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Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

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

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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

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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 $P2Y_{12}$ 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

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

In patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) the combination of aspirin plus a potent $P2Y_{12}$ receptor inhibitor (prasugrel or ticagrelor) for 1 year is superior to aspirin plus clopidogrel for 1 year in reducing ischemic events.[1,2] 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.[3,4]

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.[5-10] 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,[11,12] those deescalating DAPT based on genetic or platelet function testing,[13,14] those including clopidogrel monotherapy as de-escalation treatment,[11,12] and those not including a brief period of potent DAPT with aspirin plus prasugrel or ticagrelor[13–16] 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

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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.[17] The risk of bias was assessed using the revised Cochrane risk-of-bias tool.[18] 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.[19]

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,[7,9,10] 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).[20] 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.[5-10] 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,[6–9] whereas 2 trials included both patients with ACS and stable ischemic heart disease, with randomization stratified according to clinical presentation.[5,10] 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,[6,8] aspirin plus reduced-dose prasugrel in 1 trial with 1170 randomized patients,[9] and ticagrelor monotherapy in 3 trials with 7550 randomized patients.[5,7,10] As shown in Table S3, for 3 trials,[7,9,10] 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,[6–10] 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.[5] At 1-year follow-up 119

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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,[5,6,8] at 1 month after randomization in 2 trials,[9,10] and at 3 months after randomization in 1 trial.[7] 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.[1,21] 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.[11,22,23] Other trials have used aspirin plus clopidogrel for 1 year as the reference

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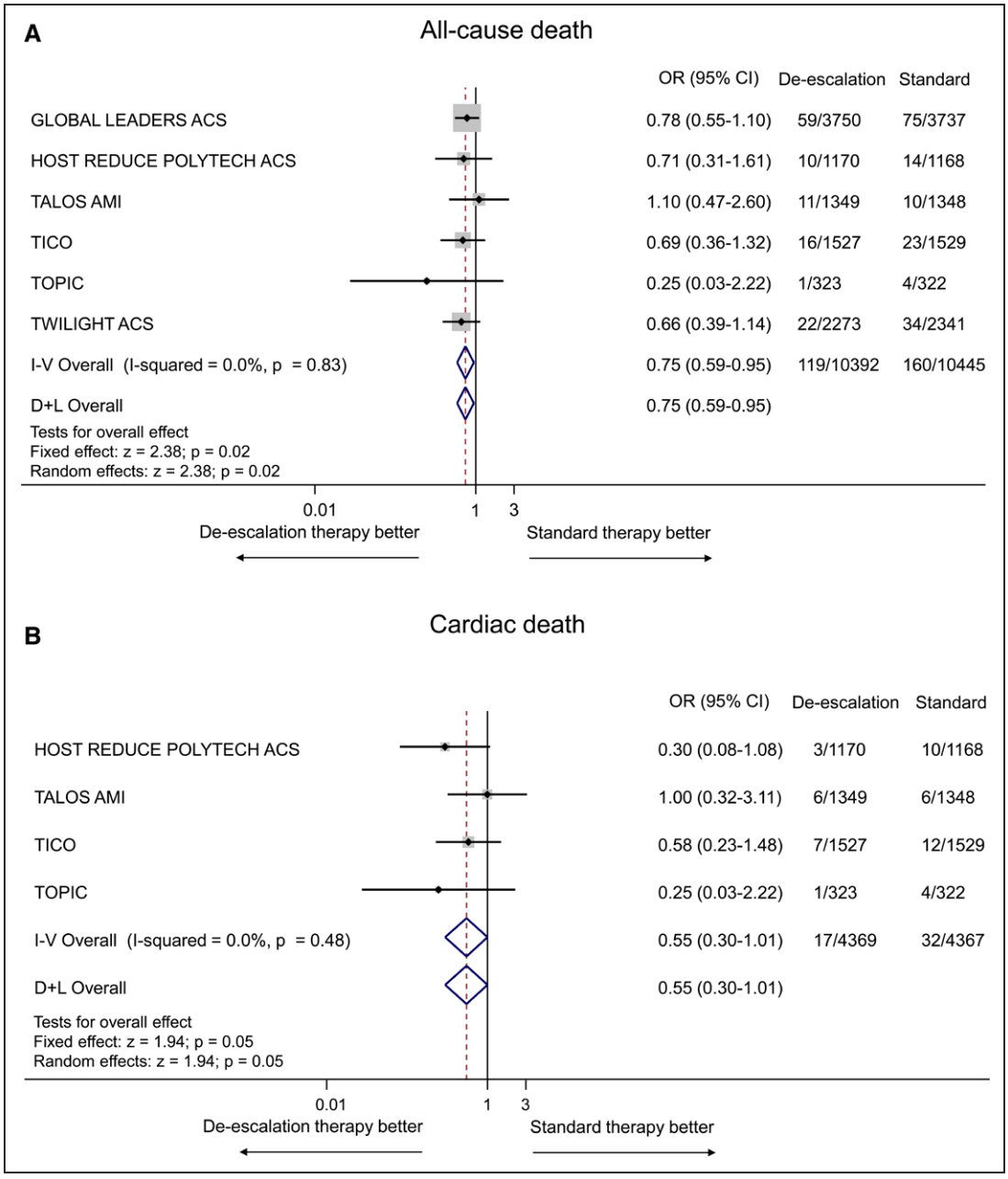

Figure 1. One-year mortality and cardiac mortality in the intention-to-treat population.
A, All-cause mortality and (**B**) cardiac mortality with de-escalation therapy compared with a standard 1-year course of potent dual antiplatelet therapy in the intention-to-treat population. Compared with standard 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.[11,12,16] While a potentially useful management strategy, genetic and platelet function testing to guide antiplatelet therapy selection and duration are rarely utilized.[13,16] 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

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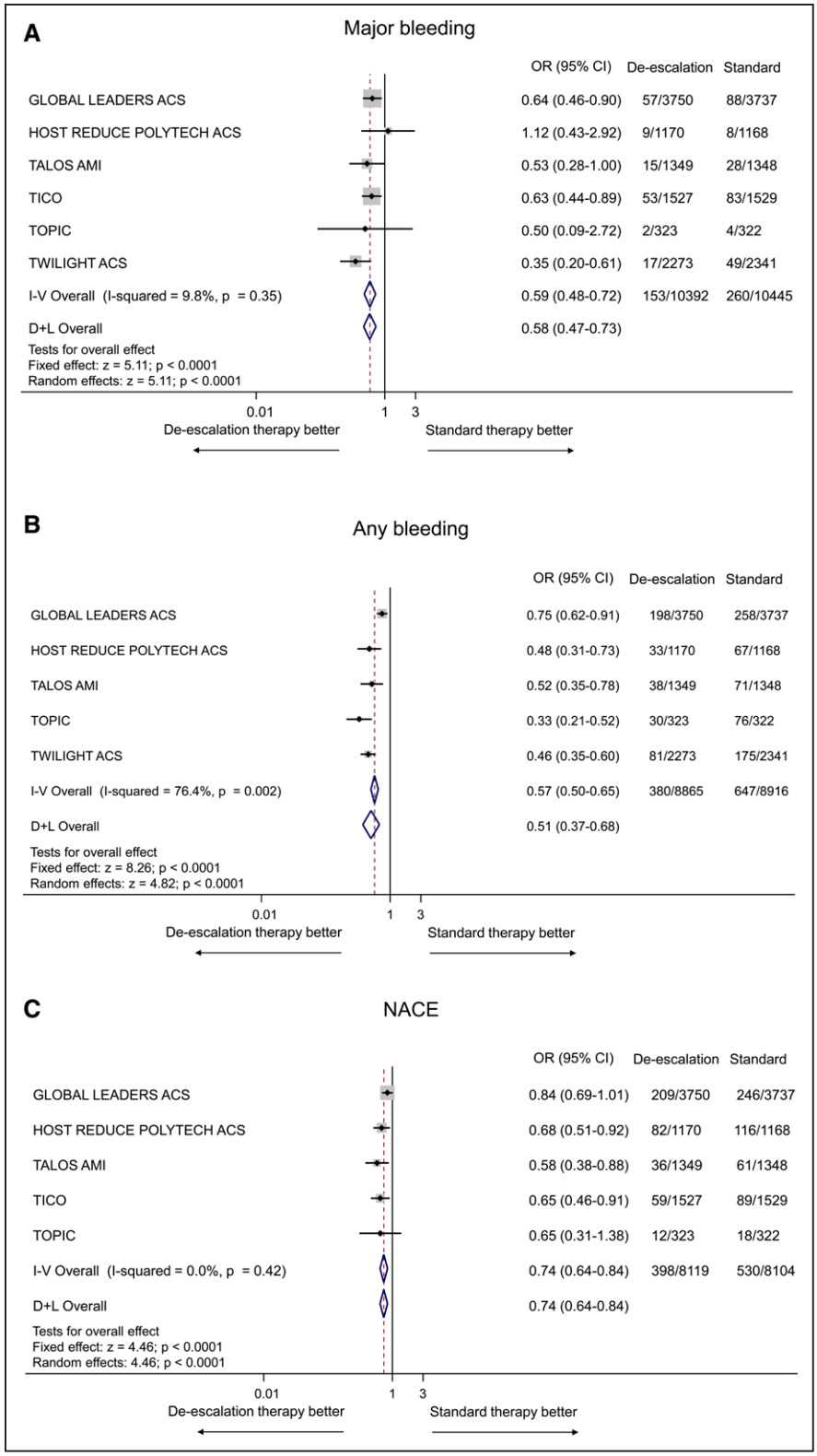

Figure 2. One-year bleeding and net adverse outcomes in the intention-to-treat population.
A, Major bleeding, (**B**) any bleeding, and (**C**) net adverse clinical outcomes (NACE) with deescalation therapy compared with standard therapy in the intention-to-treat population. Compared with standard therapy, 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.[24] 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.[11,12]

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

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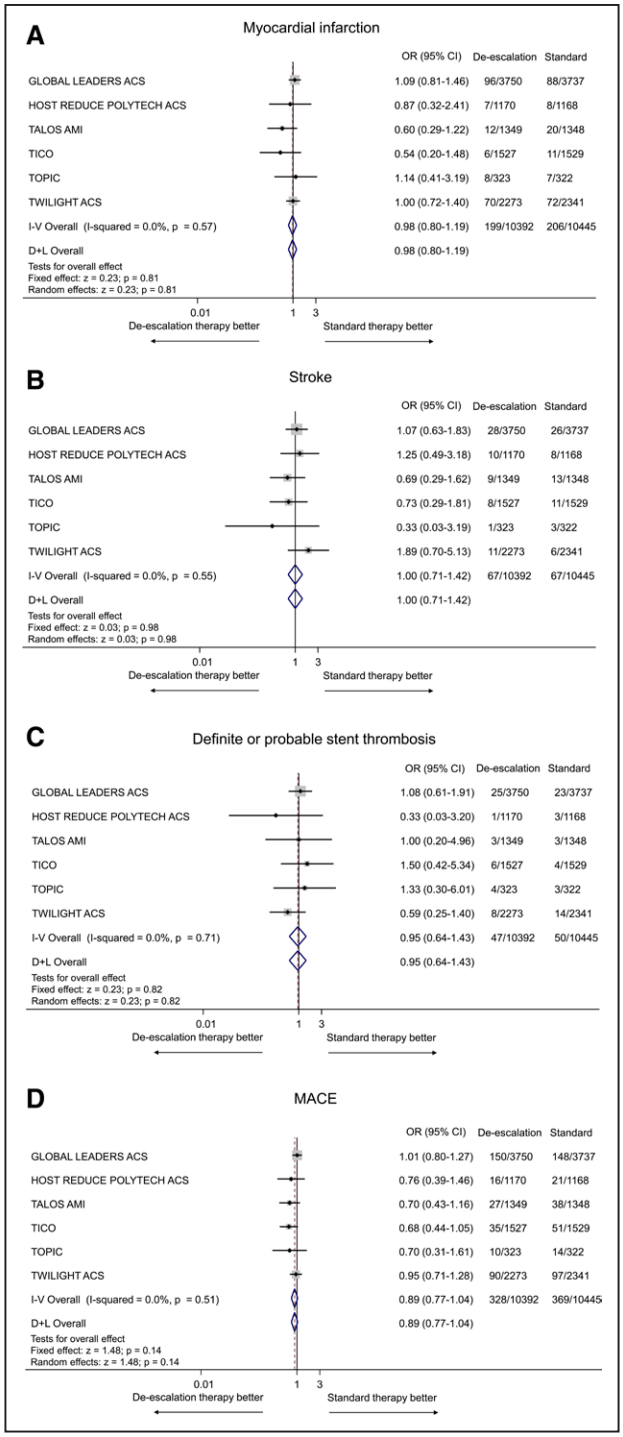

Figure 3. One-year ischemic outcomes in the intention-to-treat population.

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.[25] 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,[26] did not restrict the analysis to patients with ACS undergoing PCI,[27,28] included trials in which de-escalation therapy did not entail a brief period of potent DAPT,[28] considered deescalation as $P2Y_{12}$ monotherapy only,[28,29] or included nonrandomized studies.[30] 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.

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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 20 837 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

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Supplemental Material

Supplemental Methods
Figures S1–S5
Tables S1–S9

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