Article published online: 2022-11-07

Mortality of Escalation and Modulation Antithrombotic Therapy in Coronary Artery Disease Patients: A Meta-analysis of Randomized Controlled Trials

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Thromb Haemost 2023;123:108–117.

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Abstract

Background The net clinical benefit of antithrombotic therapy (ATT) reflects the concomitant effects of bleeding and ischemic events.

Objectives We sought to assess the overall effect of the modulation or escalation of ATT on all-cause mortality as well as ischemic and bleeding events.

Methods We performed a meta-analysis of randomized controlled trials comparing escalation or modulation of ATT versus standard ATT in patients with coronary artery disease. A total of 32 studies with 160,659 subjects were enrolled in this analysis.

Results Neither escalation nor modulation of ATT has significant effect on all-cause mortality (escalation: relative risk [RR]: 0.94, 95% confidence interval [CI]: 0.85–1.04; modulation: RR: 0.90; 95% CI: 0.81–1.01). Compared with standard ATT therapy, escalation of ATT was associated with lower risk of myocardial infarction (MI; RR: 0.84, 95% CI: 0.76–0.94), but had a higher risk of major or minor bleeding (RR: 1.38, 95% CI: 1.15–1.66). Modulation of ATT was associated with a similar risk of MI (RR: 1.07, 95% CI: 0.96–1.19), but a reduced risk for major or minor bleeding (RR: 0.58, 95% CI: 0.51–0.66). Meta-regression combining both escalation and modulation studies found that the heterogeneity of all-cause mortality was mainly attributed to the heterogeneity of major or minor bleeding (adjusted R-squared = 100.00%, $p = 0.004$), but not to MI.

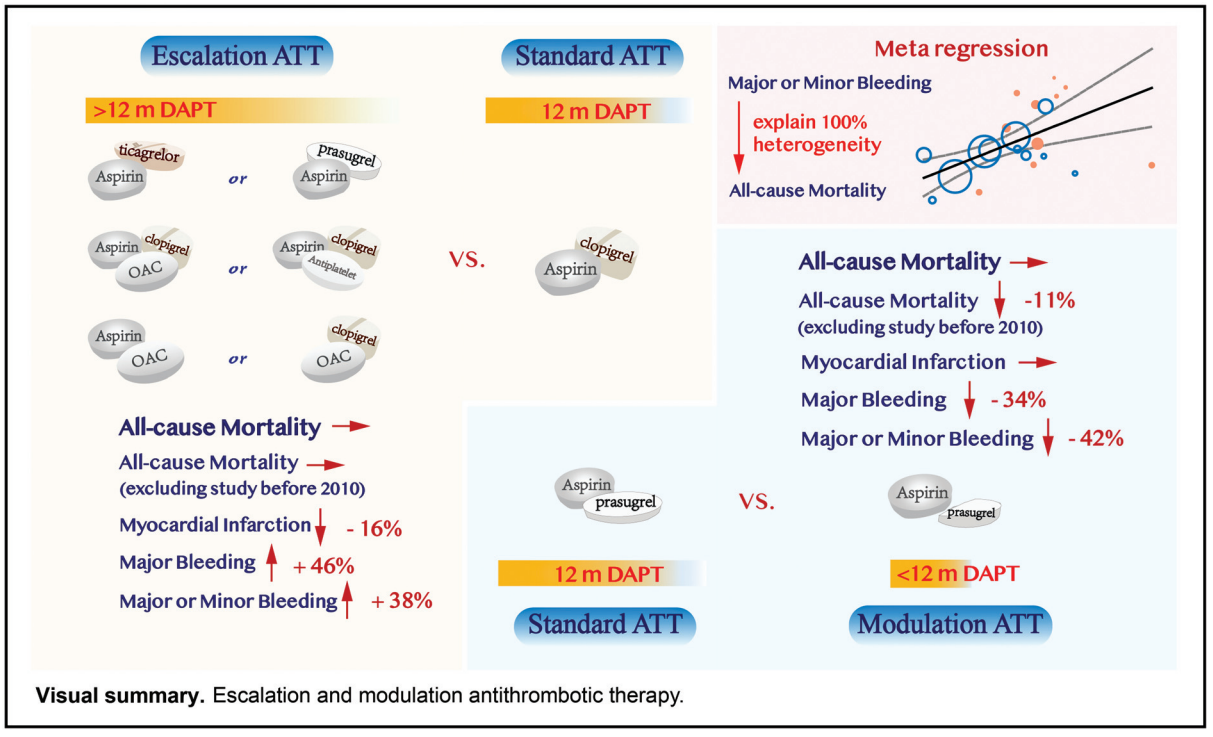
Conclusion Either escalation or modulation of ATT has little benefit in all-cause mortality. The variability of the treatment effects on all-cause mortality was mainly attributed to the variability of major or minor bleeding, but not to MI.

Keywords
- coronary artery disease
- mortality
- antiplatelet
- anticoagulant
- meta-analysis

received
March 3, 2022
accepted after revision
August 2, 2022
article published online
November 7, 2022

DOI https://doi.org/10.1055/s-0042-1757405.
ISSN 0340-6245.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



Visual summary. Escalation and modulation antithrombotic therapy.

Introduction

Antithrombotic therapy (ATT) with platelet inhibitors and/or anticoagulant drugs constitutes a key strategy for the prevention of ischemic events in patients with cardiovascular (CV) disease. Current guidelines recommend dual antiplatelet therapy (DAPT) with aspirin and a P_2Y_{12} inhibitor for 12 months in patients with acute coronary syndrome (ACS) or those undergoing percutaneous coronary intervention (PCI) given its benefit in the risk of stent-related and spontaneous recurrent ischemic events.[1,2] Despite dual pathway antiplatelet inhibition, more than 5% of patients each year develop recurrent ischemic events or vascular death.[3]

Escalation of ATT, including longer DAPT duration, more potent P_2Y_{12} inhibitors, or novel oral anticoagulant (OAC), aims to minimize residual ischemic risk, but concomitantly increases the risk of bleeding. The trade-off between thrombotic risk and bleeding risk therefore is a core part in pharmacotherapy decision making. The ischemic risk attenuates over time after the acute phase, whereas the bleeding risk remains elevated during follow-up, meaning that most benefit for potent P_2Y_{12} inhibitors is expected in the early phase of ACS.[4–6] Hence, clinicians suppose that modulation strategies, defined as switching from a more potent to less potent P_2Y_{12} inhibitor or to a lower dose of potent P_2Y_{12} inhibitor after an initial phase of DAPT, or shorten the duration of DAPT, may indeed maintain ischemic protection, but attenuate long-term bleeding risks. Emerging studies examined whether modulation of ATT can approach optimal balance between ischemia and bleeding.[7,8] Although the prognostic implication of myocardial infarction (MI) and bleeding have both been confirmed by studies, risks of bleeding events are difficult to trade-off directly against ischemic CV events due to their variability of types, sites, and severity. Accordingly, it is hard to value the risk-to-benefit ratio for any given antithrombotic strategy.

All-cause mortality is one of the most important endpoints for clinical studies which can help us balance between benefits and risks. Although several randomized controlled trials (RCTs) have tested the efficacy and safety of escalation or modulation of ATT, the results of these individual trials have not yielded consistent results in all-cause mortality, largely attributed to their limited sample sizes. Therefore, we conducted a comprehensive meta-analysis to investigate whether escalation or modulation treatment would result in a better prognosis for patients with coronary artery disease (CAD), and to explore the sources of variation in treatment effects on all-cause mortality.

Methods

Study Design

Eligible studies for this meta-analysis were RCTs of patients with CAD, comparing the escalation or modulation of dual ATT on the basis of DAPT. Escalation ATT included >12 months DAPT versus 12 months DAPT, triple ATT (DAPT plus OAC or antiplatelet therapy) versus DAPT, potent P_2Y_{12} inhibitor (ticagrelor or prasugrel) versus clopidogrel, and dual pathway inhibition versus DAPT. Modulation ATT included <12 months DAPT versus ≥12 months DAPT, and lower dose P_2Y_{12} inhibitor versus standard dose P_2Y_{12} inhibitor. Exclusion criteria are provided in the **Supplementary Material** (available in the online version).

Search Strategy

We retrieved RCTs through PubMed, EMBASE, and Cochrane Library using the keywords relating to ATT ("platelet aggregation inhibitors," "anticoagulants," "antithrombotic," "NOAC," "clopidogrel," "aspirin," "thienopyridine") and CAD ("acute coronary syndrome," "percutaneous coronary intervention"). Detailed search strategies are demonstrated in the **Supplementary Material** (available in the online version). To minimize heterogeneity due to rapidly advancing treatment strategies, we only included studies published from January 1, 1995 to January 10, 2022. Only articles written or published in English were included.

Trial Selection and Data Extraction

Two investigators (Q.Y.S. and X.T.M.) independently screened the titles, abstracts, and full texts to authenticate whether they met the inclusion criteria, and categorized the studies into escalation or modulation ATT. Data recorded included first author, journal, year of publication, study name, study population, baseline clinical characteristics, interventions, and outcomes of all-cause mortality as well as ischemic and bleeding events. When the data remained unclear or access to additional data was needed, investigators contacted authors via email. If there were several articles from the same group of subjects, we chose the one with the longest follow-up data. Conflicts between investigators were resolved by consensus and consulting a third investigator (Z. J.W.). The filtering process is shown as a flowchart in ►**Fig. 1**. The methodological quality of RCTs was assessed by Cochrane's Collaboration tool for evaluating risk of bias (►**Supplementary Table S1**, available in the online version).

Endpoints and Definitions

The primary endpoint of interest was all-cause mortality. The secondary endpoint of interest was CV mortality, non-CV mortality, MI, major bleeding, or major or minor bleeding. Since the definition of bleeding was inconsistent between studies, we extracted bleeding data in the precedence order of hemorrhage definitions according to Thrombolysis in Myocardial Infarction (TIMI),[9] Bleeding Academic Research Consortium (BARC),[10] Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO),[11] and International Society on Thrombosis and Haemostasis (ISTH).[12] If there

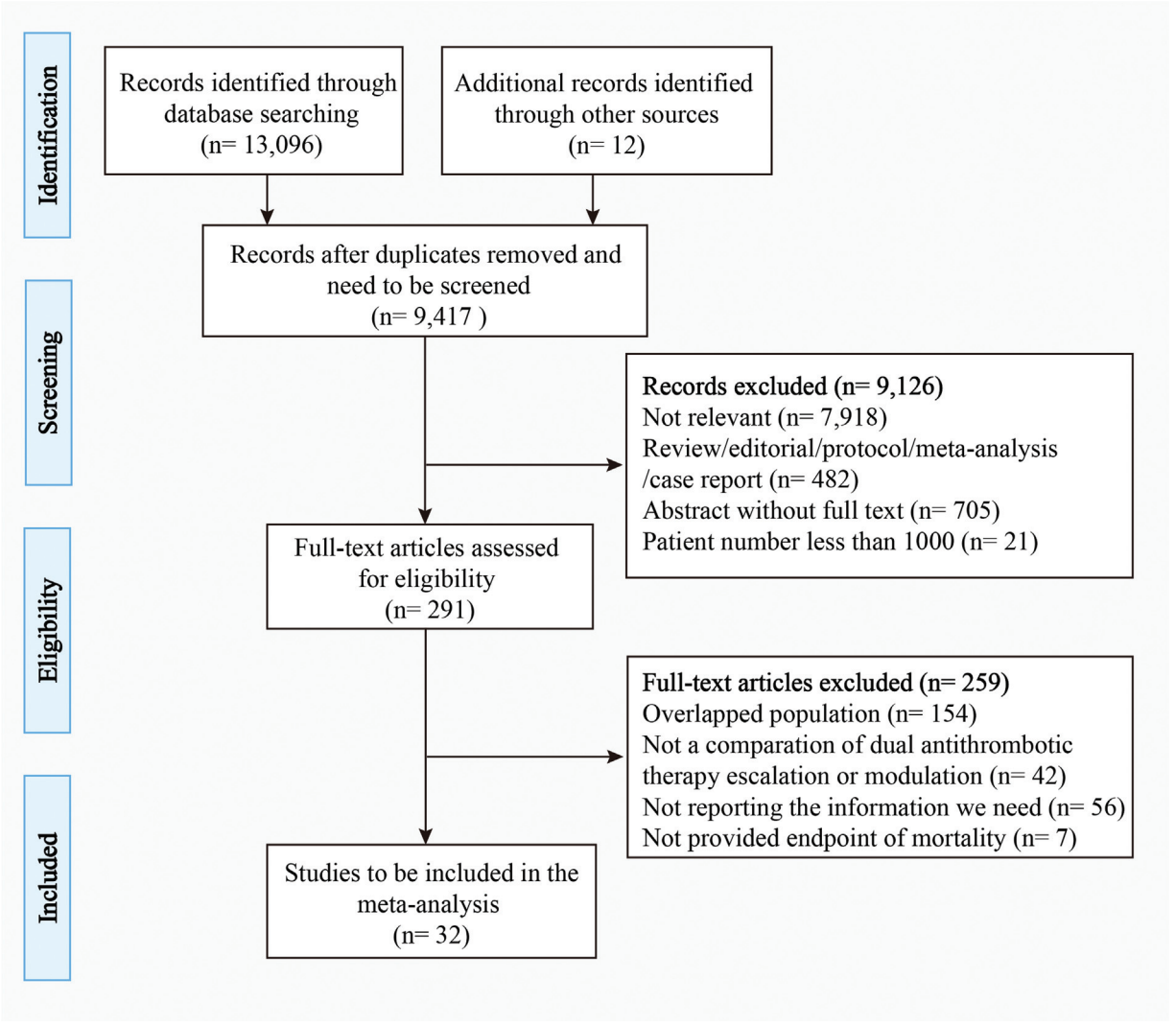


Fig. 1 Flow chart of study selection.

was not an aforementioned bleeding definition, we adopted specific bleeding criteria defined by the corresponding study. The definitions of bleeding in detail for each study are provided in ►**Supplementary Table S2** (available in the online version). The principal analyses were performed in the intention-to-treat populations.

Statistical Analysis

Individual study's baseline characteristics, risk estimates, and raw outcome data were extracted from each RCT. Data for all endpoints were pooled and analyzed using DerSimonian and Laird random-effects models.[13] The percentage of variability across studies caused by heterogeneity beyond chance was evaluated with the Cochrane test and calculated with I^2 statistic. Values <25% indicated low, 25 to 50% indicated moderate, and >50% indicated high heterogeneity.[14] Prespecified subgroup analyses were performed to investigate the potential difference in the treatment effects between types of ATT in the escalation or modulation group. Due to the different thrombotic risks in ACS patients compared with chronic coronary syndromes, subgroup analysis of ACS proportion was performed according to the presence or absence of ACS in high proportion. Subgroup analysis of PCI proportion was also conducted. Sub-analysis was performed after excluding papers published before 2010, year when the drug-eluting stents (DESs) were broadly available, to explore a source of heterogeneity. *p*-Values for between-group heterogeneity were all from meta-regression. Meta-regression analysis was performed to explore sources of heterogeneity of mortality and bleeding or ischemic events. Sensitivity analyses were examined by excluding one study at a time. Publication bias was assessed by Egger's linear regression test, Begg's test, and visual inspection of funnel plots. If the results between bias tools are different, we used the trim-and-fill method to further evaluate and adjust publication bias. Statistical analysis was performed using Stata 12.0 (Stata Corp). The results were regarded as statistically significant at two-tailed p <0.05.

Results

A total of 9,417 articles were retrieved after duplication removal, of which 291 articles warranted full-text review for detail. We finally identified 32 studies (160,659 enrolled patients) that met the inclusion criteria and provided at least one endpoint of interest (►**Fig. 1**). Among 32 RCTs comparing dual ATT escalation or modulation, 8 studies (65,754 enrolled patients) were randomized after diagnosis of ACS, which combined unstable angina, non-ST-elevation MI, and ST-elevation MI; 24 studies (94,905 enrolled patients) were patients with ACS or stable CAD undergoing PCI. The quality assessment and characteristics of the included studies are presented in ►**Supplementary Tables S1** and **S2** (available in the online version). No apparent systematic bias was found, and no individual study unduly influenced the effects estimates in the sensitivity analyses (►**Supplementary Table S3** and ►**Supplementary Figs. S1–S3** [available in the online version]).

Escalation Antithrombotic Therapy

Among 15 studies with 102,554 patients, escalation ATT was not associated with a difference in all-cause mortality (overall: relative risk [RR]: 0.94, 95% confidence interval [CI]: 0.85–1.04, $p = 0.215$; P_2Y_{12} inhibitors: RR: 0.96, 95% CI: 0.85–1.08, $p = 0.495$; OAC: RR: 0.82, 95% CI: 0.68–0.99, $p = 0.034$; others: RR: 0.90, 95% CI: 0.58–1.41, $p = 0.657$) (►**Fig. 2A**). We found no heterogeneity across individual studies in the OAC subgroup ($I^2 = 0.0\%$, $p = 0.572$), and moderate to high heterogeneity in P_2Y_{12} inhibitor subgroup ($I^2 = 45.0\%$, $p = 0.052$) and others group ($I^2 = 56.0\%$, $p = 0.132$). Compared with standard ATT therapy, escalation ATT was associated with a significant reduction in CV mortality (RR: 0.87, 95% CI: 0.81–0.94, $p < 0.001$) (►**Fig. 3A**), but with no effect on the risk of non-CV mortality (RR: 1.04, 95%

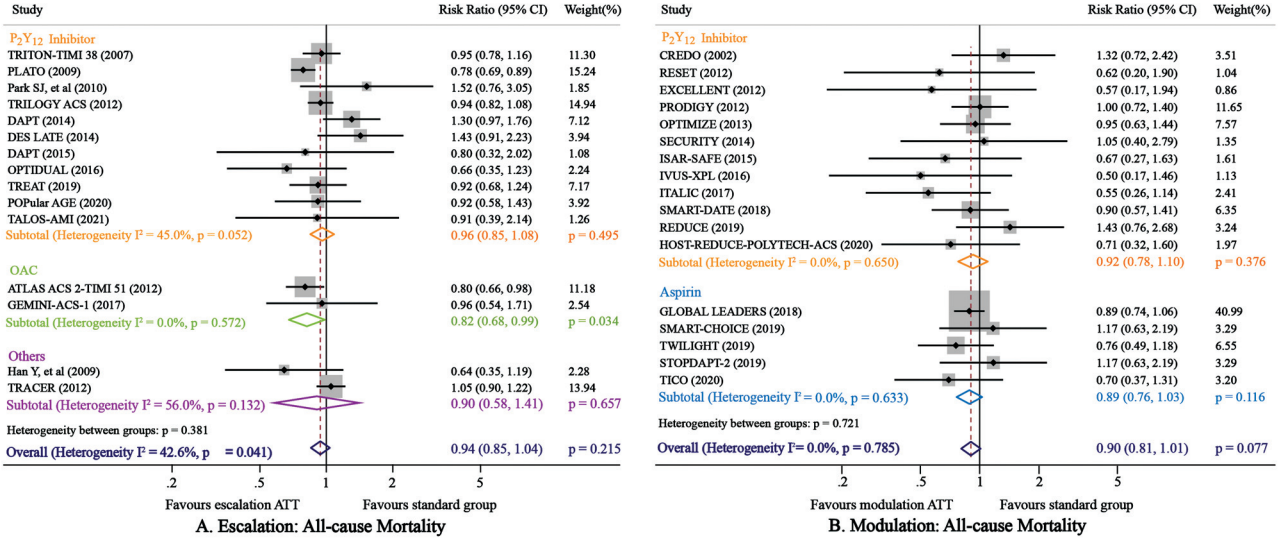


Fig. 2 Estimates of risk for all-cause mortality of escalation ATT and modulation ATT. ATT, antithrombotic therapy.

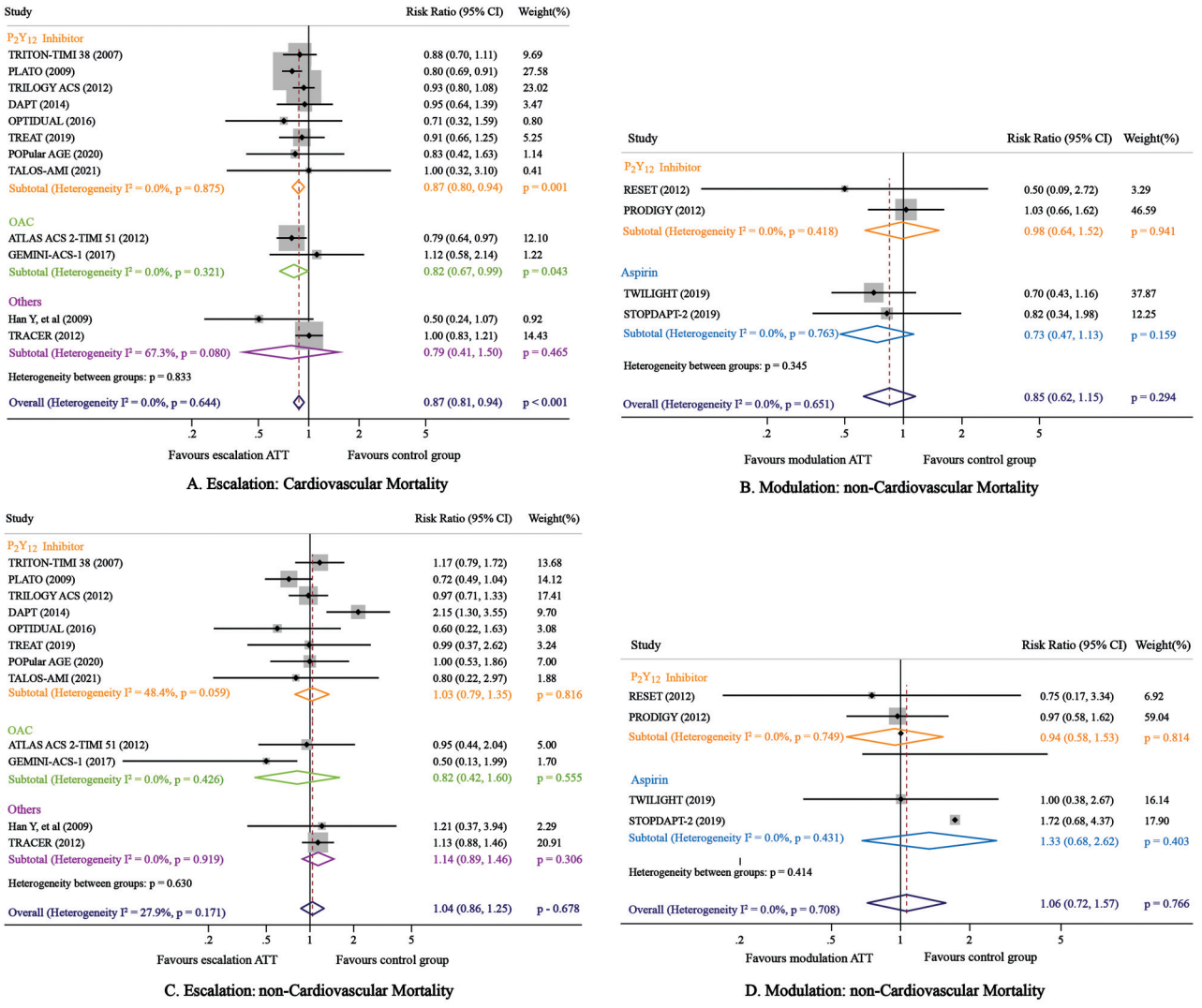


Fig. 3 Estimates of risk for cardiovascular mortality and noncardiovascular mortality of escalation ATT and modulation ATT. ATT, antithrombotic therapy.

CI: 0.86–1.25, $p = 0.678$) (►**Fig. 3C**). In a subgroup analysis of ACS proportion, escalation ATT showed a reduction in all-cause mortality in the ACS 100% subgroup (RR: 0.90, 95% CI: 0.83–0.97, $p = 0.010$), but had no effect on all-cause mortality in 50% ≤ ACS < 100% and ACS <50% subgroups (►**Supplementary Fig. S4**, available in the online version). The heterogeneity within ACS 100% and 50% ≤ ACS < 100% subgroups was low, while that in the ACS <50% subgroup was high. Escalation ATT significantly reduced all-cause mortality in the PCI <100% subgroup (RR: 0.90, 95% CI: 0.81–0.99, $p = 0.035$) with moderate heterogeneity, while it showed no effect on the PCI 100% subgroup with medial heterogeneity (►**Supplementary Fig. S5**, available in the online version). Furthermore, after excluding studies published before 2010, we also found that escalation ATT was not associated with a difference in all-cause mortality with low heterogeneity (RR: 0.98, 95% CI: 0.88–1.09, $p = 0.747$) (►**Supplementary Fig. S6**, available in the online version). Although escalation ATT was associated with a lower risk of MI (RR: 0.84, 95% CI: 0.76–0.94, $p = 0.002$; ►**Fig. 4A**), it significantly increased the risk of major bleeding (RR: 1.46, 95% CI: 1.18–1.80, $p = 0.001$; ►**Fig. 5A**) and major or minor bleeding (RR: 1.38, 95% CI: 1.15–1.66, $p = 0.001$; ►**Fig. 5C**), which counterbalances its survival benefit.

Modulation of Antithrombotic Therapy

Of all the 17 included studies (58,105 patients) referring antiplatelet therapy, 16 of which were short-term DAPT and 1 of which was a de-escalation study. Compared with standard ATT therapy, modulation of ATT was associated with a similar risk of all-cause mortality (RR: 0.90; 95% CI: 0.81–1.01; $p = 0.077$; ►**Fig. 2B**). Subgroup analysis showed that both the aspirin subgroup (RR: 0.89; 95% CI: 0.76–1.03) and the P_2Y_{12} inhibitor modulation subgroup (RR: 0.92, 95% CI: 0.78–1.10) showed a tendency for reduction of all-cause mortality with no heterogeneity ($I^2 = 0.00\%$). CV and non-CV mortalities were available for four studies. Modulation of antiplatelet therapy was not associated with a significant reduction or increase in CV mortality (RR: 0.85, 95% CI: 0.62–1.15; ►**Fig. 3B**) and non-

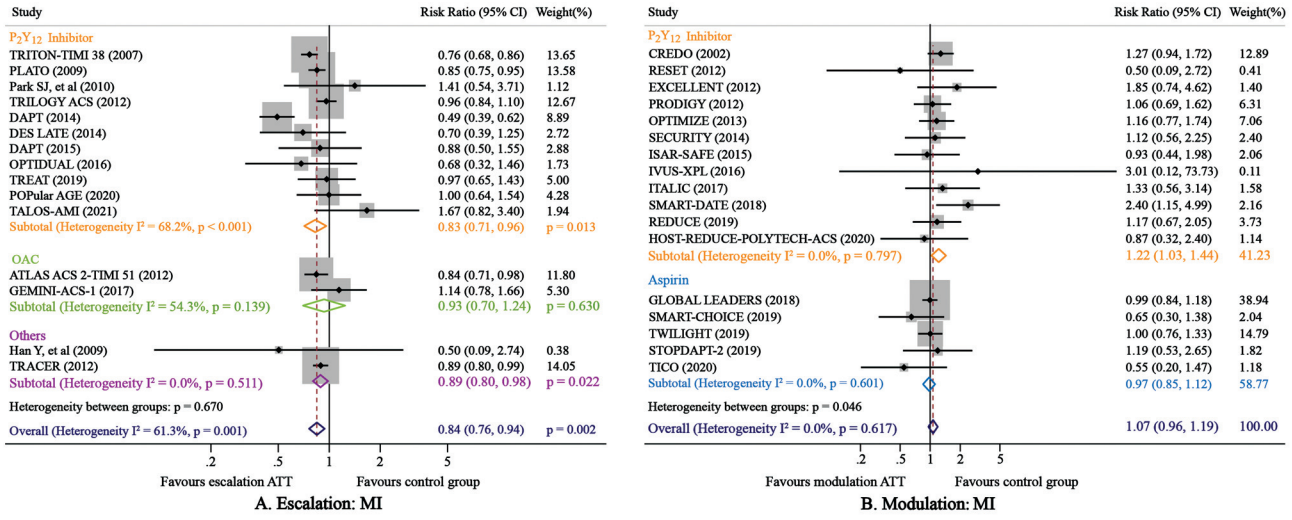


Fig. 4 Estimates of risk for MI of escalation ATT and modulation ATT. ATT, antithrombotic therapy; MI, myocardial infarction.

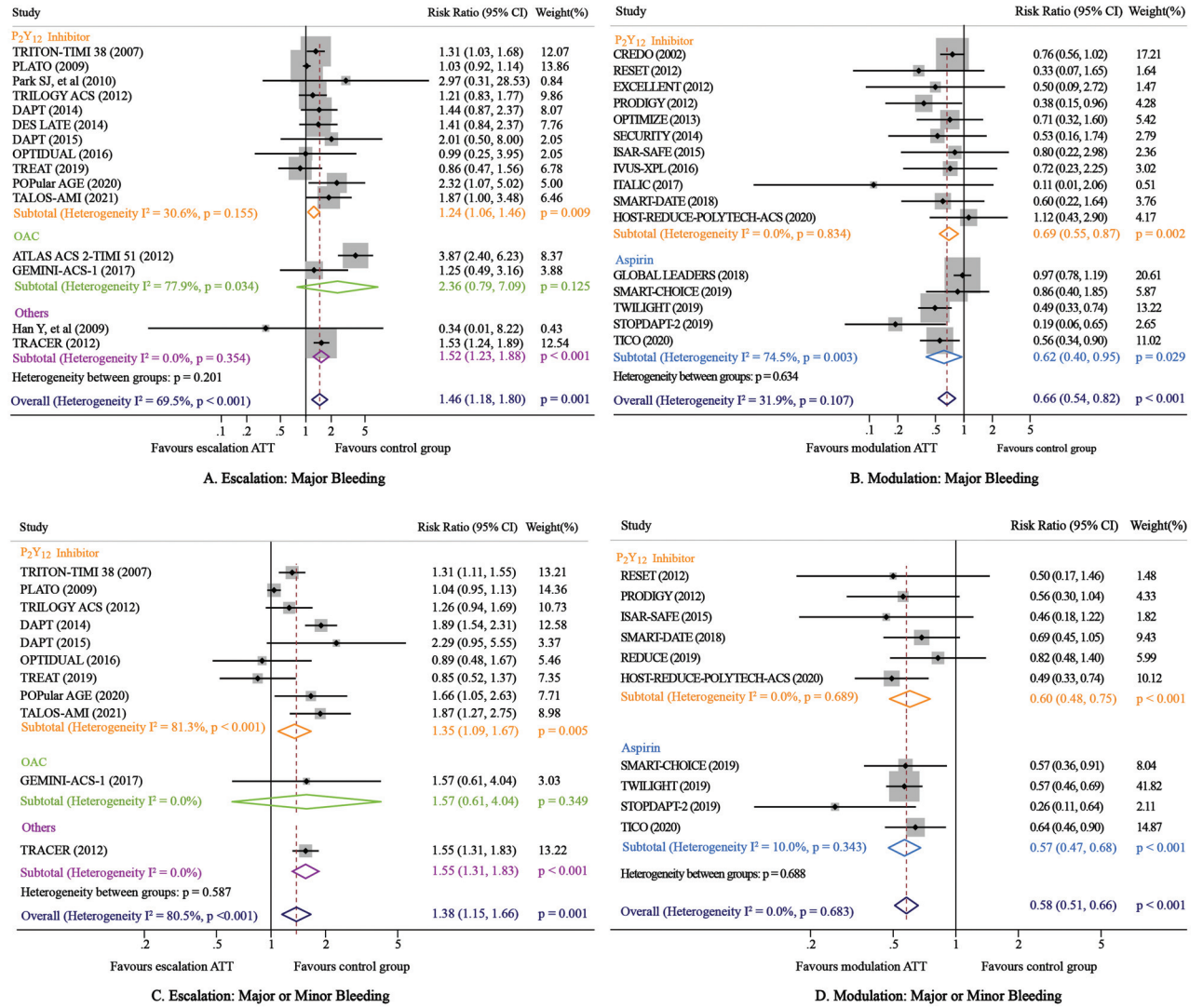


Fig. 5 Estimates of risk for major bleeding and major or minor bleeding of escalation ATT and modulation ATT. ATT, antithrombotic therapy.

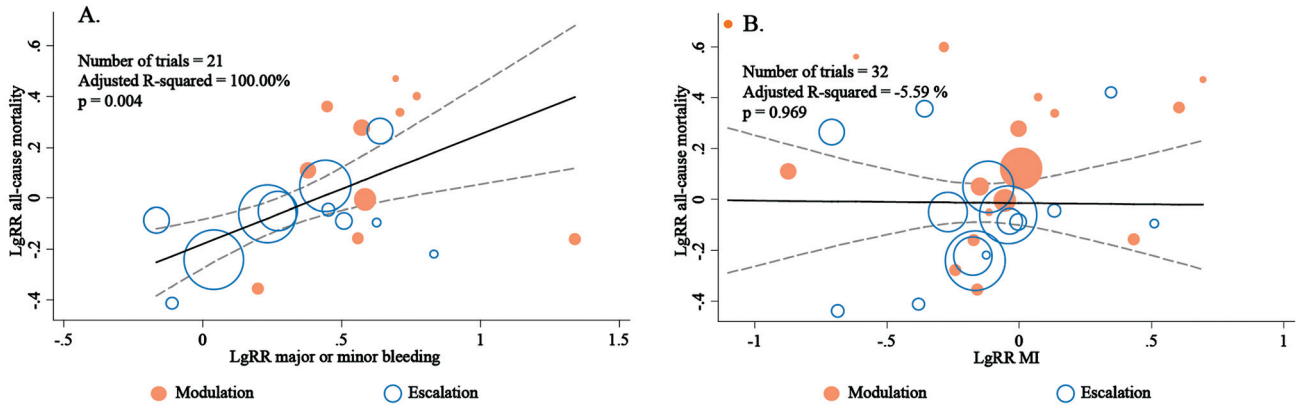


Fig. 6 Meta-regression on log relative risks between treatment effect on all-cause mortality and treatment effect on major or minor bleeding and MI across ATT escalation and ATT modulation in CAD patients. The size of the circles represents the individual study weights. ATT, antithrombotic therapy; CAD, coronary artery disease; MI, myocardial infarction.

CV mortality (RR: 1.06, 95% CI: 0.72–1.57; ►**Fig. 3D**). Subgroup analysis showed that modulated ATT had no effect on all-cause mortality with no heterogeneity, regardless of the proportion of ACS (►**Supplementary Fig. S4**, available in the online version). ATT modulation had a benefit in all-cause mortality in the subgroup of PCI 100% with no heterogeneity (RR: 0.89; 95% CI: 0.79–1.00; $p = 0.046$), while it had no effect on the PCI <100% subgroup (►**Supplementary Fig. S5**, available in the online version). Modulated ATT reduced all-cause mortality with no heterogeneity (RR: 0.89; 95% CI: 0.79–1.00; $p = 0.049$) when studies prior to 2010 were excluded (►**Supplementary Fig. S5**, available in the online version). Compared with standard ATT, modulation of ATT was relevant to similar risk in MI (RR: 1.07, 95% CI: 0.96–1.19; ►**Fig. 4B**), but significantly decreased the risk of major bleeding (RR: 0.66, 95% CI: 0.54–0.82, $p < 0.001$; ►**Fig. 5B**) and major or minor bleeding (RR: 0.58, 95% CI: 0.51–0.66, $p < 0.001$; ►**Fig. 5D**).

Meta-regression Analyses

Combining both escalation and modulation studies, we found that the treatment effect of all-cause mortality was significantly associated with the treatment effect of major or minor bleeding, which accounted for 100% variability of all-cause mortality ($p = 0.004$) (►**Fig. 6A**). The variability of MI was not associated with the variability of all-cause mortality (adjusted R-squared = −5.59%; $p = 0.969$) (►**Fig. 6B**). Upon adding both major or minor bleeding and MI as covariates into the meta-regression model, the association between major or minor bleeding and all-cause mortality remained significant, while the association between MI and all-cause mortality was still not significant (overall: adjusted R-squared = 100.00%, $p = 0.003$; major or minor bleeding: $p = 0.004$; MI: $p = 0.805$). Major bleeding was not found to be relevant to the variability of all-cause mortality (►**Supplementary Fig. S7**, available in the online version). No other study-level baseline characteristics explained the variability of all-cause mortality (►**Supplementary Table S4**, available in the online version).

Discussion

We present a meta-analysis of all published RCTs evaluating the relative safety and efficacy of escalation and modulation ATT involving 160,659 CAD patients, with an average follow-up of 17.2 months. The main findings of the present study are summarized as follows: (1) either escalation or modulation of ATT had little benefit on all-cause mortality, while modulation of ATT significantly reduced all-cause mortality after excluding studies before 2010; (2) compared with standard DAPT, escalation of ATT significantly reduced the risk of MI, but the benefit is counterbalanced by an increased risk of bleeding; (3) modulation of ATT significantly reduced the risk of major and major or minor bleeding, and had similar risk of MI; (4) the treatment effect of all-cause mortality was significantly associated with the treatment effect of major or minor bleeding, which accounts for 100.00% of the heterogeneity across trials; and (5) the variability of MI failed to explain the variability of all-cause mortality.

The escalation ATT is the common choice to prevent the occurrence of MI and stent thrombosis for patients with high ischemic risk. The greatest benefit of the potent agent is during the early phase, whereas the increase in bleeding risk is more pronounced than that of thrombotic risk in the chronic maintenance phase.[4,5,15] Although escalation ATT consistently reduces the risk of ischemic CV events, its effect on mortality varies, and it rarely confers significant benefits to total mortality. In the current analysis, despite incorporating 15 studies with 102,554 CAD patients, we did not find significant reduction in all-cause mortality with escalation ATT. Although escalation ATT was associated with a significant reduction of CV mortality, it slightly increased the risk of non-CV mortality, which counterbalances its overall survival benefit. In this regard, very few individual studies have been designed to assess mortality as the primary endpoint and are powered to detect the difference in mortality. On account of remedies and PCI strategy development, mortality has become a relatively rare event which usually requires a larger sample size and a longer time to appraise the treatment benefits.

Bleeding carries significant prognostic implications, including increased mortality, similar or worse than a recurrent ischemic event. From a post-hoc analysis of the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial, the risk of mortality following an MI was similar to that of BARC 3 bleeding (except BARC 3c), but threefold higher compared with that of BARC 2 bleeding.[6] Besides, in the Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents (ADAPT-DES) trial, postdischarge major or minor bleeding was found to be associated with a 2-year mortality with an effect size more than 2.6-fold greater than that of postdischarge MI.[16] In our meta-regression analysis, we found that the variability of the treatment effects on all-cause mortality was largely driven by the variability of major or minor bleeding, but not by MI.

Accordingly, the raising awareness of the detrimental prognostic impact of bleeding events prompted consideration of modulation ATT with the goal of limiting the burden of ischemic events without the downside of bleeding events. Modulation of the period of DAPT or potent P_2Y_{12} inhibitor could potentially achieve this goal, as the ischemic risk is higher during the acute phase and then gradually attenuates over time, whereas the bleeding risk steadily persists.[4,5] The differential distribution of ischemic risk over time might be explained by the natural course of platelet reactivity, which is highest at the time of a coronary event and subsequently declines, suggesting a lower need for more potent platelet inhibitors after the acute phase.[17] In the present analysis, 16 of the 17 trials in the modulation group explored the timing of DAPT modulation, the other 1 explored a reduced dose of a potent P_2Y_{12} inhibitor. Compared with standard ATT, modulation ATT showed a beneficial trend for all-cause mortality with no heterogeneity between studies and subgroups, despite the trials included in our analysis used different timing of DAPT modulation ranging from 1 to 12 months and different modulation regimens.

In brief, neither escalation nor modulation of ATT has significant effect on all-cause mortality, but both showed a beneficial trend. One possible reason for this is the different era in which the studies were conducted. In earlier studies, patients used first-generation DES or even bare mental stent (BMS),[18] so the risk of thrombosis was relatively high, and patients were generally treated with intensive escalation ATT strategies. However, second-generation DES or bioabsorbable stents were used in later studies. With advances in stent technology, such aggressive antithrombotic strategies are no longer indispensable, so patients have been given modulation ATT to reduce the significant prognostic implications caused by bleeding events. Hence, it is still not clear whether generalized escalation or modulation ATT for the entire population would result in a significant survival benefit, and clinicians should still implement individualized therapy decisions for their patients as would normally occur in daily practice.

Pooled the development of newer generation DES, more standardized secondary prevention, and advanced PCI strategies, and the increased understanding of the prognostic relevance of bleeding events in patients undergoing PCI, investigators were prompted to identify the more individualized ATT regimens that are potentially favorable for a balance between ischemic and bleeding risk. There is growing evidence that the reduced efficacy of clopidogrel to a great extent depends on clopidogrel's poor response with high platelet reactivity.[19,20] Against this background, several RCTs have tested the safety and efficacy of platelet function and genetic testing as tools to guide P_2Y_{12} inhibiting therapy.[21–23] Nevertheless, results of individual RCTs have not yielded consistent results, largely because of their limited sample sizes. Recent meta-analyses found that guided selection by genetic or platelet function testing (PFT) of antiplatelet therapy, as compared with standard selection of antiplatelet therapy of potent P_2Y_{12} inhibitors among patients undergoing PCI, was associated with lower rates of clinically relevant bleeding and major adverse CV events but no benefit in all-cause and CV mortality.[24,25] Another meta-analysis showed that a guided escalation of antiplatelet strategy by means of PFT or genetic testing in patients undergoing PCI significantly improves CV mortality and MI benefits, while a guided modulation strategy was not associated with mortality benefits.[26] Hence, in recent guidelines and consensus statements, the recommendations that PFT and genotyping be used in selective scenarios rather than routine use were stemmed from the fact that the available studies lacked statistical power to assess hard efficacy endpoints such as mortality.[20,27] Indeed, the results of these guided selection tests should also be integrated with numerous other clinical, angiographic, procedural, and socioeconomic variables, which together should guide optimal ATT decisions and further studies on ATT modulation and escalation are needed to refine existing treatment options.[20]

Study Limitations

First, one of the limitations of this study is that the data were derived from heterogeneous cohorts of patients (i.e., ACS, PCI), diverse procedural characteristics (i.e., use of DES or BMS), and different definitions of escalation or modulation ATT. Nevertheless, we have conducted predefined subgroup analysis of type of ATT, ACS proportion, and publication year to explore the source of heterogeneity, and the intra-group heterogeneity is low in most subgroups ($I^2 < 25\%$). Meta-regression analyses based on sample size, follow-up time, mean age, and medical history showed no significant relation between the covariates for all-cause mortality (►**Supplementary Table S4**, available in the online version). Second, there are differences in the definitions of bleeding grades in various studies. Although we tried to unify the definition of bleeding in data processing, residual differences may affect the results of meta-regression. Third, we set strict exclusion criteria, such as excluding studies with less than 1,000 participants and ATT guided by genetic or PFT, to reduce the heterogeneity of included study populations and trial methods. However, important pure de-escalation ATT trials such as TOPIC,[15] TAILOR-PCI,[28] TROPICAL-ACS,[22] and POPular Genetics[29] were excluded.

Conclusion

Compared with standard DAPT, either escalation or modulation of ATT has little benefit in all-cause mortality among patients with ACS or those undergoing PCI. The variability of the treatment effects on all-cause mortality was largely driven by the variability of major or minor bleeding, but not by MI. These results represent limitations of current antithrombotic strategies for CAD patients. More precise tools to guide the individualized therapies or novel antithrombotic drugs with more favorable balance between ischemic and bleeding risks are warranted.

What is known about this topic?

- Pooled evidence for antithrombotic therapy in patients with coronary artery disease was mainly focused on antiplatelet therapy, based on small sample sizes, short time spans, and focusing only on escalation or modulation strategies.
- Whether all-cause mortality, one of the most important endpoints for clinical studies, benefits from escalation or modulation antithrombotic strategies has not been widely considered in previous studies.
- A comprehensive pooled analysis of antithrombotic therapy in these patients is lacking.

What does this paper add?

- This large-scale individual participant-level data meta-analysis has shown that neither escalation nor modulation antithrombotic strategies based on the guideline-recommended standard DAPT therapy was associated with a significant survival benefit among patients with ACS or those undergoing PCI.
- The variability of the treatment effects on all-cause mortality was largely driven by the variability of major or minor bleeding, but not by myocardial infarction.

How might this impact on clinical practice?

- These results represent limitations of current antithrombotic strategies for CAD patients.
- More precise tools to guide the individualized therapies or novel antithrombotic drugs with more favorable balance between ischemic and bleeding risks are warranted.

Authors' Contributions

All authors contributed to study concept and design; Q.Y.S. and X.T.M. contributed to acquisition of data; Z.J.W. and Q. Y.S. did the statistical analysis; Q.Y.S. drafted the report; Z. J.W. contributed to critical revision of the manuscript for important intellectual content. All authors read and approved the final draft of the manuscript.

Funding

This project was funded by the National Key Research and Development Program of China (2017YFC0908800, to Yu-Jie Zhou), the Beijing Municipal Administration of Hospitals' Mission plan (SML20180601, to Yu-Jie Zhou), the China Postdoctoral Science Foundation (2021M692253, to Xiao-Teng Ma), the Beijing Postdoctoral Research Foundation (2021-ZZ-023, to Xiao-Teng Ma), the National Natural Science Foundation of China (81670391, to Zhi-Jian Wang).

Ethics Committee Approval

This study was approved by the institutional review board of Beijing Anzhen Hospital, Capital Medical University.

Conflict of Interest

None declared.

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