

Reduced Mortality With Antiplatelet Therapy Deescalation After Percutaneous Coronary Intervention in Acute Coronary Syndromes: A Meta-Analysis

*Original*

Reduced Mortality With Antiplatelet Therapy Deescalation After Percutaneous Coronary Intervention in Acute Coronary Syndromes: A Meta-Analysis / Palmerini, Tullio; Bruno, Antonio Giulio; Gasparini, Mauro; Rizzello, Giulia; Kim, Hyo-Soo; Kang, Jeehoon; Park, Kyung-Woo; Hahn, Joo-Yong; Song, Young Bin; Gwon, Hyeon-Cheol; Choo, Eun Ho; Park, Mahn-Won; Kim, Chan Joon; Chang, Kiyuk; Cuisset, Thomas; Taglieri, Nevio; Kim, Byeong-Keuk; Jang, Yangsoo; Nardi, Elena; Saia, Francesco; Orzalkiewicz, Matheus; Chietera, Francesco; Ghetti, Gabriele; Galiè, Nazzareno; Stone, Gregg W. - In: CIRCULATION. CARDIOVASCULAR INTERVENTIONS.. - ISSN 1941-7640. - 15:11(2022), pp. 906-914.

Availability:

10.1161/CIRCINTERVENTIONS.122.012245

This version is available at: 11583/2976410 since: 2023-02-27T16:31:14Z

*Publisher:*

LIPPINCOTT WILLIAMS & WILKINS

*Published*

DOI:10.1161/CIRCINTERVENTIONS.122.012245

*Terms of use:*

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

*Publisher copyright*

(Article begins on next page)



ORIGINAL ARTICLE

# Reduced Mortality With Antiplatelet Therapy Deescalation After Percutaneous Coronary Intervention in Acute Coronary Syndromes: A Meta-Analysis

Tullio Palmerini, MD; Antonio Giulio Bruno<sup>1</sup>, MD; Mauro Gasparini, PhD; Giulia Rizzello, MStat; Hyo-Soo Kim<sup>2</sup>, MD, PhD; Jeehoon Kang, MD; Kyung-Woo Park<sup>3</sup>, MD; Joo-Yong Hahn<sup>4</sup>, MD; Young Bin Song<sup>5</sup>, MD; Hyeon-Cheol Gwon<sup>6</sup>, MD; Eun Ho Choo<sup>7</sup>, MD; Mahn-Won Park<sup>8</sup>, MD; Chan Joon Kim, MD; Kiyuk Chang<sup>9</sup>, MD; Thomas Cuisset, MD; Nevio Taglieri, MD; Byeong-Keuk Kim<sup>10</sup>, MD, PhD; Yangsoo Jang, MD; Elena Nardi<sup>11</sup>, MStat; Francesco Saia<sup>12</sup>, MD, PhD; Matheus Orzalkiewicz<sup>13</sup>, MD; Francesco Chietera<sup>14</sup>, MD; Gabriele Ghetti<sup>15</sup>, MD; Nazzareno Galiè, MD; Gregg W. Stone<sup>16</sup>, MD

**BACKGROUND:** Antiplatelet therapy deescalation has been suggested as an alternative to standard treatment with potent dual antiplatelet therapy (DAPT) for 1 year in low bleeding risk patients with acute coronary syndromes undergoing percutaneous coronary intervention to mitigate the increased risk of bleeding. Whether this strategy preserves the ischemic and survival benefits of potent DAPT is uncertain.

**METHODS:** We performed a pairwise meta-analysis in patients with acute coronary syndrome undergoing percutaneous coronary intervention treated with either 1-year standard potent DAPT versus deescalation therapy (potent DAPT for 1–3 months followed by either reduced potency DAPT or ticagrelor monotherapy for up to 1 year). Randomized trials comparing standard DAPT versus deescalation therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention were searched through MEDLINE, EMBASE, Cochrane databases, and proceedings of international meetings. The primary end point was 1-year all-cause mortality.

**RESULTS:** The meta-analysis included 6 trials in which 20837 patients were randomized to potent DAPT for 1 to 3 months followed by deescalation therapy for up to 1 year (n=10392) or standard potent DAPT for 1 year (n=10445). Deescalation therapy was associated with lower 1-year rates of all-cause mortality compared with standard therapy (odds ratio, 0.75 [95% CI, 0.59–0.95];  $P=0.02$ ). Deescalation therapy was also associated with lower rates of major bleeding (odds ratio, 0.59 [95% CI, 0.48–0.72];  $P<0.0001$ ), with no significant difference in major adverse cardiac events (major adverse cardiovascular events; odds ratio, 0.89 [95% CI, 0.77–1.04];  $P=0.14$ ).

**CONCLUSIONS:** In low bleeding risk patients with acute coronary syndrome undergoing percutaneous coronary intervention, compared with 1-year of potent DAPT, antiplatelet therapy deescalation therapy after 1 to 3 months was associated with decreased mortality and major bleeding with similar rates of major adverse cardiovascular events.

**GRAPHIC ABSTRACT:** A [graphic abstract](#) is available for this article.

**Key Words:** acute coronary syndrome ■ ischemia ■ mortality ■ percutaneous coronary intervention ■ stent

Correspondence to: Gregg W. Stone, MD, Mount Sinai Medical Center 1 Gustave L. Levy Place New York, NY 10029. Email [gregg.stone@mountsinai.org](mailto:gregg.stone@mountsinai.org)  
This manuscript was sent to Eric A. Secemsky, Guest Editor, for review by expert referees, editorial decision, and final disposition.  
Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/CIRCINTERVENTIONS.122.012245>.  
For Sources of Funding and Disclosures, see page 913.

© 2022 American Heart Association, Inc.

Circulation: Cardiovascular Interventions is available at [www.ahajournals.org/journal/circinterventions](http://www.ahajournals.org/journal/circinterventions)

### WHAT IS KNOWN

- In low bleeding risk patients with acute coronary syndromes undergoing percutaneous coronary intervention, dual antiplatelet therapy (DAPT) with aspirin plus a potent P2Y<sub>12</sub> receptor inhibitor (prasugrel or ticagrelor) for 1 year is superior to aspirin plus clopidogrel for 1 year in reducing ischemic events, albeit at an increased risk of bleeding.
- The well-recognized association between major bleeding and mortality and the steady increase in bleeding with increasing potent DAPT duration have prompted research of alternative antiplatelet therapy regimens in patients with acute coronary syndrome undergoing percutaneous coronary intervention that might mitigate the risk of bleeding without increasing ischemic risk.

### WHAT THE STUDY ADDS

- In low bleeding risk patients presenting with acute coronary syndrome undergoing percutaneous coronary intervention, compared with a 1-year course of potent DAPT with aspirin plus prasugrel or ticagrelor, an abbreviated (1–3 months) course of potent DAPT followed by deescalation therapy with either reduced potency DAPT or ticagrelor monotherapy for 1-year was associated with lower rates of all-cause mortality and major bleeding, with no significant difference in ischemic major adverse cardiovascular events.
- The messages from the present study are directly relevant to clinical care: the demonstration for the first time of a mortality reduction with antiplatelet therapy deescalation has the strong potential to influence guidelines and current clinical practice. In this regard, this report differs from all other previous analyses on this topic.

### Nonstandard Abbreviations and Acronyms

|                       |  |
|-----------------------|--|
| <b>ACS</b>            | acute coronary syndromes   |
| <b>DAPT</b>           | dual antiplatelet therapy  |
| <b>DES</b>            | drug-eluting stents  |
| <b>GLOBAL LEADERS</b> | A Clinical Study Comparing Two Forms of Anti-Platelet Therapy After Stent Implantation |
| <b>OR</b>             | odds ratio   |
| <b>PCI</b>            | percutaneous coronary intervention   |

In patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) the combination of aspirin plus a potent P2Y<sub>12</sub> receptor inhibitor (prasugrel or ticagrelor) for 1 year is superior to aspirin plus clopidogrel for 1 year in reducing ischemic

events.<sup>1,2</sup> However, potent dual antiplatelet therapy (DAPT) is associated with a higher risk of bleeding compared with aspirin plus clopidogrel which may be associated with an increased risk of mortality.<sup>3,4</sup>

These issues have prompted research of alternative antiplatelet therapy regimens in ACS patients undergoing PCI that might mitigate the risk of bleeding without increasing ischemic risk. Specifically, the concept of antiplatelet therapy deescalation has been introduced wherein potent DAPT is used for an abbreviated term after PCI (the highest risk period for recurrent ischemia, including stent thrombosis), followed by a less potent DAPT regimen to complete 1 year of treatment.<sup>5–10</sup> For the most part these trials have been adequately powered to demonstrate a reduction in bleeding with deescalation therapy but not to ensure non-inferiority for the prevention of recurrent ischemia or mortality. Therefore, to further examine the potential safety and effectiveness of deescalation therapy (and to examine the outcomes of different deescalation regimens), we performed a meta-analysis of randomized trial enrolling patients with ACS undergoing PCI who were not at excessive risk of bleeding and thus were treated with either standard potent DAPT for 1 year or with an antiplatelet therapy deescalation regimen after a brief period of potent DAPT.

## METHODS

### Objectives and Study Design

The objective of the present study was to examine the risk-benefit profile of antiplatelet therapy de-escalation as compared to standard potent DAPT in ACS patients at low bleeding risk undergoing PCI. Standard potent DAPT was defined as aspirin plus prasugrel or ticagrelor for 1 year after PCI. Deescalation antiplatelet therapy was defined as potent DAPT for 1 to 3 months followed by either reduced potency DAPT (defined as aspirin plus clopidogrel or reduced-dose prasugrel) or ticagrelor monotherapy for up to 1 year.

The inclusion criteria for this meta-analysis were (1) enrollment of patients with ACS in whom PCI was performed; (2) control treatment consisting of aspirin plus prasugrel or ticagrelor for 1 year or up to 15 months; and (3) deescalation therapy consisting of a 1 to 3-month period of potent DAPT followed by either reduced potency DAPT or ticagrelor monotherapy for 1 year or up to 15 months (no studies were identified in which prasugrel monotherapy was used as deescalation therapy). Studies using aspirin plus clopidogrel for 1 year as control treatment,<sup>11,12</sup> those deescalating DAPT based on genetic or platelet function testing,<sup>13,14</sup> those including clopidogrel monotherapy as de-escalation treatment,<sup>11,12</sup> and those not including a brief period of potent DAPT with aspirin plus prasugrel or ticagrelor<sup>13–16</sup> were excluded from the meta-analysis. The meta-analysis thus consisted of 3 groups of treatment: (1) standard therapy with aspirin plus prasugrel or ticagrelor for 1 year; (2) deescalation therapy with potent DAPT for 1 to 3 months followed by reduced potency DAPT for up to 1 year; and (3) deescalation therapy with potent DAPT for 1 to 3 months followed by ticagrelor monotherapy for up to 1 year. The main objective

was to compare the 1-year outcomes between standard treatment versus deescalation therapy pooled across the two deescalation groups in a pairwise meta-analysis. The secondary objective of the study was to compare 1-year outcomes across the three treatment groups in a network meta-analysis. Each trial was approved by the institutional ethics committee of each participating site. The data, methods, and materials used to conduct the research are available to any researcher for purposes of reproducing the results or replicating the procedure.

### Search Strategy and Trial Validity Assessment

The search strategy is reported in the [Supplemental Material](#). In particular, we did not use the key words clopidogrel monotherapy or aspirin monotherapy because clopidogrel or aspirin alone may not provide the same ischemic protection within the first year from index PCI as potent DAPT.<sup>17</sup> The risk of bias was assessed using the revised Cochrane risk-of-bias tool.<sup>18</sup> The protocol of the meta-analysis was not reported on any website. The present review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis statement.<sup>19</sup>

### End Points and Definitions

The primary end point of the study was all-cause mortality at 1 year. Secondary end points were cardiovascular mortality, myocardial infarction, stroke, definite or probable stent thrombosis, major bleeding (defined as Bleeding Academic Research Consortium type 3–5 criteria), major adverse cardiovascular events (MACE, the composite of cardiovascular death, myocardial infarction or stroke), and net adverse clinical events (NACE, the composite of MACE or major bleeding), all at 1 year. When these exact outcomes were not available, we approximated to the closest one provided by the trial.

### Statistical Analysis

The primary analysis was performed in the intention-to-treat (ITT) population, reporting events from the time of randomization. As randomization in three trials occurred at the time of PCI and not at the time of antiplatelet therapy allocation,<sup>7,9,10</sup> sensitivity analyses were performed considering only events occurring in the landmark period after antiplatelet therapy regimen divergence, thus censoring patients with ischemic or bleeding events occurring in the first 1 to 3 months when all patients were on the same therapy, comprising a modified ITT population.

Continuous variables are displayed as means and SD, whereas categorical variables are displayed as count and percentages. Odds ratios (ORs) and 95% CIs were used as the summary statistics. Event counts were extracted from the main study publications or collected from the Principal Investigators of the included trials when not available. Pooled ORs were calculated in both fixed effect (inverse variance weighted) and random effect (DerSimonian and Laird) models. Extent of small study effects/publication bias was assessed by visual inspection of funnel plots and Egger test. Pairwise inconsistency was assessed with the  $I^2$  statistic, with values <25%, ≥25% to ≤50%, and >50% representing mild, moderate, and severe heterogeneity respectively. Pairwise meta-analysis was performed using Stata 12 SE (StataCorp, College Station, Texas). Network meta-analysis was performed using a frequentist approach with *netmeta* (<https://CRAN.R-project.org/package=netmeta>).<sup>20</sup> Two-sided  $P < 0.05$  were considered statistically significant.

### Role of the Funding Source

None of the sponsors of any of the individual trials had any role in the study design, data collection, data interpretation or drafting, or review of the article. T.P., A.B.G., and N.T. take full responsibility for the integrity of the data. All authors had full access to all the data and take the responsibility to submit the article for publication.

## RESULTS

### Trials, Treatments, and Patients

As shown in [Figure S1](#), we screened 13 450 potentially relevant articles, among which six randomized trials met the inclusion criteria and were included in the meta-analysis.<sup>5–10</sup> The major features of the included trials are shown in [Table S1](#), the inclusion and exclusion criteria are shown in [Table S2](#), the time point of randomization with event counting after PCI in the ITT and modified ITT populations is shown in [Table S3](#), the clinical characteristics of the overall patient population from the individual trials are shown in [Table S4](#), the definitions of the clinical end points from each trial are shown in [Tables S5 and S6](#), and the risk of bias for the end point all-cause mortality is shown in [Figure S2](#). Of note, as shown in [Table S7](#), none of the patients were on oral anticoagulant therapy, few had experienced major bleeding before randomization, and the majority had normal left ventricular ejection fraction with noncomplex coronary artery disease.

Four of the 6 trials included patients with ACS only,<sup>6–9</sup> whereas 2 trials included both patients with ACS and stable ischemic heart disease, with randomization stratified according to clinical presentation.<sup>5,10</sup> After excluding the non-ACS cohort from these trials, a total of 20 837 patients were included in the meta-analysis, 10 392 of whom were treated with deescalation therapy and 10 445 with standard therapy. De-escalation therapy consisted of aspirin plus clopidogrel in 2 trials with 1672 total randomized patients,<sup>6,8</sup> aspirin plus reduced-dose prasugrel in 1 trial with 1170 randomized patients,<sup>9</sup> and ticagrelor monotherapy in 3 trials with 7550 randomized patients.<sup>5,7,10</sup> As shown in [Table S3](#), for 3 trials,<sup>7,9,10</sup> randomization occurred immediately after PCI and thus events occurring within the first 1 to 3 months when both groups were on potent DAPT were included in the 1-year outcome estimates. Adherence of patients to randomized treatment in each trial is reported in [Table S8](#).

### Clinical Outcomes in the ITT Population (Pairwise Comparison)

In 5 trials the primary analyses were performed in the intention-to-treat population,<sup>6–10</sup> whereas in one trial the analyses on bleeding were performed in the intention-to-treat population and those on ischemic end points in the per-protocol population.<sup>5</sup> At 1-year follow-up 119

deaths occurred in the 10 392 patients treated with deescalation therapy compared with 160 deaths in the 10 445 patients treated with standard therapy. As shown in Figure 1, de-escalation therapy was associated with lower 1-year rates of all-cause death (OR, 0.75 [95% CI, 0.59–0.95];  $P=0.02$ ). In addition, there was not a statistical difference in rates of cardiovascular mortality ( $P=0.05$ ), even though the odds ratio was leaning in favor of deescalation (OR, 0.55 [95% CI, 0.30–1.01];  $P=0.05$ ) compared with standard therapy. No significant heterogeneity was apparent in treatment effect in relation to the type of de-escalation therapy ( $P$  value for heterogeneity=0.79).

As shown in Figure 2, de-escalation therapy was associated with lower rates of major bleeding (OR, 0.59 [95% CI, 0.48–0.72];  $P<0.0001$ ), any bleeding (OR, 0.51 [95% CI, 0.37–0.68];  $P<0.0001$ ), and NACE (OR, 0.74 [95% CI, 0.64–0.84];  $P<0.0001$ ), with no significant differences in the individual risks of myocardial infarction, stroke, stent thrombosis, or MACE (Figure 3).

### Clinical Outcomes in the Modified ITT Population (Pairwise Comparison)

Antiplatelet therapy regimen divergence occurred at the time of randomization in 3 trials,<sup>5,6,8</sup> at 1 month after randomization in 2 trials,<sup>9,10</sup> and at 3 months after randomization in 1 trial.<sup>7</sup> Results in this modified ITT population in the landmark period after antiplatelet therapy divergence were similar to the ITT population. In summary, as shown in Figure S3, deescalation therapy was associated with lower rates of all-cause death (OR, 0.75 [95% CI, 0.56–0.99];  $P=0.04$ ), major bleeding (OR, 0.49 [95% CI, 0.37–0.66];  $P<0.0001$ ), any bleeding (OR, 0.48 [95% CI, 0.38–0.59];  $P<0.0001$ ), and NACE (OR, 0.65 [95% CI, 0.50–0.85];  $P=0.002$ ). Other outcomes are reported in the Table.

### Clinical Outcomes in the Network Meta-Analysis (ITT Population)

The evidence network is shown in Figure S4, and results at 1 year comparing the 3 groups are reported in Table S9. Deescalation therapy with ticagrelor monotherapy was associated with lower rates of mortality (OR, 0.74 [95% CI, 0.56–0.96]) and major bleeding (OR, 0.55 [95% CI, 0.42–0.72]) compared with standard therapy, whereas only trends for reduced mortality and major bleeding were apparent with de-escalation therapy with reduced potency DAPT compared with standard therapy. However, no significant differences were apparent in the rates of mortality, major bleeding, or other outcomes between patients treated with de-escalation with reduced potency DAPT versus ticagrelor monotherapy.

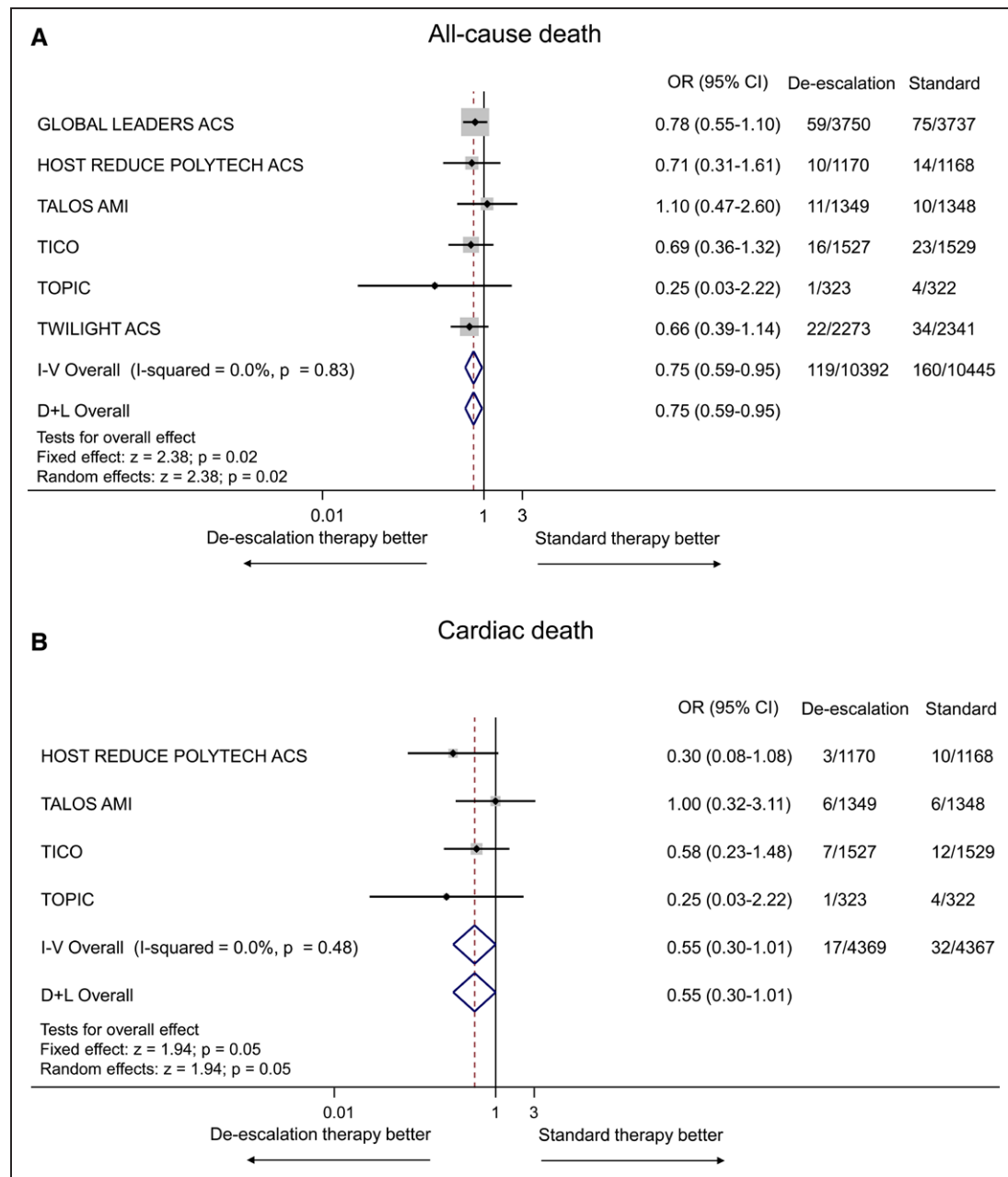
### Additional Analyses

As definite-probable stent thrombosis was not available in GLOBAL LEADERS (A Clinical Study Comparing Two Forms of Anti-Platelet Therapy After Stent Implantation), we performed a sensitivity analysis on this end point excluding this trial: results did not significantly change (OR, 0.84 [95% CI, 0.25–1.40];  $P=0.54$ ). No evidence of heterogeneity or inconsistency was apparent in the network meta-analysis. Funnel plot review and Egger test ( $P=0.52$ ) did not suggest publication bias (Figure S5). The Preferred Reporting Items for Systematic Review and Meta-Analysis checklist is reported at the end of the Supplemental Material.

### DISCUSSION

In the present study, we examined the risk-benefit profile of an abbreviated course of potent DAPT with aspirin plus prasugrel or ticagrelor followed by antiplatelet therapy deescalation versus standard potent DAPT without deescalation for 1 year in patients with ACS at low bleeding risk undergoing PCI. The principal finding of this study is that antiplatelet deescalation therapy in such patients was associated with lower 1-year rates of all-cause mortality compared with standard therapy. In addition, deescalation therapy was associated with lower rates of major bleeding, any bleeding, and NACE with no significant differences in MACE compared with standard therapy. Similar results were apparent in sensitivity analyses in which only events occurring in the landmark period after antiplatelet therapy regimen divergence were considered. Finally, no significant differences in 1-year outcomes were observed in patients treated with reduced potency DAPT and ticagrelor monotherapy as deescalation therapy.

The optimal antiplatelet therapy regimen (including type of agent as well as therapy duration) in patients with ACS undergoing PCI will suppress the risk of recurrent ischemic events while not excessively increasing the risk of major bleeding. Although an extended course of potent DAPT is no doubt effective in reducing myocardial infarction and stent thrombosis, the increased risk of major bleeding (including fatal bleeding) to some degree offsets this benefit.<sup>1,21</sup> As the highest risk for recurrent ischemia is within the first several months after ACS and PCI, antiplatelet therapy deescalation regimens have been introduced to reduce the risk of bleeding, hopefully without impacting effectiveness. However, antiplatelet therapy de-escalation trials performed to date have been heterogeneous as regards patient populations, control treatments, and deescalation regimens and duration. Specifically, some trials have included both patients with ACS and chronic coronary syndromes, potentially diluting treatment effects toward the null.<sup>11,22,23</sup> Other trials have used aspirin plus clopidogrel for 1 year as the reference

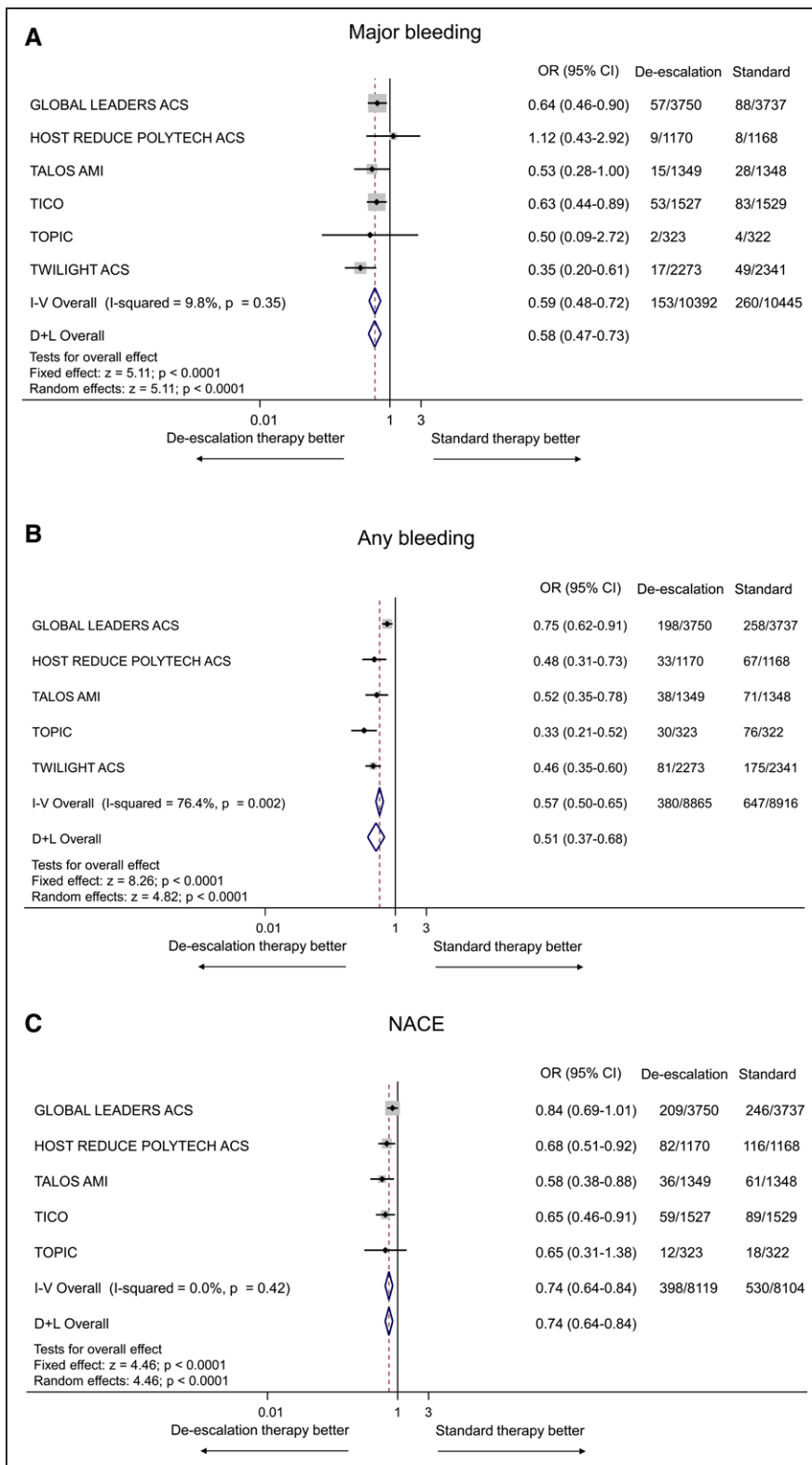


**Figure 1. One-year mortality and cardiac mortality in the intention-to-treat population.**

**A**, All-cause mortality and **(B)** cardiac mortality with de-escalation therapy compared with a standard 1-year course of potent dual antiplatelet therapy in the intention-to-treat population. Compared with standard therapy, deescalation therapy was associated with significantly lower rates of all-cause mortality and a trend toward lower rates of cardiac mortality. D+L indicates DerSimonian and Laird; GLOBAL LEADERS, A Clinical Study Comparing Two Forms of Anti-Platelet Therapy After Stent Implantation; HOST REDUCE POLYTECH ACS, Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial—Comparison of reduction of Prasugrel Dose and Polymer Technology in Acute Coronary Syndromes Patients; I-V, inverse variance; OR, odds ratio; TALOS AMI, Ticagrelor Versus Clopidogrel in Stabilized Patients With Acute Myocardial Infarction; TICO, Ticagrelor Monotherapy After 3 Months in Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndromes; TOPIC, Timing of Platelet Inhibition After Acute Coronary Syndrome; and TWILIGHT, Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention.

treatment, a less effective regimen than potent DAPT with prasugrel or ticagrelor for preventing ischemic events in ACS and PCI.<sup>11,12,16</sup> While a potentially useful management strategy, genetic and platelet function testing to guide antiplatelet therapy selection and duration are rarely utilized.<sup>13,16</sup> Moreover, trials of genetic and platelet

function testing to guide DAPT use examined a selective rather than a uniform de-escalation according to platelet reactivity to clopidogrel. Moreover, no randomized trial performed to date has had sufficient power to demonstrate non-inferiority between clopidogrel versus prasugrel or ticagrelor for the prevention of ischemic events in



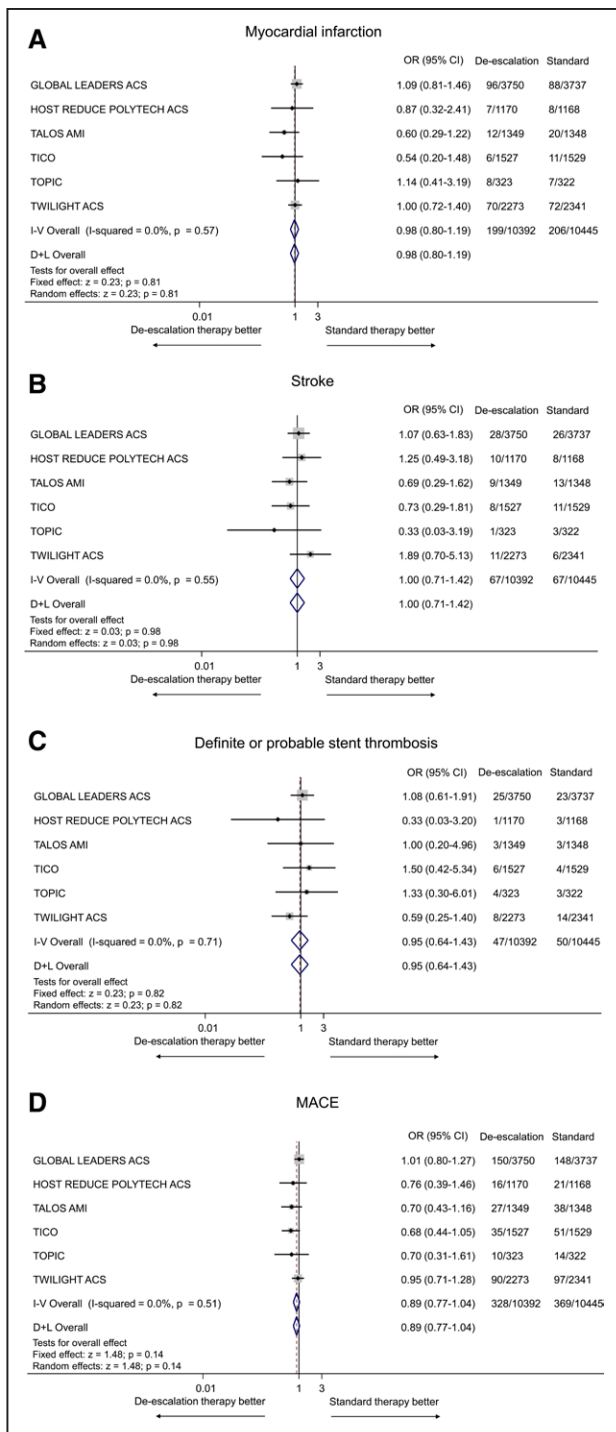
**Figure 2. One-year bleeding and net adverse outcomes in the intention-to-treat population.**

**A**, Major bleeding, **(B)** any bleeding, and **(C)** net adverse clinical outcomes (NACE) with deescalation therapy compared with standard therapy in the intention-to-treat population. Compared with standard therapy, de-escalation therapy was associated with significantly lower rates of major bleeding, any bleeding, and NACE. D+L indicates DerSimonian and Laird; GLOBAL LEADERS, A Clinical Study Comparing Two Forms of Anti-Platelet Therapy After Stent Implantation; HOST REDUCE POLYTECH ACS, Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial—Comparison of reduction of Prasugrel Dose and Polymer Technology in Acute Coronary Syndromes Patients; I-V, inverse variance; OR, odds ratio; TALOS AMI, Ticagrelor Versus Clopidogrel in Stabilized Patients With Acute Myocardial Infarction; TICO, Ticagrelor Monotherapy After 3 Months in Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndromes; TOPIC, Timing of Platelet Inhibition After Acute Coronary Syndrome; and TWILIGHT, Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention.

low bleeding risk ACS patients undergoing PCI. In addition, the broad selection criteria of prior meta-analyses that have examined this issue have introduced a high degree of heterogeneity and reliance mainly on indirect evidence.<sup>24</sup> Finally, clopidogrel monotherapy has been used as deescalation treatment in several trials (mostly

in patients at high risk for bleeding, such as those on chronic oral anticoagulant therapy), a regimen that may be less effective than ticagrelor monotherapy or reduced potency DAPT for prevention of ischemic events.<sup>11,12</sup>

Considering the timing of ischemic and bleeding events after PCI in ACS, the ideal treatment in patients at low risk



**Figure 3. One-year ischemic outcomes in the intention-to-treat population.** **A**, Myocardial infarction, **(B)** stroke, **(C)** definite or probable stent thrombosis, and **(D)** major adverse cardiovascular events (MACE) with deescalation therapy compared with standard therapy in the intention-to-treat population. No significant differences were apparent between deescalation therapy and standard therapy for any of these end points. D+L indicates DerSimonian and Laird; GLOBAL LEADERS, A Clinical Study Comparing Two Forms of Anti-Platelet Therapy After Stent Implantation; HOST REDUCE POLYTECH ACS, Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial—Comparison of reduction of Prasugrel Dose and Polymer Technology in Acute Coronary Syndromes Patients; (Continued)

for bleeding might employ potent DAPT for a brief period (1–3 months after PCI) to blunt the early high risk of ischemic events followed by antiplatelet therapy de-escalation thereafter to mitigate the later risk of bleeding.<sup>25</sup> There is little doubt that this approach will reduce bleeding, but prior trials have not been adequately powered to convincingly demonstrate non-inferiority for recurrent ischemia and to examine net effects on mortality. We thus restricted the present meta-analysis to randomized trials of PCI in patients with ACS in which the control arm consisted of a 1-year course of potent DAPT with aspirin plus prasugrel or ticagrelor (the most effective regimen to suppress ischemic MACE) and in which the treatment arm utilized potent DAPT for 1–3 months followed by deescalation thereafter with either reduced potency DAPT or ticagrelor monotherapy for up to 1 year. Compared with a 1-year course of potent DAPT, antiplatelet de-escalation therapy was associated with lower 1-year rates of all-cause mortality as well as lower rates of major bleeding, any bleeding, and NACE, with nonsignificantly different rates of ischemic MACE.

In this regard, the present study differs from previous meta-analyses in several important aspects. Previous meta-analyses considered deescalation guided therapy regimens only,<sup>26</sup> did not restrict the analysis to patients with ACS undergoing PCI,<sup>27,28</sup> included trials in which deescalation therapy did not entail a brief period of potent DAPT,<sup>28</sup> considered deescalation as P2Y<sub>12</sub> monotherapy only,<sup>28,29</sup> or included nonrandomized studies.<sup>30</sup> With >20,000 randomized patients, the present meta-analysis is to our knowledge the first to present evidence for a reduction in all-cause mortality with antiplatelet deescalation therapy compared with the standard potent DAPT for 1 year in low bleeding risk ACS patients undergoing PCI.

By network meta-analysis ticagrelor monotherapy, but not reduced potency DAPT, was associated with lower rates of all-cause mortality and lower rates of major bleeding compared to standard therapy. However, differences in outcomes between the 2 deescalation regimens were not significant, and the cohort treated with ticagrelor monotherapy was almost 4× larger than that treated with reduced potency DAPT. This finding may therefore have been due to chance. Further study is needed to investigate the relative safety and effectiveness of these 2 deescalation therapy approaches.

**Limitations**

As a study level-based meta-analysis, we were unable to examine the timing of the differences in survival between

**Figure 3 Continued.** I-V, inverse variance; OR, odds ratio; TALOS AMI, Ticagrelor Versus Clopidogrel in Stabilized Patients With Acute Myocardial Infarction; TICO, Ticagrelor Monotherapy After 3 Months in Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndromes; TOPIC, Timing of Platelet Inhibition After Acute Coronary Syndrome; and TWILIGHT, Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention.

**Table. One-Year Clinical Outcomes in the Modified Intention-to-Treat Population**

| End points                            | Odds ratio (95% CI) | P value |
|---------------------------------------|---------------------|---------|
| All-cause death                       | 0.75 (0.56–0.99)    | 0.04    |
| Myocardial infarction                 | 0.91 (0.73–1.14)    | 0.41    |
| Definite or probable stent thrombosis | 0.90 (0.51–1.58)    | 0.72    |
| Stroke                                | 1.03 (0.69–1.54)    | 0.89    |
| Major bleeding                        | 0.49 (0.37–0.66)    | <0.0001 |
| Any bleeding                          | 0.48 (0.38–0.59)    | <0.0001 |
| Major adverse cardiovascular events   | 0.88 (0.74–1.05)    | 0.14    |
| Net adverse clinical events           | 0.65 (0.50–0.85)    | 0.002   |

groups or identify patient subgroups that might particularly benefit (or be harmed) by de-escalation therapy. Definitions of some clinical end points differed slightly across trials, potentially introducing effect modifiers, and most trials were unblinded, potentially introducing bias. However, our primary end point was all-cause of mortality which is less affected by these issues. The comparison between reduced potency DAPT and ticagrelor monotherapy was based on indirect evidence only and therefore should be interpreted with caution. Given the limited number of studies included in the meta-analysis, the assessment of publication bias should be interpreted with caution. Finally, as with any meta-analysis, our report shares the limitations of the original studies. Specifically, patients included in the component trials were not at high risk for bleeding, and most had normal left ventricular ejection fraction with noncomplex coronary artery disease. Thus, while the present results apply to many patients undergoing PCI (and might intuitively be extended to those at high bleeding risk with low coronary complexity), the risk:benefit profile of a DAPT deescalation strategy in patients at especially high risk for ischemia warrants further study.

## Conclusions

In a pairwise meta-analysis of 6 trials and 20837 randomized patients with ACS and low bleeding risk undergoing PCI, antiplatelet therapy de-escalation after 1 to 3 months of potent DAPT with either reduced potency DAPT or ticagrelor monotherapy was associated with lower rates of all-cause mortality, major bleeding, and NACE, with nonsignificantly different rates of ischemic MACE compared with an uninterrupted 1-year course of aspirin plus prasugrel or ticagrelor. Further studies are warranted to examine the optimal timing of DAPT deescalation after PCI in ACS and to determine whether major differences in safety or effectiveness exist between a reduced potency DAPT versus a ticagrelor (or prasugrel) monotherapy deescalation regimen.

## ARTICLE INFORMATION

Received May 18, 2022; accepted September 29, 2022.

## Affiliations

Division of Cardiology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy (T.P., A.G.B., N.T., E.N., F.S., M.O., F.C., G.G., N.G.). Dipartimento di Scienze Matematiche, Politecnico di Torino, Italy (M.G., G.R.). Severance Cardiovascular Hospital and Science Institute, Yonsei University College of Medicine, Seoul, South Korea (H.-S.K., J.K., K.-W.P.). Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea (J.-Y.H., Y.B.S., H.-C.G.). Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of South Korea (E.H.C., K.C.). Division of Cardiology, Department of Internal Medicine, Daejeon St. Mary's Hospital, The Catholic University of South Korea (M.-W.P.). Division of Cardiology, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, The Catholic University of South Korea (C.J.K.). Department of Cardiology, CHU Timone, Marseille, France (T.C.). Division of Cardiology, Yonsei University Severance Cardiovascular Hospital, Seoul, South Korea (B.-K.K.). Department of Cardiology, CHA Bundang Medical Center, CHA University College of Medicine, Seongnam, South Korea (Y.J.). Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY (G.W.S.).

## Sources of Funding

None.

## Disclosures

Dr Palmerini has received speaker fee from Abbott Vascular, Biotronik, Edwards Lifesciences, and research grant from Eli Lilly. Kim received research grants Abbott, Medtronic, Biotronik, B Braun, and Daiichi Sankyo as well as fees for lecture and consultation from Edwards Lifesciences, Medtronic, Novartis, Pfizer, Sankyo, Amgen, AstraZeneca, and Boehringer Ingelheim; Dr Gwon has received research grants from Abbott Vascular, Boston Scientific, and Medtronic; and speaker's fees from Abbott Vascular, Boston Scientific, and Medtronic; Dr Hahn has received research grants from Abbott Vascular, Biotronik, Boston Scientific, Daiichi Sankyo, and Medtronic; and speaker's fees from AstraZeneca, Daiichi Sankyo, and Sanofi-Aventis; Dr Cuisset has received consulting and lectures fees for Abbott Vascular Boston Scientific Medtronic and Edwards; Dr Stone has received speaker or other honoraria from Cook, Infraredx; has served as a consultant to Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Vectorious, Miracor, Neovasc, Abiomed, Ancora, Elucid Bio, Occlutech, CorFlow, Apollo Therapeutics, Impulse Dynamics, Reva, Vascular Dynamics, Shockwave, V-Wave, Cardiomech, Gore; and has equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, MedFocus family of funds. The other authors report no conflicts.

## Supplemental Material

Supplemental Methods  
Figures S1–S5  
Tables S1–S9

## REFERENCES

- Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057. doi: 10.1056/NEJMoa0904327
- Wiviott SD, Braunwald E, McCabe CH, Horvath I, Keltai M, Herrman JP, Van de Werf F, Downey WE, Scirica BM, Murphy SA, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. *Lancet*. 2008;371:1353–1363. doi: 10.1016/S0140-6736(08)60422-5
- Palmerini T, Bacchi Reggiani L, Della Riva D, Romanello M, Feres F, Abizaid A, Gilard M, Morice MC, Valgimigli M, Hong MK, et al. Stone GW. bleeding-related deaths in relation to the duration of dual-antiplatelet therapy after coronary stenting. *J Am Coll Cardiol*. 2017;69:2011–2022. doi: 10.1016/j.jacc.2017.02.029
- Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, Abizaid A, Hong MK, Kim BK, Jang Y, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. *Lancet*. 2015;385:2371–2382. doi: 10.1016/S0140-6736(15)60263-X
- Baber U, Dangas G, Angiolillo DJ, Cohen DJ, Sharma SK, Nicolas J, Briguori C, Cha JY, Collier T, Dudek D, et al. Ticagrelor alone vs. ticagrelor

- plus aspirin following percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: TWILIGHT-ACS. *Eur Heart J*. 2020;41:3533–3545. doi: 10.1093/eurheartj/ehaa670
6. Cuisset T, Deharo P, Quilici J, Johnson TW, Deffarges S, Bassez C, Bonnet G, Fourcade L, Mouret JP, Lambert M, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. *Eur Heart J*. 2017;38:3070–3078. doi: 10.1093/eurheartj/ehx175
  7. Kim BK, Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, Cho JY, Her AY, Cho S, Jeon DW, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA*. 2020;323:2407–2416. doi: 10.1001/jama.2020.7580
  8. Kim CJ, Park MW, Kim MC, Choo EH, Hwang BH, Lee KY, Choi YS, Kim HY, Yoo KD, Jeon DS, et al. Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): an investigator-initiated, open-label, multicentre, non-inferiority, randomised trial. *Lancet*. 2021;398:1305–1316. doi: 10.1016/S0140-6736(21)01445-8
  9. Kim HS, Kang J, Hwang D, Han JK, Yang HM, Kang HJ, Koo BK, Rhew JY, Chun KJ, Lim YH, et al. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. *Lancet*. 2020;396:1079–1089. doi: 10.1016/S0140-6736(20)31791-8
  10. Tomaniak M, Chichareon P, Onuma Y, Deliaris EN, Takahashi K, Kogame N, Modolo R, Chang CC, Rademaker-Havinga T, Storey RF, et al. Benefit and risks of aspirin in addition to ticagrelor in acute coronary syndromes: a post hoc analysis of the randomized GLOBAL LEADERS trial. *JAMA Cardiol*. 2019;4:1092–1101. doi: 10.1001/jamacardio.2019.3355
  11. Hahn JY, Song YB, Oh JH, Chun WJ, Park YH, Jang WJ, Im ES, Jeong JO, Cho BR, Oh SK, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA*. 2019;321:2428–2437. doi: 10.1001/jama.2019.8146
  12. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, 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: the STOP-DAPT-2 randomized clinical trial. *JAMA*. 2019;321:2414–2427. doi: 10.1001/jama.2019.8145
  13. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, van der Harst P, Barbato E, Morisco C, Tjon Joe Gin RM, et al. A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. *N Engl J Med*. 2019;381:1621–1631. doi: 10.1056/NEJMoa1907096
  14. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, Orban M, Hadamitzky M, Merkely B, Kiss RG, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet*. 2017;390:1747–1757. doi: 10.1016/S0140-6736(17)32155-4
  15. Notarangelo FM, Maglietta G, Bevilacqua P, Cereda M, Merlini PA, Villani GQ, Moruzzi P, Patrizi G, Malagoli Tagliacuzzi G, Crocamo A, et al. Pharmacogenomic approach to selecting antiplatelet therapy in patients with acute coronary syndromes: the PHARMCLO trial. *J Am Coll Cardiol*. 2018;71:1869–1877. doi: 10.1016/j.jacc.2018.02.029
  16. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, Bell M, Bae JH, Jeong MH, Chavez I, et al. Effect of genotype-guided oral p2y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. *JAMA*. 2020;324:761–771. doi: 10.1001/jama.2020.12443
  17. Watanabe H, Morimoto T, Natsuaki M, Yamamoto K, Obayashi Y, Ogita M, Suwa S, Isawa T, Domei T, Yamaji K, et al. Comparison of clopidogrel monotherapy after 1 to 2 months of dual antiplatelet therapy with 12 months of dual antiplatelet therapy in patients with acute coronary syndrome: the STOPDAPT-2 ACS Randomized clinical trial. *JAMA Cardiol*. 2022;7:407–417. doi: 10.1001/jamacardio.2021.5244
  18. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi: 10.1136/bmj.l4898
  19. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700. doi: 10.1136/bmj.b2700
  20. Rucker G, Schwarzer G, Krahn U, König J. *netmeta: network meta-analysis with R*. <https://CRAN.R-project.org/package=netmeta>. R package version 0.6-0; 2014.
  21. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015. doi: 10.1056/NEJMoa0706482
  22. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. *N Engl J Med*. 2019;381:2032–2042. doi: 10.1056/NEJMoa1908419
  23. Vranckx P, Valgimigli M, Juni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet*. 2018;392:940–949. doi: 10.1016/S0140-6736(18)31858-0
  24. Galli M, Benenati S, Franchi F, Rollini F, Capodanno D, Biondi-Zoccai G, Vescovo GM, Cavallari LH, Bickdeli B, Ten Berg J, et al. Comparative effects of guided vs. potent P2Y12 inhibitor therapy in acute coronary syndrome: a network meta-analysis of 61 898 patients from 15 randomized trials. *Eur Heart J*. 2022;43:959–967. doi: 10.1093/eurheartj/ehab836
  25. Rodriguez F, Harrington RA. Management of antithrombotic therapy after acute coronary syndromes. *N Engl J Med*. 2021;384:452–460. doi: 10.1056/NEJMra1607714
  26. Galli M, Benenati S, Capodanno D, Franchi F, Rollini F, D'Amario D, Porto I, Angiolillo DJ. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *Lancet*. 2021;397:1470–1483. doi: 10.1016/S0140-6736(21)00533-X
  27. Shoji S, Kuno T, Fujisaki T, Takagi H, Briassoulis A, Deharo P, Cuisset T, Latib A, Kohnsaka S. De-escalation of dual antiplatelet therapy in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2021;78:763–777. doi: 10.1016/j.jacc.2021.06.012
  28. Valgimigli M, Gragnano F, Branca M, Franzona A, Baber U, Jang Y, Kimura T, Hahn JY, Zhao Q, Windecker S, et al. P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials. *BMJ*. 2021;373:n1332. doi: 10.1136/bmj.n1332
  29. O'Donoghue ML, Murphy SA, Sabatine MS. The safety and efficacy of aspirin discontinuation on a background of a P2Y12 inhibitor in patients after percutaneous coronary intervention: a systematic review and meta-analysis. *Circulation*. 2020;142:538–545. doi: 10.1161/CIRCULATIONAHA.120.046251
  30. Guo C, Li M, Lv YH, Zhang MB, Wang ZL. De-escalation versus standard dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *Platelets*. 2020;31:15–25. doi: 10.1080/09537104.2019.1574969