Current Problems in Cardiology 49 (2024) 102635

Contents lists available at ScienceDirect

Current Problems in Cardiology

journal homepage: www.elsevier.com/locate/cpcardiol

Invited Review Article

Efficacy and Safety of $P2Y_{12}$ monotherapy vs standard DAPT in patients undergoing percutaneous coronary intervention: meta-analysis of randomized trials

Marta Casula, MD [a,b,c,1], Gavino Casu, MD [a,b,c,1], Giuseppe Talanas, MD [a,c,1], Andrea Spano, MD [a,b], Udaya Tantry, PhD [d], Ferruccio Bilotta, MD, PhD [a,c], Valentina Micheluzzi, MSN [a,c], Pierluigi Merella, MD [a,b,c], Tomaso Porcheddu, MD [a,b,c], Diana A. Gorog, MD [e,f], Marc Bonaca, MD, MPH [g], Young-Hoon Jeong, MD, PhD [h,i], Michael E. Farkouh, MD, MSc [j], Jacek Kubica, MD, PhD [k], Mehriban Isgender, MD [l], Paul A. Gurbel, MD [d], Eliano Pio Navarese, MD, PhD [a,b,c,*]

[a] Clinical Experimental Cardiology, Clinical and Interventional Cardiology, University of Sassari, Sassari, Sardinia Island, Italy
[b] Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy
[c] SIRIO MEDICINE Research Network, Sassari, Italy
[d] Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital of Baltimore, Baltimore, MD, USA
[e] Cardiology Department, East and North Hertfordshire NHS Trust, Stevenage, UK
[f] Faculty of Medicine, National Heart and Lung Institute, Imperial College, London, UK
[g] CPC Clinical Research, University of Colorado School of Medicine, USA
[h] CAU Thrombosis and Biomarker Center, Heart and Brain Hospital, Chung-Ang University, Gwangmyeong Hospital, Gwangmyeong, South Korea
[i] Department of Internal Medicine, Chung-Ang University School of Medicine, Seoul, South Korea
[j] Cedars Sinai Health System, Los Angeles, CA, USA
[k] Department of Cardiology and Internal Medicine, Nicolaus Copernicus University, Bydgoszcz, Poland
[l] Republican Clinical Hospital, Department of Cardiology, Azerbaijan Medical University, Department of Family Medicine, Baku, Azerbaijan

ARTICLE INFO

Keywords:
Meta-analysis
P2Y12
PCI
Randomised trials
Short DAPT

ABSTRACT

Background: Debates persist regarding the optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) in coronary artery disease (CAD). Recent trials have introduced a novel approach involving P2Y12 inhibitor monotherapy with ticagrelor or clopidogrel, after a short DAPT. However, the effectiveness and safety of this strategy remains to be established. We aimed to perform a meta-analysis comparing monotherapy with P2Y12 inhibitors versus standard DAPT in patients undergoing PCI at 12 months.

Methods: Multiple databases were searched. Six RCTs with a total of 24877 patients were included. The primary endpoint was all-cause mortality at 12 months of follow-up. The secondary endpoints were cardiovascular mortality, myocardial infarction, probable or definite stent thrombosis, stroke events, and major bleeding. The study is registered with PROSPERO (CRD42024499529).

Results: Monotherapy with P2Y12 inhibitor ticagrelor significantly reduced both allcause mortality (HR 0.71, 95 CI [0.55-0.91], P = 0.007) and cardiovascular mortality (HR 0.66, 95% CI

* Corresponding author at: Clinical and Experimental Cardiology, University of Sassari, Sassari, Sardinia Island, Italy.
E-mail addresses: epnavarese@uniss.it, elianonavarese@gmail.com (E.P. Navarese).

[1] The first three authors equally contributed.

https://doi.org/10.1016/j.cpcardiol.2024.102635

Available online 13 May 2024

[0.49-0.89], P = 0.006) compared to standard DAPT. In contrast, clopidogrel monotherapy did not demonstrate a similar reduction. The decrease in mortality associated with ticagrelor was primarily due to a lower risk of major bleeding (HR 0.56, 95% CI [0.43-0.72], P < 0.001), while the risk of myocardial infarction (MI) remained unchanged (HR 0.90, 95% CI [0.73-1.11], P = 0.32). The risk of stroke was found to be similar across treatments.
Conclusions: In comparison to standard DAPT, P2Y12 inhibitor monotherapy with ticagrelor may lead to a reduced mortality. The clinical benefits are driven by a reduction of bleeding risk without ischemic risk trade-off.

Introduction

Dual antiplatelet therapy (DAPT) is the cornerstone in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) with the scope of treating or preventing atherothrombotic events.[1]

The need to balance the thrombotic risk, particularly during the first month after drug-eluting stent (DES) implantation, with the concurrent bleeding risk of the patient, has led to the development of different and personalised antithrombotic therapy strategies.[2]

Recently, trials have suggested that monotherapy with P2Y12 inhibitors and discontinuing aspirin after a short course of dual antiplatelet therapy (DAPT), might be a promising option. However, these studies were not specifically designed to evaluate individual endpoints.[3] Moreover, the question of whether the particular P2Y12 inhibitor chosen for monotherapy has a distinct influence on safety and efficacy remains a topic of discussion.

P2Y12 inhibitors play a crucial role in preventing thrombotic events by inhibiting platelet P2Y12 receptors.[4] Most studies have evaluated the efficacy of DAPT therapy after PCI, and currently only a limited number of trials have evaluated the efficacy of a single P2Y12 inhibitor after P2Y12 inhibitor monotherapy in patients undergoing PCI.[5–10] Thus, the evaluation of individual outcomes is crucial to ascertain the comparative efficacy and safety of P2Y12 monotherapy versus standard DAPT. We aimed to perform a meta-analysis of randomized controlled trials (RCTs) investigating the clinical outcomes of P2Y12 monotherapy versus standard DAPT.

Methods

The current study adhered to established guidelines for systematic reviews and meta-analyses, as described in the published Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[11] The current meta-analysis is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42024499529.

Search strategy

Six databases were used to search for RCT studies: MEDLINE, EMBASE, TCTMD, ClinicalTrials.gov, Scopus, Embase, and Cochrane Library in the month of December 2023. The search criteria encompassed trials comparing $P2Y_{12}$ monotherapy vs standard DAPT. The studies were selected from databases by two reviewers who independently scanned the titles and abstracts. In addition to electronic searches, we manually examined the references of selected studies and meta-analyses to identify any additional eligible studies.

Backward snowballing was performed and abstracts from major congress proceedings were searched. Published meta-analyses on the subject were screened, and the data critically appraised and cross-checked with the original studies. To ensure comprehensive coverage, we also searched conference abstracts from medical proceedings, including the American Heart Association, the American College of Cardiology, the European Society of Cardiology, Transcatheter Therapeutics (TCT), Transcatheter Valve Therapies, and EuroPCR. Eligible studies were selected by comparing individual studies with inclusion and exclusion criteria and then evaluating full-text studies. The search strategy for the studies is shown in the Table I and Fig. 1 in the Supplement.

Inclusion criteria

The main inclusion criteria were: 1) patients with an age >18 years with acute coronary syndrome (ACS) or chronic coronary syndrome (CCS) undergoing PCI; 2) only RCTs according to the intention-to-treat analysist; 3) comparisons between P2Y12 monotherapy ($\leq$ 3 months) followed by $P2Y_{12}$ monotherapy versus standard DAPT (12 months) according to the intention-to-treat analysis; 4) considering clinical outcomes as all-cause mortality, cardiovascular mortality, major bleeding, myocardial infarction, stroke events, probable or definite stent thrombosis.

To enhance the accuracy and reduce the risk of bias in adjudication[12] we only included studies where events were reviewed by a dedicated event committee. Consequently, we did not include the GLOBAL LEADERS study, an open-label study that relied on investigator-reported events and lacked 12-month reported time-to-event outcome data. Instead, we selected the Adjudicated-Events study from the parent GLOBAL LEADERS trial, the GLASSY study[5]In GLASSY, an independent clinical-event adjudication committee, unaware of the participants' group assignments or the trial's primary outcomes, categorized the events. The clinical outcomes estimate for GLASSY were derived from a prior analysis, which was based on individual patient data provided by the chief investigators.[13]

Exclusion criteria were: 1) $P2Y_{12}$ monotherapy followed by aspirin monotherapy versus standard DAPT; 2) no prevalence of a single $P2Y_{12}$ type during SAPT; 3) studies evaluating antiplatelet therapy in patients undergoing coronary artery bypass; 4) studies evaluating de-escalation strategies; 5) observational studies.

Endpoints

The primary endpoint of our analysis is all-cause mortality using data obtained from individual trials. The secondary selected endpoints are cardiovascular mortality, myocardial infarction, probable or definitive stent thrombosis, stroke events, and major bleeding during the first 12 months of follow-up. Outcome definitions are those reported in the individual trials.

Data extraction

Two investigators (MC and AS), not involved in any of the selected studies, independently extracted data using predefined forms, assessed the accuracy of the abstractions, and resolved any discrepancies by consensus after discussion with a third investigator (EPN). The studies that were excluded by a classification with relative justification. One unblinded investigator, for each RCT included in the evaluation, extracted the following data: first author, study year, participant characteristics, study design, sample size, strategies therapy, outcomes measures at follow-up.

Data analysis

In our analysis, we used the Cochrane Risk of Bias 2.0 tool to evaluate included RCTs.[14] We conducted an outcomes analysis on an intention-to-treat basis. For clinical outcomes, we pooled hazard ratios (HRs), along with their 95 % confidence intervals (CI) which account for time-to event data and follow-up. Twelve-month follow-up data were abstracted. For the meta-analysis, pooled HRs were calculated using the DerSimonian and Laird random effects model. Heterogeneity was assessed by the Cochran Q test and I2 statistic, with an I2 value of 0 % indicating no observed heterogeneity, up to 25 % low heterogeneity, 26–50 % moderate heterogeneity, and above 50 % high heterogeneity. The potential publication bias was estimated visually and by linear regression.[9] The trials were classified into two groups based on P2Y12 inhibitors. Significance testing was performed at a two-tailed 5 % significance level.[15] To strengthen evidence and account for uncertainty, a meta-analysis using Bayesian hierarchical methods, with a random-effects model, and Cauchy priors was conducted pooling HRs of each individual trial. Four chains with 2000 iterations were used to estimates Bayesian results for all-cause mortality. Pooled Bayesian posterior HRs and their 95 % credible intervals were calculated. Sensitivity analyses for mortality were performed by excluding each study at time. Analyses were conducted using R Project version 4.0.2 for

Table 1
Key trial characteristics.

TRIAL	Patients	Study Design	Presentation	Event adjudication	$P2Y_{12}$ inhibitor	Standard DAPT definition
TWILIGHT	7519	Randomized, double-blind placebo-controlled, multicenter trial	ACS CCS	External independent committee, unaware of the treatment group assignments.	Ticagrelor	15-month DAPT (ticagrelor)
TICO	3056	Randomized, investigator-initiated, multicenter, unblinded trial.	ACS	Independent clinical event committee blinded to the treatment assignments and primary results of the trial	Ticagrelor	12-month DAPT (ticagrelor)
STOP DAPT-2	3045	Multicenter, open-label, randomized trial	ACS CCS	Independent clinical event committee blinded to randomized treatment group.	Clopidogrel	12-month DAPT (clopidogrel)
SMART CHOICE	2993	Investigator-initiated, multicenter, open-label, noninferiority, randomized study.	ACS CCS	Independent clinical event adjudication committee, unaware of the study-group assignments.	Clopidogrel	12-month DAPT (clopidogrel)
T-PASS	2850	Investigator-initiated, multicenter, open-label, randomized clinical trial	ACS	Independent clinical-event adjudication committee whose members were unaware of the assignment group or the primary results of the trial.	Ticagrelor	12-month DAPT (ticagrelor)
GLASSY/ GLOBAL LEADERS	7585	Investigator-initiated, multicenter, open-label, randomized clinical trial	ACS CCS	GLASSY: independent clinical-event adjudication committee, unaware of the assignment group or the primary results of the trial.	Ticagrelor	12-month DAPT (ticagrelor)

ACS= acute coronary syndrome; CCS= chronic coronary syndrome;TWILIGHT= Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention; TICO= Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; STOP DAPT-2= ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study; SMART CHOICE= Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy After DES; T-PASS= Ticagrelor Monotherapy in PAtients Treated With New-generation Drug-eluting Stents for Acute Coronary Syndrome; GLASSY= GLOBAL LEADERS Adjudication Sub-Study.

statistical computing and JASP version 0.16.4.

Results

Study selection and patient population

Six trials were included with a total of 24877 patients randomly assigned to P2Y12 monotherapy (n = 13297) or standard DAPT (n=11580) were included.[5–10] Trial follow-up was 12 months. Majority of trials included both patients with ACS and patients with stable coronary artery disease. Two studies enrolled only patients with ACS. In four trials ticagrelor was administered as P2Y12 monotherapy, whereas clopidogrel in two. The key characteristics of the included trials are presented in the Table 1. The risk of bias assessment is reported in Table II in the Supplement. Egger's test was not significant and did not provide evidence of publication bias for any of the explored outcomes (Table III in the Supplement).

We stratified patients into two groups: the ticagrelor group and the clopidogrel group. In the P2Y12 monotherapy arm, there were 10302 ticagrelor groups and 2995 clopidogrel groups, compared to the 8673 ticagrelor groups and 3007 clopidogrel group in the standard DAPT arm.

Mortality

All-cause mortality

A total of 6 trials including 24877 patients contributed to all-cause mortality. Overall, 160 of 13297 patients (1.20 %) randomised to $P2Y_{12}$ monotherapy vs 165 of 11580 patients (1.42 %) randomized to standard DAPT experienced death for all cause with differences between strategies therapies (HR 0.81, 95 % CI [0.64–1.03], P=0.08) (Fig. 1A) and with low statistical heterogeneity observed (I^2=3 %).

In the analysis by type of $P2Y_{12}$ inhibitor, compared to standard DAPT, P2Y12 monotherapy with ticagrelor significantly reduced the risk of all-cause mortality (1.14 % vs 1.50 %, HR 0.71[0.55-0.91]), but not $P2Y_{12}$ monotherapy with clopidogrel (1.40 % vs 1.19 %,

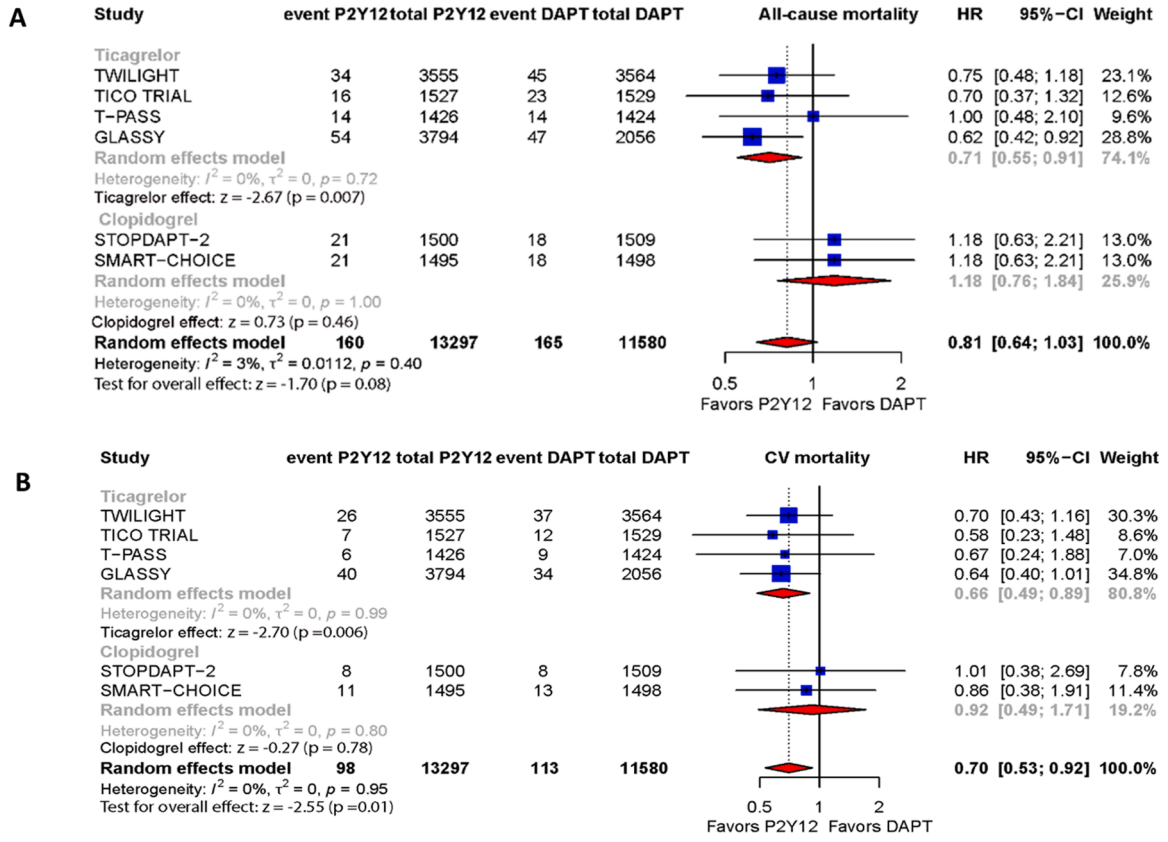


Fig. 1. Individual and summary hazard ratios (HRs) with their confidence intervals (CI) for all cause (panel A) and CV mortality (panel B) of studies comparing P2Y12 monotherapy vs standard DAPT stratified by P2Y12 inhibitor type. DAPT= dual antiplatelet therapy. HR = hazard ratio. CI = confidence interval. DAPT= dual antiplatelet therapy. P2Y12 = P2Y12 inhibitor monotherapy.

HR 1.18 [0.76-1.84]) (Fig. 1A).

Cardiovascular mortality

A total of 6 trials including 24877 patients contributed to cardiovascular mortality. Overall, 98 of 13297 patients (0.73 %) randomised to P2Y12 monotherapy vs 113 of 11580 patients (0.97 %) randomized to standard DAPT died from cardiovascular cause. There was no statistical heterogeneity (I^2=0 %). cardiovascular mortality was significantly reduced with P2Y12 monotherapy (HR 0.70 [95 % CI 0.53–0.92], P=0.95) (Fig. 1B).

In the stratified analysis, compared to standard DAPT, $P2Y_{12}$ monotherapy followed by ticagrelor significantly decreased the risk of cardiovascular mortality (0.76 % vs 1.07 %, HR 0.66 [0.49-0.89]), than $P2Y_{12}$ monotherapy with clopidogrel (0.63 % vs 0.69 %, HR 0.92 [0.49-1.71]) (Fig. 1B).

Sensitivity analyses for mortality

Consistent with the frequentist standard meta-analysis, a Bayesian meta-analysis showed that P2Y12 monotherapy was associated with a reduction in all-cause mortality (HR 0.75 [95 % CrI,0.52-1.01]) (Fig. 2A) that became significant with ticagrelor (HR 0.68 [95 % CrI, 0.44-0.93] and not with clopidogrel vs DAPT (HR 1.02 [95 % CrI, 0.25-1.72]. A significant CV mortality reduction was observed with $P2Y_{12}$ monotherapy HR 0.67 [95 % CrI,0.43-0.91]) (Fig. 2B).

By a meta-regression analysis, the variation in the percentage of patients with ACS included across trials was found not to significantly impact the results for the primary endpoint of mortality (p = 0.80, beta = -0.00) (Figure II in the Supplement).

Sensitivity analyses for all-cause and cardiovascular mortality conducted excluding one study at time, showed consistently directional mortality reduction with $P2Y_{12}$ monotherapy vs DAPT (Figure III in the Supplement).

Myocardial Infarction

A total of 6 trials including 24877 patients contributed to the myocardial infarction outcome. Overall, 215 of 13297 patients (1.61 %) randomized to $P2Y_{12}$ monotherapy vs 197 of 11580 patients (1.70 %) randomized to standard DAPT experienced a myocardial infarction. Overall, there were no significant differences in myocardial infarction between strategies (HR 0.90 [0.74–1.09], P=0.72) (Fig. 3).

In the stratified analysis by type of $P2Y_{12}$ inhibitor, compared to standard DAPT, P2Y12 monotherapy with ticagrelor did not increase the risk of myocardial infarction (1.85 % vs 1.97 %, HR 0.90 [0.73- 1.11]), nor clopidogrel (0.80 % vs 0.93 %, HR 0.87[0.49-1.55]) (Fig. 3).

Major bleeding

A total of 6 trials including 24877 patients, contributed to the major bleeding outcome. Overall, 194 of 13297 patients (1.45 %) randomized to $P2Y_{12}$ monotherapy vs 295 of 11580 patients (2.54 %) randomized to standard DAPT had a major bleeding event. There was moderate statistical heterogeneity (I^2=43 %). Overall, there were no significant differences in major bleeding between strategies therapies (HR 0.55 [95 % CI 0.43–0.71], P=0.12) (Fig. 4).

In the stratified analysis, when compared to standard DAPT, $P2Y_{12}$ monotherapy with ticagrelor significantly reduced major bleeding (0.76 % vs 1.07 %, HR 0.66 [0.49-0.89]). Evidence on clopidogrel was limited to two trials, showing a nominal reduction in

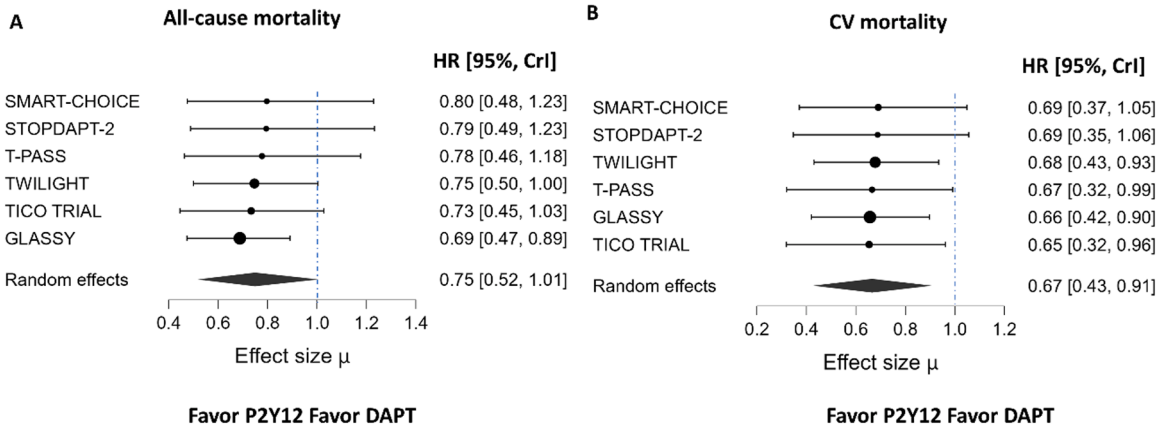


Fig. 2. Individual and pooled log Bayesian hazard ratios and 95 % % credible intervals for all-cause (panel A) and CV mortality with P2Y12 inhibitor monotherapy vs DAPT (panel B). HR = hazard ratio. CrI = credible interval.

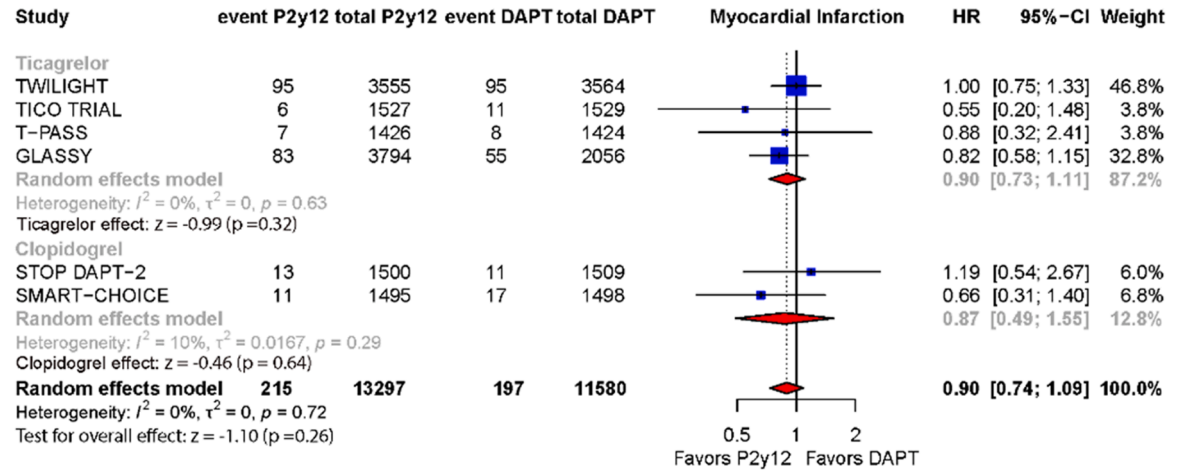


Fig. 3. Individual and summary hazard ratios (HRs) with their confidence intervals (CI) for myocardial infarction of P2Y12 monotherapy vs standard DAPT stratified by P2Y12 inhibitor type. HR = hazard ratio. CI = confidence interval. DAPT= dual antiplatelet therapy. P2Y12 = P2Y12 inhibitor monotherapy.

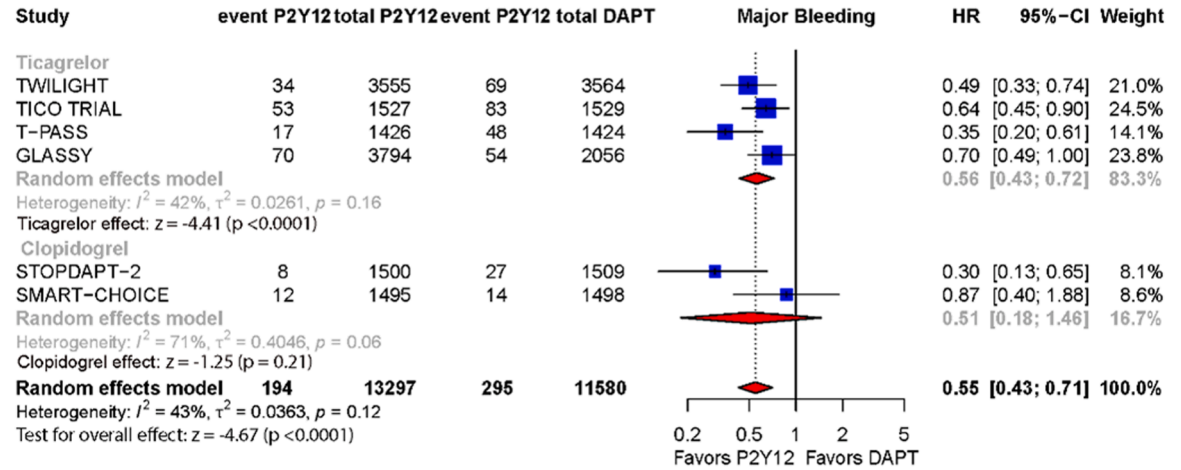


Fig. 4. Individual and summary hazard ratios (HRs) with their confidence intervals (CI) for major bleeding of studies comparing P2Y12 monotherapy vs standard DAPT stratified by P2Y12 inhibitor type. HR = hazard ratio. CI = confidence interval. DAPT= dual antiplatelet therapy. P2Y12 = P2Y12 inhibitor monotherapy.

bleeding risk with clopidogrel that did not reach significance (Fig. 4).

Stroke

A total of 6 trials including 24877 patients contributed to the stroke outcome. Overall, 83 of 13297 patients (0.62 %) randomized to $P2Y_{12}$ monotherapy vs 63 of 11580 patients (0.54 %) randomized to standard DAPT had a stroke event. There was a moderate statistical heterogeneity (I^2=46 %). In general, there were no significant differences in stroke events between strategies therapies (HR 1.09 [95 % CI 0.68–1.75], *P*=0.10) (Fig. 5).

In the stratified analysis, results were comparable for ticagrelor (0.62 % vs 0.48 %, HR 1.17 [0.74 -1.86]), and clopidogrel (0.63 % vs 0.69 %, HR 1.02[0.24 - 4.40]) (Fig. 5).

Definite or probable stent thrombosis

A total of 6 trials including 24877 patients contributed to definite or probable stent thrombosis outcome. Overall, 62 of 13297 patients (0.46 %) randomized to P2Y12 monotherapy vs 74 of 11580 patients (0.63 %) assigned to standard DAPT experienced a definite or probable stent thrombosis. Overall, there were no significant differences in definite or probable stent thrombosis between strategies therapies (HR 0.83 [0.59–1.17], *P*=0.57) (Figure IV in the Supplement).

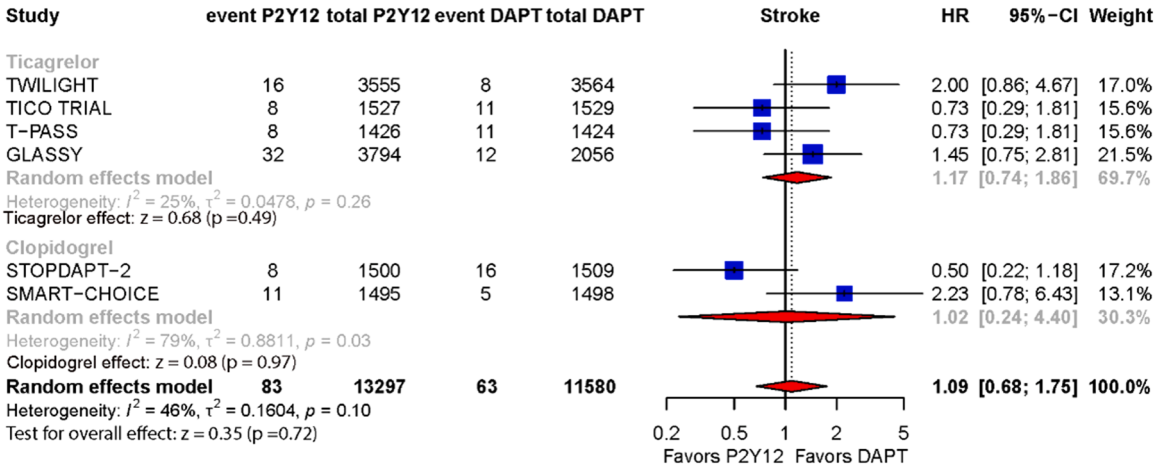


Fig. 5. Individual and summary hazard ratios (HRs) with their confidence intervals (CI) for stroke outcome of studies comparing P2Y12 inhibitor monotherapy vs standard DAPT stratified by P2Y12 inhibitor type. DAPT= dual antiplatelet therapy. HR = hazard ratio. CI = confidence interval. DAPT= dual antiplatelet therapy. P2Y12 = P2Y12 inhibitor monotherapy.

In the analysis by $P2Y_{12}$ inhibitor types, compared to standard DAPT, $P2Y_{12}$ monotherapy with ticagrelor yielded a nominally although not significantly lower risk of definite or probable stent thrombosis (0.53 % vs 0.68 %, HR 0.78 [0.55-1.11]) than clopidogrel (0.23 % vs 0.09 %, HR 2.24 [0.56 - 8.97]) (Figure IV in the Supplement).

Discussion

There are four main findings of the present large-scale meta-analysis of randomized trials which encompassed 24877 patients. These patients were followed for 12 months to assess clinical outcomes after receiving standard dual antiplatelet therapy (DAPT) versus P2Y12 inhibitor monotherapy. In comparison to standard DAPT, the findings were as follows: 1) all-cause and cardiovascular mortality were significantly lower in patients treated with $P2Y_{12}$ monotherapy; 2) these reductions in mortality were paralleled by a decrease in bleeding risk; 3) On stratified analysis by $P2Y_{12}$ inhibitor type, all-cause and cardiovascular mortality were significantly lower with ticagrelor than with clopidogrel therapy; 4) P2Y12 monotherapy was associated with a risk of myocardial infarction (MI) that was not significantly different from that of standard DAPT.

To our knowledge, the present meta-analysis is the largest source that compare $P2Y_{12}$ inhibitor monotherapy vs standard DAPT based on various types of $P2Y_{12}$ inhibitor with respect to individual outcomes. This report provides a comprehensive overview of the relative effectiveness and safety of P2Y12 inhibitor monotherapy after a short course of DAPT.

Over time, the paradigm of antithrombotic therapy has evolved from focusing solely on ischemia prevention to a more comprehensive approach focusing on the net clinical benefit. This includes evaluating the trade-off between the risk of bleeding, which is linked to heightened mortality, and the antithrombotic benefits. Consequently, mortality is emerging as the most robust endpoint for evaluating the balance between the advantages and hazards of antithrombotic treatments.[16]

Taken together our findings suggest that DAPT therapy for $\leq$ 3 months, followed by a P2Y12 inhibitor monotherapy may lead to a significant reduction in mortality in comparison to standard DAPT. These results are consistent with a recent network meta-analysis (NMA) incorporating indirect evidence in which ticagrelor 90 mg was associated with lower mortality compared to aspirin alone or aspirin plus clopidogrel, an observation driven by a reduction of bleeding without an ischemic risk trade-off. Our current analysis corroborates and expands upon previous evidence by including only direct comparisons from the most current and updated randomized trial evidence available.

The mortality benefit observed with ticagrelor monotherapy in our study aligns with findings from a recent meta-analysis and landmark trials that compared oral P2Y12 inhibitors in acute coronary syndrome (ACS) as part of the DAPT strategy. This analysis demonstrated that adding ticagrelor to aspirin led to the most significant reduction in mortality.[17] Our current findings underscore that the mortality advantage previously seen in patients managed with DAPT may indeed stem from ticagrelor. Moreover, this benefit appears to be enhanced when ticagrelor is used as monotherapy, effectively reducing the risk of bleeding without diminishing its anti-ischemic effectiveness.

A potential strength of this current meta-analysis is that it included data from randomized trials with outcomes analyzed by a central event committee and reporting hazard ratios which are the most robust measure to analyze results at follow-up, minimizing biases. Of note, in our study the I2 value was 0 % for mortality with ticagrelor and clopidogrel monotherapy vs standard DAPT, indicating no observed heterogeneity and consistency of effect across trials.

The noted reduction in mortality may be explained by the concurrent decrease in the risk of bleeding shown with P2Y12 monotherapy. A potential mechanistic explanation for the greater mortality reduction observed in our report is that ticagrelor is a potent reversible P2Y12 receptor inhibitor, that is associated with a quicker restoration of platelet function than thienopyridines. The

reversibility of antiplatelet effect may be of clinical importance in patients experiencing bleeding, which is in turn associated with long-term mortality during follow-up.[18–20]

In conclusion, the current study involving 24,877 patients over a 12-month follow-up period provides significant insights into the efficacy and safety of P2Y12 inhibitor monotherapy vs standard DAPT. The study's key findings demonstrate that P2Y12 inhibitor monotherapy with ticagrelor may significantly reduce both all-cause and cardiovascular mortality compared to standard DAPT. This reduction in mortality is primarily attributed to a decreased risk of bleeding, further highlighting the importance of balancing therapeutic anti ischemic benefits against potential bleeding risks.

This systematic review and meta-analysis have some limitations.

Trial-level data were included. However, consistency between the overall and the sensitivity analyses supports the robustness of the findings.

The available data on prasugrel, irreversible P2Y12 inhibitor, were scarce. A recent investigation compared prasugrel monotherapy with standard dual antiplatelet therapy (DAPT) with comparable bleeding rates to the DAPT arm. However, as the follow-up in this study was only 30 days, it was unsuitable for inclusion in the current meta-analysis, which required a 12-month follow-up period. Moreover, the availability of one study only with prasugrel would have not been informative. More data are needed before drawing conclusions on the role of prasugrel monotherapy.

Finally, given that a direct comparison between ticagrelor monotherapy and clopidogrel monotherapy has not yet been conducted, with dual antiplatelet therapy serving as the common comparator, any distinctions drawn between these two approaches should be approached with caution.

Conclusions

P2Y12 inhibitor monotherapy, specifically with ticagrelor is superior to standard dual antiplatelet therapy (DAPT) in reducing both all-cause and cardiovascular mortality. This finding is attributed mainly to the lowered bleeding risk, emphasizing the critical need for a balanced approach in antithrombotic therapy that weighs anti-ischemic benefits against bleeding hazards. Thus, P2Y12 inhibitor monotherapy, particularly with ticagrelor, is a potentially safe and effective strategy in managing patients post-PCI at 12 months. Further studies are needed to confirm the long-term efficacy and safety of P2Y12 monotherapy.

Non-standard abbreviations and acronyms

ACS	acute coronary syndrome
MI	myocardial infarction
RCT	randomized controlled trials
HR	hazard ratio
CI	confidence intervals
CrI	Credible intervals

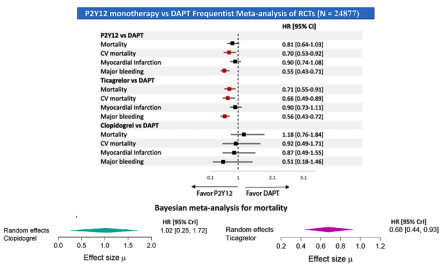
Financial contributions to authors

The authors did not receive financial sponsorship for the preparation of the article and/or the conduct of the study.

Central Illustration

Overall and stratified HRs (ticagrelor and clopidogrel separately) estimates from meta-analysis and individual trials of P2Y12 inhibitor monotherapy vs standard dual antiplatelet therapy (DAPT). When confidence intervals cross unity value the result is not significant.

The red squares indicate significant results for the investigated outcome. CV indicates cardiovascular. (**Panel A**). Bayesia n metaa-analysis for mortality stratified by clopidogrel or ticagrelor. (**Panel B**). HR = hazard ratio. CI = confidence intervals. CrI= credible intervals. DAPT = dual antiplatelet therapy.



Central Illustration

CRediT authorship contribution statement

Marta Casula: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Gavino Casu:** Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Giuseppe Talanas:** Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Andrea Spano:** Data curation, Writing – review & editing. **Udaya Tantry:** Writing – review & editing. **Ferruccio Bilotta:** Data curation, Writing – review & editing. **Valentina Micheluzzi:** Methodology, Data curation, Writing – original draft, Writing – review & editing. **Pierluigi Merella:** Data curation, Writing – review & editing. **Tomaso Porcheddu:** Writing – review & editing. **Diana A. Gorog:** Data curation, Writing – review & editing. **Marc Bonaca:** Data curation, Writing – review & editing. **Young-Hoon Jeong:** Data curation, Writing – review & editing. **Michael E. Farkouh:** Data curation, Writing – review & editing. **Jacek Kubica:** Data curation, Writing – review & editing. **Mehriban Isgender:** Data curation, Writing – review & editing. **Paul A. Gurbel:** Data curation, Writing – review & editing. **Eliano Pio Navarese:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Tantry has received honoraria from Wolters Kluwer Pharma.

Dr. Farkouh received research grant support from Astra Zeneca and Novartis and served as a consultant to Otitopic. Dr. Gurbel has received consulting fees and/or honoraria from Bayer, Vectura/Otitopic, Janssen, Cleveland Clinic foundation, Wolters Kluwer Pharma, Web MD Medscape, Baron and Budd, Premier Health Care Resource, Baim Institute, and Medforce; institutional research grants from Accriva Diagnostics, AstraZeneca, Bayer, Cronos, Haemonetics, Hikari Dx, Idorisa, Labcorp Drug Development, Novartis, Prolocor, Recor Medical, Vectura Limited, Zoll Medical Corporation; in addition, Dr. Gurbel has two patents, Detection of restenosis risk in patients issued and Assessment of cardiac health and thrombotic risk in a patient. Dr. Gurbel was an expert witness in a lawsuit associated with Plavix.

Dr Bonaca has received consulting fees/honoraria from AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Pfizer, and Daiichi Sankyo, outside the submitted work. oung-Hoon Jeong reports honoraria for lectures from AstraZeneca, Sanofi-Aventis, Daiichi Sankyo, Otsuka, Han-mi Pharmaceuticals, Yuhan Pharmaceuticals, and research grants or support from AstraZeneca, Han-mi Pharmaceuticals, Yuhan Pharmaceuticals, and Haemonetics. Dr Navarese received speaker fees from Astra-Zeneca, outside the submitted work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cpcardiol.2024.102635.

References

1. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA Versus ESC Guidelines on Dual Antiplatelet Therapy. *J Am Coll Cardiol.* 2018;72(23):2915–2931. https://doi.org/10.1016/j.jacc.2018.09.057.
2. El Alaoui El Abdallaoui O, Tornyos D, Lukács R, Komócsi A. Abatement of potent P2Y12 antagonist-based dual antiplatelet therapy after coronary intervention: A network meta-analysis of randomized controlled trials. *Front Cardiovasc Med.* 2023;9. https://doi.org/10.3389/fcvm.2022.1008914.
3. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J.* 2023;44(38):3720–3826. https://doi.org/10.1093/eurheartj/ehad191.
4. Valgimigli M, Bueno H, Byrne RA, et al. ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur J Cardiothorac Surg.* 2017;53(1):34–78. https://doi.org/10.1093/ejcts/ezx334.
5. Franzone A, McFadden E, Leonardi S, et al. Ticagrelor Alone Versus Dual Antiplatelet Therapy From 1 Month After Drug-Eluting Coronary Stenting. *J Am Coll Cardiol.* 2019;74(18):2223–2234. https://doi.org/10.1016/j.jacc.2019.08.1038.
6. Hahn J-Y, Song Y Bin, Oh J-H, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention. *JAMA.* 2019;321(24):2428. https://doi.org/10.1001/jama.2019.8146.
7. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI. *JAMA.* 2019;321(24):2414. https://doi.org/10.1001/jama.2019.8145.
8. Hong S-J, Lee S-J, Suh Y, et al. Stopping aspirin within 1 month after stenting for ticagrelor monotherapy in acute coronary syndrome: the t-pass randomized noninferiority trial. *Circulation.* 2024;149(8):562–573. https://doi.org/10.1161/CIRCULATIONAHA.123.066943.
9. Kim B-K, Hong S-J, Cho Y-H, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome. *JAMA.* 2020;323(23):2407. https://doi.org/10.1001/jama.2020.7580.
10. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. *N Engl J Med.* 2019;381(21):2032–2042. https://doi.org/10.1056/NEJMoa1908419.
11. Moher D, Liberati A, Tetzlaff J, Altman DG, Group PRISMA. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097.
12. Kahan BC, Feagan B, Jairath V. A comparison of approaches for adjudicating outcomes in clinical trials. *Trials.* 2017;18(1):266. https://doi.org/10.1186/s13063-017-1995-3.
13. Navarese EP, Landi A, Oliva A, et al. Within and beyond 12-month efficacy and safety of antithrombotic strategies in patients with established coronary artery disease: two companion network meta-analyses of the 2022 joint clinical consensus statement of the European Association of Percutaneous Cardiovascular

Interventions (EAPCI), European Association for Acute CardioVascular Care (ACVC), and European Association of Preventive Cardiology (EAPC). *Eur Heart J Cardiovasc Pharmacother*. 2023;9(3):271–290. https://doi.org/10.1093/ehjcvp/pvad016.
14. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898.
15. Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA*. 1991;266(1):93–98.
16. Tornyos D, Komócsi A, Bálint A, et al. Antithrombotic therapy for secondary prevention in patients with stroke or transient ischemic attack: A multiple treatment network meta-analysis of randomized controlled trials. *PLoS One*. 2022;17(8), e0273103. https://doi.org/10.1371/journal.pone.0273103.
17. Navarese EP, Khan SU, Kołodziejczak M, et al. Comparative Efficacy and Safety of Oral P2Y $_{12}$ Inhibitors in Acute Coronary Syndrome. *Circulation*. 2020;142(2):150–160. https://doi.org/10.1161/CIRCULATIONAHA.120.046786.
18. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045–1057. https://doi.org/10.1056/NEJMoa0904327.
19. Tjerkaski J, Jernberg T, Alfredsson J, et al. Comparison between ticagrelor and clopidogrel in myocardial infarction patients with high bleeding risk. *Eur Heart J Cardiovasc Pharmacother*. 2023;9(7):627–635. https://doi.org/10.1093/ehjcvp/pvad041.
20. Kazi DS, Leong TK, Chang TI, Solomon MD, Hlatky MA, Go AS. Association of spontaneous bleeding and myocardial infarction with long-term mortality after percutaneous coronary intervention. *J Am Coll Cardiol*. 2015;65(14):1411–1420. https://doi.org/10.1016/j.jacc.2015.01.047.