clinical outcomes to directly compare ticagrelor with prasugrel, which also included a fair percentage of patients with NSTE-ACS, is the ISAR-REACT 5 study (the Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction (PRAGUE) 18 trial included a very small proportion of patients with NSTE-ACS). In NSTE-ACS, higher rates of the primary end point (all-cause death, non-fatal MI, non-fatal stroke) were observed with ticagrelor. As a consequence, a recommendation was included in the latest 2020 NSTE-ACS ESC guidelines with a preference for prasugrel over ticagrelor in patients managed invasively. However, the trial has received criticism mainly because of its open-label design, modest sample size and slightly higher rates of ticagrelor discontinuation, and therefore some suggest that its results should not be over-interpreted and cannot form the basis of a recommendation for prasugrel over ticagrelor in that setting. On the other hand, the PLATO trial has been subject to criticism because approximately half of its patients were treated with a conservative treatment, therefore making difficult an extrapolation exclusively to the invasively managed population, whereas the TRITON-TIMI 38 and ISAR-REACT 5 trials were designed to have PCI as first-line treatment. Our results suggest that prasugrel ranked as most effective in ischaemic event reduction and mortality over ticagrelor and in particular the impact of the ISAR-REACT study on the prasugrel versus ticagrelor in the network was not dominant over the other two large RCTs, PLATO and TRITON-TIMI 38. In addition, the sensitivity analysis excluding the ISAR-REACT 5 trial did not alter the ranking of treatments.

The ISAR-REACT 5 study required the administration of prasugrel after knowledge of the coronary anatomy, whereas ticagrelor was routinely administered pretreatment and thus, the observed efficacy of prasugrel over ticagrelor in the NSTE-ACS population may confirm that there is no apparent benefit for pretreatment. The decision of invasively treating the NSTE-ACS patient is an important one, requiring robust risk stratification and has direct implications on the use of a P2Y12 inhibitor prior to the revascularisation. Following the Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) trial, pretreatment with prasugrel, before knowledge of the coronary anatomy, is prohibited because of the lack of any ischaemic benefit and increased risk of bleeding. A recent meta-analysis suggests that pretreatment with oral P2Y12 inhibitors prior to angiography, compared with after knowledge of coronary anatomy at the time of PCI, is associated with no difference in cardiovascular outcomes and with increased bleeding risk, irrespective of the P2Y12 inhibitor type and, thus, routine pretreatment in NSTE-ACS is not supported.

A network meta-analysis on the overall ACS population was recently conducted. A significant reduction in cardiovascular death and all-cause mortality was found only with ticagrelor compared with clopidogrel, while prasugrel effectively reduced MI compared with clopidogrel. Notably, in none of the explored outcomes there was a difference between ticagrelor and prasugrel,
but they both increased major bleeding compared with clopidogrel. Other meta-analyses of the total ACS population have focused solely on the prasugrel versus ticagrelor comparison by analysing RCTs and observational studies together or by including studies not designed to primarily explore clinical outcomes. Yet, they found no difference in cardiovascular outcomes between prasugrel and ticagrelor. Our meta-analysis differs from the already published evidence in focusing on the NSTE-ACS population and especially in those managed invasively.

Of note, ticagrelor and not prasugrel reduced the cardiovascular death outcome compared with clopidogrel. The PLATO trial showed an impressive 23% significant reduction of death due to vascular causes with ticagrelor compared with clopidogrel in patients with NSTE-ACS, which had a major impact in the network analysis, while there was not such a significant effect of prasugrel in the TRITON-TIMI 38 trial.

In contrast, non-fatal MIs were effectively reduced with prasugrel compared with both clopidogrel and ticagrelor in patients managed invasively. Our analysis included all MIs, both spontaneous and periprocedural and it was not possible to conduct a separate analysis for each type of MI. In the ISAR-REACT 5 study, MIs of all types were numerically higher in the ticagrelor group than in the prasugrel group, although there was no significant difference between groups. However, the impact of ISAR-REACT 5 to the network for the prasugrel versus ticagrelor comparison in the MI outcome was lower than the impact of PLATO, implying that the results are not exclusively driven by the ISAR-REACT 5 trial.

Lastly, stent thrombosis rates were significantly reduced with prasugrel compared with clopidogrel, but not with ticagrelor and there was not a significant difference between the potent P2Y₁₂ inhibitors. A network meta-analysis in the overall ACS population reports similar results.

Studies focusing on the effect of P2Y₁₂ inhibitors on the platelet function and endothelial function could also be relevant. A prespecified substudy of the ISAR-REACT 5 study compared the pharmacodynamic effects of prasugrel and ticagrelor through the use of platelet function testing. Prasugrel resulted in lower platelet aggregation both at the first and second 24-hour interval after loading dose administration. Lower platelet aggregation values significantly predicted lower incidence of the primary end point, denoting the clinical value of the observation. In a recent RCT of invasively managed patients with STElevation myocardial infarction and NSTE-ACS, treatment with prasugrel before stenting resulted in stronger platelet inhibition, improved endothelial function and reduced inflammation than both clopidogrel and ticagrelor. In contrast to the aforementioned studies, a meta-analysis of 14 pharmacodynamic studies revealed increased platelet reactivity with prasugrel than ticagrelor. These discrepancies between studies imply the inconsistency between testing methods and arrays in the studies and render difficult the translation to clinical value.

**Strengths and limitations**

To our knowledge, this is the first study to generate a network meta-analysis of randomised and outcome-driven trials and to assess the comparative efficacy and safety profiles of oral P2Y₁₂ inhibitors in a NSTE-ACS context. A previous meta-analysis in the NSTE-ACS population jointly assessed the potent P2Y₁₂ inhibitors in comparison to clopidogrel. However, given the relative small number of RCTs to directly compare ticagrelor and prasugrel, a network approach has certain advantages as it allows the incorporation of indirect evidence to the overall effect. In the current study, there was no difference between direct and indirect source of evidence for any of the comparisons in all outcomes, enhancing thus the robustness of our results. Nevertheless, certain limitations should be noted. The results are based on trial-level data and not on individual patient-level data. Randomisation in the included RCTs was not performed based on the ACS status, therefore undiscovered confounders may exist. Other confounders, such as differences in loading regimens and timing of P2Y₁₂ administration (pretreatment or not), differences in access sites and stent preferences may have also played a role. In the sensitivity analysis, some smaller studies had a mixed population of revascularisation and conservative management but were not able to be selectively excluded from the analysis due to lack of individual patient data reporting. However, the vast majority of patients in these studies received revascularisation. There was not a unified approach to the reporting of bleeding outcomes across studies. All studies reported the composite primary outcome of cardiovascular death, non-fatal MI or non-fatal stroke, but there may be variability in the exact definitions.

**Conclusion**

In patients with NSTE-ACS intended to receive invasive management, an antiplatelet strategy with prasugrel was superior to ticagrelor on a moderate level of evidence, mainly due to more favourable rates in the composite cardiovascular efficacy outcome, all-cause death, MI and definite stent thrombosis. This analysis supports the current recommendations by the ESC guidelines.

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Supplementary Material 1: Search strategy.

SEARCH SYNTAX and SEARCH STRING (in PubMed) for RCTs

1. Clopidogrel
2. Ticagrelor
3. Prasugrel
4. P2y12 inhibitor
5. ADP receptor antagonist
6. 1 OR 2 OR 3 OR 4 OR 5
7. acute coronary syndrome
8. acute myocardial infarction
9. st elevation myocardial infarction
10. non-st elevation myocardial infarction
11. non-st elevation acute coronary syndrome
12. unstable angina
13. 7 OR 8 OR 9 OR 10 OR 11 OR 12
14. Precision-sensitivity maximizing RCT search filter from Cochrane
15. 6 AND 13 AND 14

((((((clopidogrel) OR (ticagrelor)) OR (prasugrel)) OR (p2y12 inhibitor)) OR (adp receptor antagonist)) AND (((((acute coronary syndrome) OR (acute myocardial infarction)) OR (st elevation myocardial infarction)) OR (non-st elevation myocardial infarction)) OR (non-st elevation acute coronary syndrome)) OR (unstable angina))) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp]) OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))) (((("clopidogrel"[MeSH Terms] OR "clopidogrel"[All Fields]) OR "clopidogrel s"[All Fields]) OR ("ticagrelor"[MeSH Terms] OR "ticagrelor"[All Fields])) OR ((("prasugrel hydrochloride"[MeSH Terms] OR ("prasugrel"[All Fields] AND "hydrochloride"[All Fields]) OR "prasugrel hydrochloride"[All Fields]) OR "prasugrel"[All Fields])) OR "prasugrel s"[All Fields]) OR ("p2y12"[All Fields] AND ((("antagonists and inhibitors"[MeSH Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields])) OR "antagonists and inhibitors"[All Fields]) OR "inhibitors"[All Fields]) OR "inhibitor"[All Fields]) OR "inhibitor s"[All Fields])) OR ((("receptors, purinergic p2"[MeSH Terms] OR ("receptors"[All Fields] AND "purinergic p2 receptors"[All Fields]) OR "purinergic p2 receptors"[All Fields])) OR ("adp"[All Fields] AND "receptor"[All Fields]) OR "adp receptor"[All Fields]) AND ((("antagonist"[All Fields] OR "antagonists and inhibitors"[MeSH Subheading]) OR ("antagonists"[All Fields] AND "inhibitors"[All Fields])) OR "antagonists and inhibitors"[All Fields]) OR "antagonists"[All Fields]) AND ((("acute coronary syndrome"[MeSH Terms] OR ("acute"[All Fields] AND "coronary"[All Fields]) OR "syndrome"[All Fields]) OR "acute coronary syndrome"[All Fields]) OR ("acute"[All Fields] OR "acutely"[All Fields] OR "acutes"[All Fields]) AND ("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields])) OR "myocardial infarction"[All Fields])) OR ("st elevation myocardial infarction"[MeSH Terms] OR ("st"[All Fields] AND "elevation"[All Fields] AND "myocardial"[All Fields]) OR "infarction"[All Fields]) OR "st elevation myocardial infarction"[All Fields]) OR ((("non-st elevated myocardial infarction"[MeSH Terms] OR ((("non-st"[All Fields] AND "elevated"[All Fields]) AND "myocardial"[All Fields]) AND "infarction"[All Fields]) OR ("non-st elevated myocardial infarction"[All Fields])) OR "non st
elevated myocardial infarction[All Fields] OR ((("non"[All Fields] AND "st"[All Fields]) AND "elevation"[All Fields]) AND "myocardial"[All Fields]) AND "infarction"[All Fields]) OR "non st elevation myocardial infarction"[All Fields]) OR ("non-st"[All Fields] AND (((("elevate"[All Fields] OR "elevated"[All Fields]) OR "elevates"[All Fields]) OR "elevating"[All Fields]) OR "elevation"[All Fields]) OR "elevational"[All Fields]) OR "elevations"[All Fields]) AND (("acute coronary syndrome"[MeSH Terms] OR ("acute"[All Fields] AND "coronary"[All Fields]) AND "syndrome"[All Fields]) OR "acute coronary syndrome"[All Fields])) OR (((("angina, unstable"[MeSH Terms] OR ("angina"[All Fields] AND "unstable"[All Fields]) OR "unstable angina"[All Fields]) OR ("unstable"[All Fields] AND "angina"[All Fields]))) AND ((("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type]) OR "randomized"[Title/Abstract]) OR "placebo"[Title/Abstract]) OR "clinical trials as topic"[MeSH Terms:noexp]) OR "randomly"[Title/Abstract]) OR "trial"[Title]) NOT ("animals"[MeSH Terms]) NOT "humans"[MeSH Terms])

Translations

clopidogrel: "clopidogrel"[MeSH Terms] OR "clopidogrel"[All Fields] OR "clopidogrel's"[All Fields]
ticagrelor: "ticagrelor"[MeSH Terms] OR "ticagrelor"[All Fields] OR "ticagrelor's"[All Fields]
prasugrel: "prasugrel hydrochloride"[MeSH Terms] OR ("prasugrel"[All Fields] AND "hydrochloride"[All Fields]) OR "prasugrel hydrochloride"[All Fields] OR "prasugrel"[All Fields] OR "prasugrel's"[All Fields]
inhibitor: "antagonists and inhibitors"[Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields] OR "inhibitor"[All Fields] OR "inhibitor's"[All Fields]
adp receptor: "receptors, purinergic p2"[MeSH Terms] OR ("receptors"[All Fields] AND "purinergic"[All Fields] AND "p2"[All Fields]) OR "purinergic p2 receptors"[All Fields] OR ("adp"[All Fields] AND "receptor"[All Fields]) OR "adp receptor"[All Fields]
antagonist: "antagonist"[All Fields] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR ("antagonists and inhibitors"[All Fields] OR "antagonists"[All Fields]) OR "antagonists"[All Fields]
acute coronary syndrome: "acute coronary syndrome"[MeSH Terms] OR ("acute"[All Fields] AND "coronary"[All Fields] AND "syndrome"[All Fields]) OR "acute coronary syndrome"[All Fields]
acute: "acute"[All Fields] OR "acutely"[All Fields] OR "acutes"[All Fields]
myocardial infarction: "myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields]
st elevation myocardial infarction: "st elevation myocardial infarction"[MeSH Terms] OR ("st"[All Fields] AND "elevation"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "st elevation myocardial infarction"[All Fields] OR "st elevation myocardial infarction"[All Fields]
non-st elevation myocardial infarction: "non-st elevated myocardial infarction"[MeSH Terms] OR ("non-st"[All Fields] AND "elevated"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "non-st elevated myocardial infarction"[All Fields] OR ("non"[All Fields] AND "st"[All Fields] AND "elevation"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "non st elevation myocardial infarction"[All Fields]
elevation: "elevate"[All Fields] OR "elevated"[All Fields] OR "elevates"[All Fields] OR "elevating"[All Fields] OR "elevation"[All Fields] OR "elevational"[All Fields] OR "elevations"[All Fields]
acute coronary syndrome: "acute coronary syndrome"[MeSH Terms] OR ("acute"[All Fields] AND "coronary"[All Fields] AND "syndrome"[All Fields]) OR "acute coronary syndrome"[All Fields]

unstable angina: "angina, unstable"[MeSH Terms] OR ("angina"[All Fields] AND "unstable"[All Fields]) OR "unstable angina"[All Fields] OR ("unstable"[All Fields] AND "angina"[All Fields])

clinical trials as topic[mesh:noexp]: "clinical trials as topic"[MeSH Terms:noexp]

animals[mh]: "animals"[MeSH Terms]

humans [mh]: "humans"[MeSH Terms]
## Supplementary Material 2: Table with Characteristics of eligible trials

| STUDY AND YEAR OF PUBLICATION | POPULATION | N OF PATIENTS WITH E-ACS (% OF TOTAL) | INVASIVE TREATMENT ARMS | EFFICACY OUTCOME | MAJOR BLEEDING DEFINITION | FOLLOW-UP DURATION (MONTHS) |
|-------------------------------|------------|--------------------------------------|-------------------------|-----------------|---------------------------|-----------------------------|
| **Wiviott et al. 2007** (Triton-TIMI 38) | ACS with scheduled PCI | 1007 (74%) | 1. Prasugrel (n = 6813) | Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke | TIMI major bleeding not related to CABG | 14.5 |
| | Hospitalized for ACS, with or without ST-segment elevation, with onset of symptoms during the previous 24 hours | 1108 (59.5%) | 1. Ticagrelor (n = 9333) | Composite of death from vascular causes, myocardial infarction, or stroke | PLATO major bleeding | 9.2 |
| **Roe et al. 2012** (Trilogy-ACS) | ACS patients selected for a final treatment strategy of medical management without revascularization within 10 days after the index event | 9326 (100%) | 1. Prasugrel (n = 4663) | Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke | TIMI major bleeding not related to CABG | 17 |
| **Saito et al. 2014** (Prasfis-T-ACS) | Japanese ACS patients | 680 (49.1%) | 1. Prasugrel reduced dose (n = 685) | Composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke | TIMI major bleeding not related to CABG | 12 |
| STUDY AND YEAR OF PUBLICATION | POPULATION | N OF PATIENTS WITH NSTE-ACS (% OF TOTAL) | TREATMENT ARMS | EFFICACY OUTCOME | MAJOR BLEEDING DEFINITION | FOLLOW-UP DURATION (MEDIAN) |
|-------------------------------|------------|------------------------------------------|----------------|-----------------|---------------------------|---------------------------|
| GOTO ET AL. 2015 (PHILO)      | Japanese, Korean and Taiwanese ACS patients | 368 (45.9%) | 1. Ticagrelor (n = 401) 2. Clopidogrel (n = 400) | Time to first occurrence of MI, stroke or death from vascular causes | PLATO major bleeding | 7 months |
| MOTOVSKA ET AL. 2017 (PRAGUE-E-18) | Patients with AMI treated with a primary PCI strategy | 72 (5.9%) | 1. Prasugrel (n = 634) 2. Ticagrel or (n = 596) | Occurrence of cardiovascular death, non-fatal MI, or stroke | Not provided | 12 months |
| PARK ET AL. 2019 (TICAKOREA) | Korean ACS with or without ST elevation | 474 (59.3%) | 1. Ticagrelor (n = 400) 2. Clopidogrel (n = 400) | Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke | PLATO major bleeding | 12 months |
| SCHÜPE ET AL. 2019 (ISAR-REACT 5) | ACS patients | 2365 (58.9%) | 1. Ticagrelor (n = 2012) 2. Prasugrel (n = 2006) | Composite of death, myocardial infarction, or stroke | BARC type 3 to 5 | 12 months |
| GIMBEL ET AL. 2020 (POPULAR AGE) | Patients aged 70 years or older with NSTE-ACS | 1002 (100%) | 1. Clopidogrel (n = 500) 2. Ticagrel or prasugrel (n = 502) | First primary outcome: any bleeding requiring medical intervention, defined as PLATO major or minor bleeding. Second primary outcome: net clinical benefit of all-cause death, myocardial infarction, stroke and PLATO major or minor bleeding | PLATO major bleeding | 12 months |
Supplementary Material 3: Quality assessment of included studies.

Summary of RoB 2.0 assessments

- Bias arising from the randomization process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

Risk of bias domains

RoB 2.0 study by study assessment

Domains:
- D1: Bias due to randomization
- D2: Bias due to deviations from intended interventions
- D3: Bias due to missing data
- D4: Bias due to outcome measurement
- D5: Bias due to selection of reported result

Judgement:
- High risk of bias
- Some concerns
- Low risk of bias

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**Supplementary Material 4: Assessment of inconsistency, funnel plot and impact of individual studies for the primary efficacy outcome.**

Table C.1. Node-splitting method for assessment of inconsistency in network meta-analysis.

| Comparison          | k | prop | NMA   | Direct | Indirect | RoR  | z    | p-value |
|---------------------|---|------|-------|--------|----------|------|------|---------|
| Clopidogrel : Prasugrel | 4 | 0.86 | 1.23  | 1.20   | 1.44     | 0.83 | -0.64| 0.52    |
| Clopidogrel : Ticagrelor | 3 | 0.74 | 0.99  | 1.04   | 0.86     | 1.20 | 0.64 | 0.52    |
| Prasugrel : Ticagrelor | 2 | 0.40 | 0.80  | 0.72   | 0.86     | 0.83 | -0.64| 0.52    |

*K: Number of studies providing direct evidence, prop: Direct evidence proportion, NMA: Estimated treatment effect (HR) in network meta-analysis, Direct: Estimated treatment effect (HR) derived from direct evidence, Indirect: Estimated treatment effect (HR) derived from indirect evidence, RoR: Ratio of ratios (direct versus indirect), z: z-value of test for disagreement (direct versus indirect), p-value: p-value of test for disagreement (direct versus indirect).

Figure C.1. Forest plot of the direct and indirect evidence for the individual comparisons.
Table C.2. Node-splitting method for assessment of inconsistency in network meta-analysis after excluding patients with conservative management.

| Comparison         | k | prop | NMA  | Direct | Indirect | RoR  | z    | p-value |
|--------------------|---|------|------|--------|----------|------|------|---------|
| Clopidogrel : Prasugrel | 3 | 0.81 | 1.32 | 1.31   | 1.37     | 0.96 | -0.16| 0.88    |
| Clopidogrel : Ticagrelor | 3 | 0.72 | 0.97 | 0.99   | 0.94     | 1.05 | 0.16| 0.88    |
| Prasugrel : Ticagrelor   | 2 | 0.48 | 0.74 | 0.72   | 0.76     | 0.96 | -0.16| 0.88    |

*Note: Number of studies providing direct evidence, prop: Direct evidence proportion, NMA: Estimated treatment effect (HR) in network meta-analysis, Direct: Estimated treatment effect (HR) derived from direct evidence, Indirect: Estimated treatment effect (HR) derived from indirect evidence, RoR: Ratio of ratios (direct versus indirect), z: z-value of test for disagreement (direct versus indirect), p-value: p-value of test for disagreement (direct versus indirect).

Figure C.2. Forest plot of the direct and indirect evidence for the individual comparisons after excluding patients with conservative management.
Figure C.3. Funnel plot of studies contributing in the network for the primary outcome.

Table C.3. Impact of individual studies in the network meta-analysis for the primary efficacy outcome.

| Study          | Clopidogrel : Prasugrel | Clopidogrel : Ticagrelor | Prasugrel : Ticagrelor |
|---------------|--------------------------|--------------------------|------------------------|
| Wiviott 2007  | 0.35                     | 0.03                     | 0.12                   |
| Wallentin 2009| 0.07                     | 0.56                     | 0.39                   |
| Roe 2012      | 0.36                     | 0.03                     | 0.12                   |
| Saito 2014 UA | 0.07                     | 0.004                    | 0.02                   |
| Saito 2014 NSTEMI | 0.09                 | 0.005                    | 0.02                   |
| Goto 2015     | 0.005                    | 0.08                     | 0.04                   |
| Motovska 2017 | 0.006                    | 0.01                     | 0.03                   |
|            |       |       |       |
|------------|-------|-------|-------|
| Park 2019  | 0.007 | 0.10  | 0.06  |
| Schüpke 2019 | 0.13  | 0.24  | 0.37  |
Supplementary Material 5: Network meta-analysis of interventions for the cardiovascular death outcome.

![Network graph of interventions for the cardiovascular death outcome.](image)

*Figure D.1. Network graph of interventions for the cardiovascular death outcome.*
Figure D.2. Forest plot of the network estimates of the potent P2Y12 inhibitors for the cardiovascular death outcome.
Figure D.3. Funnel plot of studies contributing in the network for the cardiovascular death outcome.
Figure D.4. Forest plot of the network estimates of the potent P2Y12 inhibitors for the cardiovascular death outcome in the sensitivity analysis.

Table D.1. Impact of individual studies in the network meta-analysis for the cardiovascular death outcome.

| Study   | Clopidogrel : Prasugrel | Clopidogrel : Ticagrelor | Prasugrel : Ticagrelor |
|---------|-------------------------|--------------------------|------------------------|
| Wiviott 2007 | 0.21                    | 0.01                     | 0.08                   |
| Wallentin 2009 | 0.04                    | 0.83                     | 0.75                   |
| Roe 2012       | 0.73                    | 0.02                     | 0.47                   |
| Schüpke 2019  | 0.06                    | 0.10                     | 0.16                   |
| Gimbel 2020   | 0.01                    | 0.06                     | 0.04                   |
Supplementary Material 6: Network meta-analysis of interventions for the all-cause mortality outcome.

![Network graph of interventions for the all-cause death outcome.](image)

**Figure E.1.** Network graph of interventions for the all-cause death outcome.

| Comparison          | Number of Studies | Direct Evidence | Random effects model | HR   | 95%-CI |
|---------------------|-------------------|-----------------|----------------------|------|--------|
| Clopidogrel : Prasugrel | Direct estimate: 1 | 0.72            |                      | 1.06 [0.68; 1.66] |
|                     | Indirect estimate |                 |                      | 1.76 [0.87; 3.56] |
|                     | Network estimate  |                 |                      | 1.23 [0.84; 1.78] |
| Clopidogrel : Ticagrelor | Direct estimate: 2 | 0.81            |                      | 1.23 [0.85; 1.77] |
|                     | Indirect estimate |                 |                      | 0.74 [0.35; 1.57] |
|                     | Network estimate  |                 |                      | 1.12 [0.80; 1.55] |
| Prasugrel : Ticagrelor | Direct estimate: 1 | 0.48            |                      | 0.70 [0.38; 1.28] |
|                     | Indirect estimate |                 |                      | 1.16 [0.65; 2.05] |
|                     | Network estimate  |                 |                      | 0.91 [0.60; 1.38] |

**Figure E.2.** Forest plot of the network estimates of the potent P2Y12 inhibitors for the all-cause mortality outcome.
Figure E.3. Funnel plot of studies contributing in the network for the all-cause death outcome.

Figure E.4. Forest plot of the network estimates of the potent P2Y12 inhibitors for the all-cause death outcome in the sensitivity analysis.
Table E.1. Impact of individual studies in the network meta-analysis for the all-cause death outcome.

| Study       | Clopidogrel : Prasugrel | Clopidogrel : Ticagrelor | Prasugrel : Ticagrelor |
|-------------|-------------------------|--------------------------|------------------------|
| Wallentin 2009 | 0.10                    | 0.53                     | 0.23                   |
| Roe 2012    | 0.72                    | 0.19                     | 0.52                   |
| Schüpke 2019 | 0.28                    | 0.19                     | 0.48                   |
| Gimbel 2020 | 0.04                    | 0.28                     | 0.09                   |
Supplementary Material 7: Network meta-analysis of interventions for the myocardial infarction outcome.

Figure F.1. Network graph of interventions for the myocardial infarction outcome.
### Forest plot of the network estimates of the potent P2Y12 inhibitors for the myocardial infarction outcome

| Comparison          | Number of Studies | Direct Evidence | Random effects model | HR    | 95% CI     |
|---------------------|-------------------|-----------------|----------------------|-------|------------|
| Clopidogrel : Prasugrel | 2                 | 0.88            |                      |       |            |
| Direct estimate     |                   |                 |                      | 1.17  | [0.95; 1.44]|
| Indirect estimate   |                   |                 |                      | 1.60  | [0.92; 2.80]|
| Network estimate    |                   |                 |                      | 1.22  | [1.00; 1.48]|
| Clopidogrel : Ticagrelor | 2              | 0.81            |                      |       |            |
| Direct estimate     |                   |                 |                      | 1.12  | [0.87; 1.45]|
| Indirect estimate   |                   |                 |                      | 0.82  | [0.48; 1.40]|
| Network estimate    |                   |                 |                      | 1.06  | [0.84; 1.33]|
| Prasugrel : Ticagrelor | 1               | 0.31            |                      |       |            |
| Direct estimate     |                   |                 |                      | 0.70  | [0.43; 1.15]|
| Indirect estimate   |                   |                 |                      | 0.96  | [0.69; 1.33]|
| Network estimate    |                   |                 |                      | 0.87  | [0.66; 1.14]|

*Figure F.2. Forest plot of the network estimates of the potent P2Y12 inhibitors for the myocardial infarction outcome.*
Figure F.3. Funnel plot of studies contributing in the network for the myocardial infarction outcome.

Figure F.4. Forest plot of the network estimates of the potent P2Y12 inhibitors for the myocardial infarction outcome in the sensitivity analysis.
Table F.1. Impact of individual studies in the network meta-analysis for the myocardial infarction outcome.

| Study         | Clopidogrel : Prasugrel | Clopidogrel : Ticagrelor | Prasugrel : Ticagrelor |
|---------------|--------------------------|--------------------------|------------------------|
| Wiviott 2007  | 0.44                     | 0.02                     | 0.20                   |
| Wallentin 2009| 0.05                     | 0.62                     | 0.45                   |
| Roe 2012      | 0.43                     | 0.02                     | 0.19                   |
| Schüpke 2019  | 0.12                     | 0.19                     | 0.31                   |
| Gimbel 2020   | 0.01                     | 0.20                     | 0.11                   |
Supplementary Material 8: Network meta-analysis of interventions for the stroke outcome.

Figure G.1. Network graph of interventions for the stroke outcome.

| Comparison            | Number of Studies | Direct Evidence | Random effects model | HR   | 95%-CI       |
|-----------------------|-------------------|-----------------|----------------------|------|-------------|
| Clopidogrel : Prasugrel| 2                 | 0.92            |                      | 1.04 | [0.80; 1.35]|
|                       |                   |                 |                      | 1.28 | [0.52; 3.15]|
|                       |                   |                 |                      | 1.06 | [0.82; 1.36]|
| Clopidogrel : Ticagrelor| 2              | 0.89            |                      | 0.99 | [0.72; 1.35]|
|                       |                   |                 |                      | 0.80 | [0.33; 1.93]|
|                       |                   |                 |                      | 0.96 | [0.72; 1.30]|
| Prasugrel : Ticagrelor| 1                 | 0.19            |                      | 0.77 | [0.33; 1.79]|
|                       |                   |                 |                      | 0.95 | [0.63; 1.43]|
|                       |                   |                 |                      | 0.91 | [0.63; 1.32]|

Figure G.2. Forest plot of the network estimates of the potent P2Y12 inhibitors for the stroke outcome.
Figure G.3. Funnel plot of studies contributing in the network for the stroke outcome.

| Comparison          | Number of Studies | Direct Evidence | Random effects model | HR      | 95%-CI    |
|---------------------|-------------------|-----------------|----------------------|---------|-----------|
| Clopidogrel : Prasugrel | 1                 | 0.86            |                      | 0.93    | [0.62; 1.40] |
|                     |                   |                 |                      | 0.95    | [0.34; 2.63] |
|                     |                   |                 |                      | 0.94    | [0.64; 1.37] |
| Clopidogrel : Ticagrelor | 2               | 0.73            |                      | 0.73    | [0.41; 1.30] |
|                     |                   |                 |                      | 0.72    | [0.28; 1.83] |
|                     |                   |                 |                      | 0.73    | [0.44; 1.18] |
| Prasugrel : Ticagrelor | 1               | 0.41            |                      | 0.77    | [0.33; 1.79] |
|                     |                   |                 |                      | 0.78    | [0.39; 1.58] |
|                     |                   |                 |                      | 0.78    | [0.45; 1.33] |

Figure G.4. Forest plot of the network estimates of the potent P2Y12 inhibitors for the stroke outcome in the sensitivity analysis.
Table G.1. Impact of individual studies in the network meta-analysis for the myocardial infarction outcome.

| Study       | Clopidogrel : Prasugrel | Clopidogrel : Ticagrelor | Prasugrel : Ticagrelor |
|-------------|--------------------------|--------------------------|------------------------|
| Wiviott 2007| 0.39                     | 0.01                     | 0.19                   |
| Wallentin 2009 | 0.05                   | 0.81                     | 0.70                   |
| Roe 2012    | 0.53                     | 0.01                     | 0.29                   |
| Schüpke 2019 | 0.08                    | 0.11                     | 0.19                   |
| Gimbel 2020 | 0.01                     | 0.08                     | 0.04                   |
Supplementary Material 9: Network meta-analysis of interventions for the stent thrombosis outcome.

![Network graph of interventions](image-url)  

*Figure H.1. Network graph of interventions for the stent thrombosis outcome.*
Figure H.2. Forest plot of the network estimates of the potent P2Y12 inhibitors for the stent thrombosis outcome.

Figure H.3. Funnel plot of studies contributing in the network for the stent thrombosis outcome.
Table H.1. Impact of individual studies in the network meta-analysis for the stent thrombosis outcome.

| Study          | Clopidogrel : Prasugrel | Clopidogrel : Ticagrelor | Prasugrel : Ticagrelor |
|----------------|--------------------------|--------------------------|------------------------|
| Wiviott 2007   | 0.92                     | 0.13                     | 0.79                   |
| Wallentin 2009 | 0.08                     | 0.87                     | 0.79                   |
| Schüpke 2019   | 0.08                     | 0.13                     | 0.21                   |
Supplementary Material 10: Network meta-analysis of interventions for the safety outcomes.

![Network graph of interventions for the major bleeding safety outcome](image)

**Figure I.1.** Network graph of interventions for the major bleeding safety outcome.

**Table I.1.** Node-splitting method for assessment of inconsistency in network meta-analysis for the major bleeding outcome

| Comparison          | k | prop | NMA  | Direct | Indirect | RoR  | z     | p-value |
|---------------------|---|------|------|--------|----------|------|-------|---------|
| Clopidogrel : Prasugrel | 2 | 0.75 | 0.87 | 0.76   | 1.32     | 0.58 | -1.11 | 0.27    |
| Clopidogrel : Ticagrelor | 2 | 0.77 | 0.73 | 0.83   | 0.48     | 1.73 | 1.11  | 0.27    |
| Prasugrel : Ticagrelor | 2 | 0.49 | 0.84 | 0.63   | 1.10     | 0.58 | -1.11 | 0.27    |

*k: Number of studies providing direct evidence, prop: Direct evidence proportion, NMA: Estimated treatment effect (HR) in network meta-analysis, Direct: Estimated treatment effect (HR) derived from direct evidence, Indirect: Estimated treatment effect (HR) derived from indirect evidence, RoR: Ratio of ratios (direct versus indirect), z: z-value of test for disagreement (direct versus indirect), p-value: p-value of test for disagreement (direct versus indirect).
Table I.2. Impact of individual studies in the network meta-analysis for the major bleeding outcome.

| Study          | Clopidogrel : Prasugrel | Clopidogrel : Ticagrelor | Prasugrel : Ticagrelor |
|----------------|--------------------------|--------------------------|------------------------|
| Wiviott 2007   | 0.40                     | 0.06                     | 0.19                   |
| Wallentin 2009 | 0.08                     | 0.45                     | 0.21                   |
| Roe 2012       | 0.35                     | 0.05                     | 0.16                   |
| Motovska 2017  | 0.02                     | 0.02                     | 0.05                   |
| Schüpke 2019   | 0.22                     | 0.21                     | 0.44                   |
| Gimbel 2020    | 0.05                     | 0.32                     | 0.13                   |
Figure 1.2. Funnel plot of studies contributing in the network for the major bleeding outcome.
Figure I.3. Network graph of interventions for the major or minor bleeding safety outcome.
Table I.3. Node-splitting method for assessment of inconsistency in network meta-analysis for the major or minor bleeding outcome

| Comparison                  | k | Prop | NMA | Direct | Indirect | RoR | z | p-value |
|-----------------------------|---|------|-----|--------|----------|-----|---|---------|
| Clopidogrel : Prasugrel     | 2 | 1    | 0.73| 0.73   | -        | -   | - | -       |
| Clopidogrel : Ticagrelor    | 3 | 1    | 0.78| 0.78   | -        | -   | - | -       |
| Prasugrel : Ticagrelor      | 0 | 0    | 1.07| -      | 1.07     | -   | - | -       |

*k: Number of studies providing direct evidence, prop: Direct evidence proportion, NMA: Estimated treatment effect (HR) in network meta-analysis, Direct: Estimated treatment effect (HR) derived from direct evidence, Indirect: Estimated treatment effect (HR) derived from indirect evidence, RoR: Ratio of ratios (direct versus indirect), z: z-value of test for disagreement (direct versus indirect), p-value: p-value of test for disagreement (direct versus indirect).

Table I.4. Impact of individual studies in the network meta-analysis for the major or minor bleeding outcome.

| Study          | Clopidogrel : Prasugrel | Clopidogrel : Ticagrelor | Prasugrel : Ticagrelor |
|----------------|-------------------------|--------------------------|------------------------|
| Wiviott 2007   | 0.60                    | 0.00                     | 0.46                   |
| Wallentin 2009 | 0.00                    | 0.61                     | 0.39                   |
| Roe 2012       | 0.40                    | 0.00                     | 0.29                   |
| Park 2019      | 0.00                    | 0.08                     | 0.04                   |
| Gimbel 2020    | 0.00                    | 0.31                     | 0.16                   |
Figure I.4. Funnel plot of studies contributing in the network for the major or minor bleeding outcome.
Supplementary Material 11: Rankogram for every outcome in the main analysis.
Supplementary Material 12: Grading of evidence.

Table K.1. Grading of evidence in the network meta-analysis of P2Y12 inhibitors for the efficacy outcomes in the main analysis.

| Pairwise comparison          | Network meta-analysis estimate | Confidence | Downgrading due to          |
|------------------------------|--------------------------------|------------|-----------------------------|
| **Composite efficacy outcome** |                                |            |                             |
| Clopidogrel : Prasugrel      | 1.23 (1.01;1.49)                | Low        | Heterogeneity               |
| Clopidogrel : Ticagrelor     | 0.99 (0.78;1.27)                | Low        | Imprecision, Heterogeneity  |
| Prasugrel : Ticagrelor       | 0.80 (0.61;1.06)                | Low        | Imprecision, Heterogeneity  |
| **Ranking of treatments**    | Moderate                       |            | Inconsistency               |

| **Cardiovascular death**     |                                |            |                             |
| Clopidogrel : Prasugrel      | 1.09 (0.96;1.25)                | Low        | Heterogeneity, Incoherence  |
| Clopidogrel : Ticagrelor     | 1.22 (1.04;1.46)                | Low        | Heterogeneity, Incoherence  |
| Prasugrel : Ticagrelor       | 1.12 (0.91;1.38)                | Very low   | Imprecision, Heterogeneity, Incoherence |
| **Ranking of treatments**    | High                           |            |                             |

| **All-cause death**          |                                |            |                             |
| Clopidogrel : Prasugrel      | 1.23 (0.84;1.78)                | Low        | Imprecision, Heterogeneity  |
| Clopidogrel : Ticagrelor     | 1.12 (0.80;1.55)                | Low        | Imprecision, Heterogeneity  |
| Prasugrel : Ticagrelor       | 0.91 (0.60;1.38)                | Low        | Imprecision                 |
| **Ranking of treatments**    | Low                            |            | Imprecision, Inconsistency  |

| **Myocardial infarction**    |                                |            |                             |
| Clopidogrel : Prasugrel      | 1.22 (1.01;1.49)                | Low        | Heterogeneity               |
| Clopidogrel : Ticagrelor     | 1.06 (0.84;1.33)                | Low        | Imprecision, Heterogeneity  |
| Prasugrel : Ticagrelor       | 0.87 (0.66;1.14)                | Low        | Imprecision, Heterogeneity  |
| **Ranking of treatments**    | Moderate                       |            | Inconsistency               |

| **Stroke**                  |                                |            |                             |
| Clopidogrel : Prasugrel      | 1.06 (0.82;1.36)                | Low        | Heterogeneity               |
| Pairwise comparison | Network meta-analysis estimate | Confidence | Downgrading due to |
|---------------------|--------------------------------|------------|-------------------|
| **Major bleedings** |                                |            |                   |
| Mixed evidence. Hazard Ratio (95% Confidence Interval) | | | |
| Clopidogrel : Prasugrel | 0.87 (0.57;1.33) | Low | Imprecision Heterogeneity |
| Clopidogrel : Ticagrelor | 0.73 (0.49;1.11) | Low | Imprecision Heterogeneity |
| Prasugrel : Ticagrelor | 0.84 (0.52;1.38) | Low | Imprecision Heterogeneity |
| **Ranking of treatments** | Very low | | Imprecision Indirectness Inconsistency |
| **Major or minor bleedings** | | | |
| Mixed evidence. Hazard Ratio (95% Confidence Interval) | | | |
| Clopidogrel : Prasugrel | 0.73 (0.57;0.94) | Very low | Heterogeneity Incoherence |
| Clopidogrel : Ticagrelor | 0.78 (0.63;0.96) | Very low | Within-study bias Heterogeneity Incoherence |
| **Indirect evidence. Hazard Ratio (95% Confidence Interval)** | | | |
| Prasugrel : Ticagrelor | 1.07 (0.77;1.47) | Very low | Heterogeneity Incoherence |
| **Ranking of treatments** | Moderate | | Indirectness |

Imprecision: Confidence intervals include values favoring either treatment. Incoherence: Disagreement between direct and indirect estimates. Heterogeneity: Substantial between-study variance within the comparison. Inconsistency: Evidence of heterogeneity in the network.
Heterogeneity: Substantial between-study variance within the comparison.
Indirectness: Absence of agreement in outcome definition.
Inconsistency: Evidence of heterogeneity in the network.

Table K3. Grading of evidence in the network meta-analysis of P2Y₁₂ inhibitors for the outcomes in patients managed invasively (sensitivity analysis).

| Pairwise comparison | Network meta-analysis estimate | Confidence | Downgrading due to |
|---------------------|--------------------------------|------------|--------------------|
| **Composite efficacy outcome** | Mixed evidence. Hazard Ratio (95% Confidence Interval) | | |
| Clopidogrel : Prasugrel | 1.32 (1.05;1.64) | Moderate | Heterogeneity |
| Clopidogrel : Ticagrelor | 0.97 (0.76;1.25) | Low | Imprecision, Heterogeneity |
| Prasugrel : Ticagrelor | 0.74 (0.56;0.98) | Moderate | Heterogeneity |
| **Ranking of treatments** | High | | |
| **Cardiovascular death** | Mixed evidence. Hazard Ratio (95% Confidence Interval) | | |
| Clopidogrel : Prasugrel | 1.13 (0.84;1.52) | Low | Imprecision, Heterogeneity |
| Clopidogrel : Ticagrelor | 1.13 (0.83;1.55) | Low | Imprecision, Heterogeneity |
| Prasugrel : Ticagrelor | 1.00 (0.70;1.43) | Low | Imprecision |
| **Ranking of treatments** | Moderate | Imprecision | |
| **All-cause death** | Mixed evidence. Hazard Ratio (95% Confidence Interval) | | |
| Clopidogrel : Prasugrel | 1.83 (1.16;2.91) | Very low | Heterogeneity, Incoherence |
| Clopidogrel : Ticagrelor | 1.29 (1.10;1.51) | Very low | Heterogeneity, Incoherence |
| Prasugrel : Ticagrelor | 0.70 (0.45;1.08) | Very low | Heterogeneity, Incoherence |
| **Ranking of treatments** | High | | |
| **Myocardial infarction** | Mixed evidence. Hazard Ratio (95% Confidence Interval) | | |
| Clopidogrel : Prasugrel | 1.33 (1.17;1.52) | Low | Heterogeneity |
| Clopidogrel : Ticagrelor | 1.04 (0.84;1.29) | Low | Imprecision, Heterogeneity |
| Prasugrel : Ticagrelor | 0.78 (0.62;0.99) | Low | Heterogeneity |
| **Ranking of treatments** | High | | |
| **Stroke** | Mixed evidence. Hazard Ratio (95% Confidence Interval) | | |
| Clopidogrel : Prasugrel | 0.94 (0.64;1.37) | Low | Imprecision, Heterogeneity |
| Pairwise comparison       | Network meta-analysis estimate | Confidence | Downgrading due to | Reason       |
|--------------------------|-------------------------------|------------|-------------------|--------------|
| Clopidogrel : Prasugrel  | 2.34 (1.61;3.40)              | Low        |                   | Heterogeneity|
| Clopidogrel : Ticagrelor | 1.40 (0.86;2.22)              | Low        |                   | Imprecision  |
| Prasugrel : Ticagrelor   | 0.60 (0.34;1.04)              | Low        |                   | Imprecision  |

**Definite stent thrombosis**  
*Mixed evidence. Hazard Ratio (95% Confidence Interval)*

| Pairwise comparison       | Network meta-analysis estimate | Confidence | Downgrading due to | Reason       |
|--------------------------|-------------------------------|------------|-------------------|--------------|
| Clopidogrel : Ticagrelor  | 0.73 (0.45;1.19)              | Low        |                   | Imprecision  |
| Prasugrel : Ticagrelor   | 0.78 (0.45;1.33)              | Low        |                   | Heterogeneity|

**Major bleedings**  
*Mixed evidence. Hazard Ratio (95% Confidence Interval)*

| Pairwise comparison       | Network meta-analysis estimate | Confidence | Downgrading due to | Reason       |
|--------------------------|-------------------------------|------------|-------------------|--------------|
| Clopidogrel : Prasugrel  | 0.89 (0.50;1.59)              | Low        |                   | Imprecision  |
| Clopidogrel : Ticagrelor | 0.72 (0.45;1.18)              | Low        |                   | Imprecision  |
| Prasugrel : Ticagrelor   | 0.82 (0.45;1.47)              | Low        |                   | Imprecision  |

**Major or minor bleedings**  
*Mixed evidence. Hazard Ratio (95% Confidence Interval)*

| Pairwise comparison       | Network meta-analysis estimate | Confidence | Downgrading due to | Reason       |
|--------------------------|-------------------------------|------------|-------------------|--------------|
| Clopidogrel : Prasugrel  | 0.70 (0.53;0.93)              | Very low   |                   | Heterogeneity|
| Clopidogrel : Ticagrelor | 0.73 (0.59;0.91)              | Very low   |                   | Incoherence  |

*Indirect evidence. Hazard Ratio (95% Confidence Interval)*

| Pairwise comparison       | Network meta-analysis estimate | Confidence | Downgrading due to | Reason       |
|--------------------------|-------------------------------|------------|-------------------|--------------|
| Prasugrel : Ticagrelor   | 1.05 (0.73;1.50)              | Very low   | Heterogeneity     | Incoherence  |

**Ranking of treatments**  

- Imprecision: Confidence intervals include values favoring either treatment.
- Incoherence: Disagreement between direct and indirect estimates.
- Within-study bias: Dominated by evidence at high or moderate risk of bias.
- Heterogeneity: Substantial between-study variance within the comparison.
- Indirectness: Absence of agreement in outcome definition.
- Inconsistency: Evidence of heterogeneity in the network.
## Supplementary Material 13: Hazard ratios of all outcomes across studies included in the systematic review

| Study                   | Composite CV efficacy | CV death | All-cause death | MI | StROKE | Definite stent thrombosis | Major bleeding | Major or minor bleeding |
|-------------------------|-----------------------|----------|-----------------|----|--------|--------------------------|----------------|------------------------|
| TRITON-TIMI 38          | 0.82 (0.73;0.93)      | 0.98 (0.73;1.31) | -               | 0.76 (0.66;0.87) | 1.07 (0.71;1.6) | 0.43 (0.29;0.63) | 1.4 (1.05;1.88) | 1.43 (1.17;1.76) |
| PLATO *                | 0.83 (0.74;0.93)      | 0.77 (0.64;0.93) | 0.76 (0.64;0.9) | 0.86 (0.74;0.99) | 0.95 (0.69;1.33) | 0.71 (0.43;1.17) | 1.07 (0.95;1.19) | 1.14 (1.03;1.25) |
| TRILGY-ACS**           | 0.96 (0.86;1.07)      | 0.93 (0.8;1.09)  | 0.94 (0.82;1.08) | 0.96 (0.83;1.11) | 0.89 (0.63;1.26) | -               | 1.23 (0.84;1.81) | 1.28 (0.95;1.73) |
| PRASF IT-ACS (UA)      | 0.73 (0.38;1.43)      | -         | -               | -  | -      | -                        | -              | -                     |
| PRASF IT-ACS (NSTE MI) | 0.56 (0.31;1.01)      | -         | -               | -  | -      | -                        | -              | -                     |
| PHILO                   | 1.01 (0.45;2.25)      | -         | -               | -  | -      | -                        | -              | -                     |
| PRAGUE-18              | 0.47 (0.09;2.56)      | -         | -               | -  | -      | -                        | -              | -                     |
| TICAKOREA              | 2.11 (1.05;4.23)      | -         | -               | -  | -      | -                        | -              | 2.16 (1.11;4.23) |
| ISAR-REACT 5           | 1.35 (0.97;1.86)***   | 1.32 (0.79;2.21)*** | 1.43 (0.93;2.21)*** | 1.43 (0.94;2.19) | 1.3 (0.44;2.37) | 1.78 (0.52;6.08) | 1.9 (0.72;1.65) | -                     |
| POPULAR AGE            | -                     | 1.19 (0.6;2.37) | 1.08 (0.68;1.72) | 1 (0.63;1.57) | 0.5 (0.17;1.46) | -                        | -              | 0.71 (0.47;1.08) | 0.71 (0.54;0.94)**** |

*Data for the sensitivity analysis were used from Lindholm D 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 Aug 14;35(31):2083-93.

**Excluded from the sensitivity analysis

***Provided by Authors of ISAR-REACT 5

****Data for the sensitivity analysis in the Supplement of the main paper