ESC European Society of Cardiology

European Heart Journal (2023) **00**, 1–11
https://doi.org/10.1093/eurheartj/ehac829

CLINICAL RESEARCH
Interventional cardiology

Dual antiplatelet therapy de-escalation in acute coronary syndrome: an individual patient meta-analysis

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Received 30 May 2022; revised 8 December 2022; accepted 28 December 2022

See the editorial comment for this article 'P2Y12 inhibitor intensity de-escalation in patients with acute coronary syndromes', by G. Ndrepepa and A. Kastrati, https://doi.org10.1093/eurheartj/ehad050.

Abstract

Aims Dual-antiplatelet therapy (DAPT) with aspirin and a potent P2Y12 inhibitor is the standard treatment for patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). De-escalation of the potent P2Y12 inhibitor is an appealing concept to balance the ischaemic and bleeding risks after PCI. An individual patient data meta-analysis was performed to compare de-escalation versus standard DAPT in patients with ACS.

Methods and results Electronic databases, including PubMed, Embase, and the Cochrane database, were searched to identify randomised clinical trials (RCTs) comparing the de-escalation strategy with the standard DAPT after PCI in patients with ACS. Individual patient-level data were collected from the relevant trials. The co-primary endpoints of interest were the ischaemic composite endpoint (a composite of cardiac death, myocardial infarction, and cerebrovascular events) and bleeding endpoint (any bleeding) at 1-year post-PCI. Four RCTs (the TROPICAL-ACS, POPular Genetics, HOST-REDUCE-POLYTECH-ACS, and TALOS-AMI trials) including 10 133 patients were analysed. The ischaemic endpoint was significantly lower in the patients assigned to the de-escalation strategy than in those assigned to the standard strategy (2.3% vs. 3.0%, hazard ratio [HR] 0.761, 95% confidence interval [CI] 0.597-0.972, log rank $P = 0.029$). Bleeding was also significantly lower in the de-escalation strategy group (6.5% vs. 9.1%, HR 0.701, 95% CI 0.606-0.811, log rank $P < 0.001$). No significant intergroup differences were observed in terms of all-cause death and major bleeding events. Subgroup analyses revealed that compared to guided de-escalation, unguided de-escalation had a significantly larger impact on bleeding endpoint reduction (P for interaction = 0.007); no intergroup differences were observed for the ischaemic endpoints.

Conclusion In this individual patient data meta-analysis, DAPT-based de-escalation was associated with both decreased ischaemic and bleeding endpoints. Reduction in bleeding endpoints was more prominent for the unguided than the guided de-escalation strategy.

Study registration number This study was registered in the PROSPERO (ID: CRD42021245477).

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Structured Graphical Abstract

Key Question

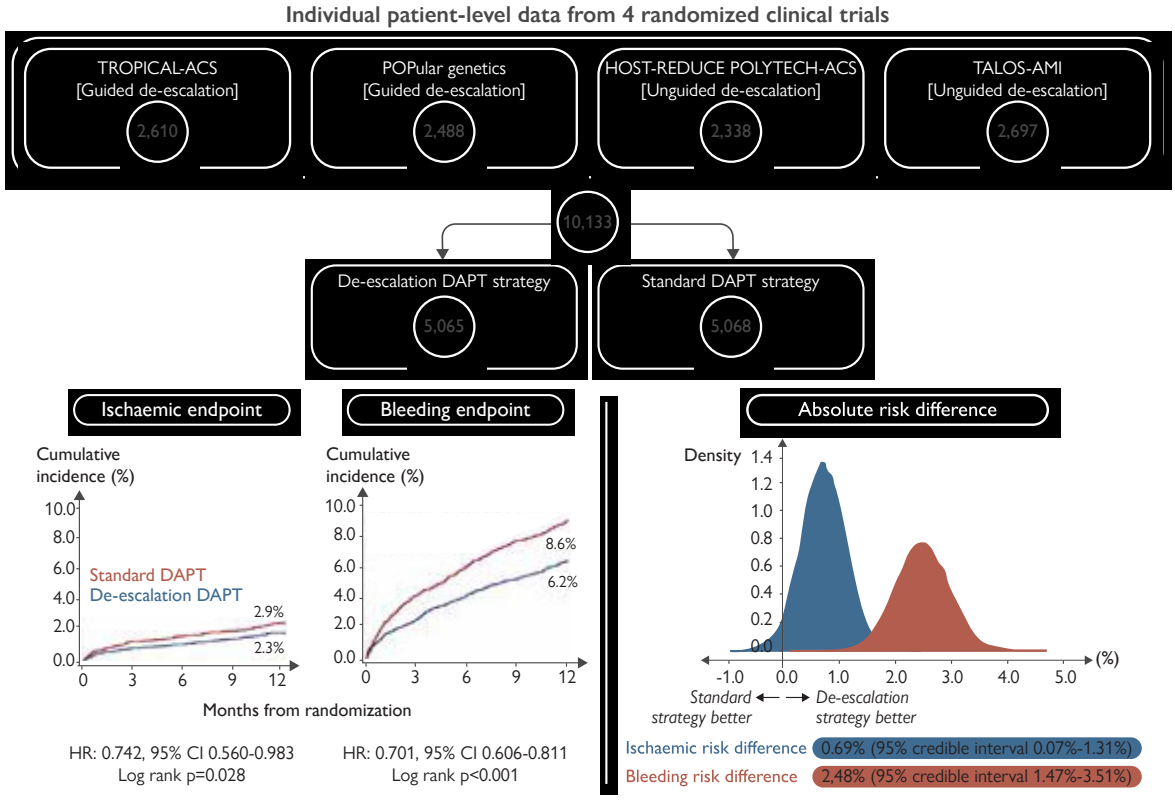
What is the impact of dual antiplatelet therapy-based de-escalation strategy on ischaemic and bleeding risks, in patients with acute coronary syndrome?

Key Finding

In this individual patient-level meta-analysis including four randomized clinical trials, ischaemic and bleeding endpoints were significantly lower in the de-escalation antiplatelet strategy group compared to the standard antiplatelet strategy group.

Take Home Message

De-escalation of dual antiplatelet therapy compared with standard strategy may be a safe method which reduced both ischaemic and bleeding endpoints in patients with acute coronary syndrome who receive percutaneous coronary intervention.



A total of 10 133 patients from four randomized clinical trials were analysed. During the first year after percutaneous coronary intervention, the de-escalation strategy was associated with a lower risk of the ischaemic and bleeding endpoints. The absolute risk difference of endpoints between the two astrategies was 0.69% for the ischaemic endpoint and 2.48% for the bleeding endpoint. CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio.

Keywords De-escalation • Antiplatelet therapy • Acute coronary syndrome • Ischemic outcome • Bleeding outcome

Introduction

Dual antiplatelet therapy (DAPT), consisting of aspirin and a potent P2Y12 inhibitor, is the standard treatment strategy after percutaneous coronary intervention (PCI) for patients with acute coronary syndrome (ACS).[1] Platelet inhibition for reducing thrombotic complications is essential within the first year after PCI, especially in those with high thrombotic risk such as ACS. Although potent P2Y12 inhibitors have proven beneficial for reducing the ischaemic outcomes, they are inherently associated with an increased risk of bleeding. Bleeding complications in these patients are not benign, because they have been associated with higher mortality and morbidity.[2] The increased bleeding risk can particularly outweigh the thrombotic risk after the acute phase when thrombotic risk significantly decreases.[3]

Various antiplatelet strategies have been studied to reduce adverse outcomes by taking into account the change over time in the

thrombotic and bleeding risks and balance the relative trade-off.[3] Among these, DAPT de-escalation, which is defined as switching between oral P2Y12 inhibitors from a more potent to a less potent agent, may be a promising method and has been evaluated in various trials.[4] Such de-escalation strategies, including both guided and unguided, have been included in the recent guidelines.[1,5] Previous study-level meta-analyses of randomized clinical trials (RCTs) have reported the outcomes of de-escalation strategies. However, these analyses focused on vastly heterogeneous strategies, wherein obtaining meaningful insights into the individual strategies was prohibitive.[6–8] Because of the inherent limitation of study-level analyses, investigators could not account for the time-dependent risk of de-escalation nor could they assess heterogeneity among studies for various outcomes. The absence of patient-level data prohibits the assessment of various characteristics that are related to safety and efficacy outcomes, including the individual ischaemic and bleeding risk profile.[9,10] The availability of individual data would allow the investigation of the association of these factors with de-escalation on adverse events and identification of those who could benefit the most from de-escalation.[11] A patient-level analysis based on a large cohort is needed to provide more insights into the impact of de-escalation strategies on thrombotic and bleeding risks. Given the clinical importance of understanding the potential benefits and safety of de-escalation strategies in patients with ACS, we aimed to conduct an individual patient meta-analysis of RCTs evaluating a DAPT de-escalation strategy in patients with ACS. We also performed landmark analyses of the de-escalation time points and subgroup analyses to compare different de-escalation methods, including guided and unguided de-escalation.

Methods

Search strategy and selection criteria

This individual patient data meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The protocol was prospectively registered in the PROSPERO registry (ID: CRD42021245477). We searched the PubMed, Embase, and Cochrane databases to identify RCTs that evaluated the efficacy and safety of de-escalation strategies which were published before 31 December 2021. We used the following search terms: ('acute coronary syndrome' OR 'ACS' OR 'myocardial infarction') AND ('primary' OR 'percutaneous coronary intervention' OR 'PCI') AND ('de-escalation' OR 'guided' OR 'guide') AND ('antiplatelet' OR 'P2Y12 inhibitor' OR 'P2Y12' OR 'dual antiplatelet therapy' OR 'DAPT'). Multicentre RCTs that included more than 1000 patients were included, while there were no language restrictions. Two authors (J.K. and J.C.) independently identified the studies that met the search criteria. Only published studies were included in the analysis; abstracts or conference presentations were not included. Conflicts over inclusion were resolved by consensus with a third author (K.W.P.). All studies were reviewed to identify any irrelevant duplicated studies. Four trials met the search criteria, and individual patient-level data were obtained from them. The search strategy is provided in the Supplementary Appendix. These data were reviewed by each trial investigator and compared with the data from previously published trials.

Study endpoints

The co-primary endpoints for this analysis were ischaemic and bleeding endpoints at 12 months post-PCI. The ischaemic endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, and cerebrovascular events. The bleeding endpoint comprised type 2 or higher bleeding events (according to the Bleeding Academic Research Consortium [BARC] criteria) or major or minor bleeding events (according to the Platelet Inhibition and Patient Outcomes [PLATO] criteria). The secondary endpoints were the individual components of the primary endpoints, such as all-cause death, myocardial infarction, stent thrombosis, repeat revascularization, stroke, major bleeding (type 3 or 5 [according to the BARC criteria] or major [according to the PLATO criteria]). The endpoints in each trial were defined according to the definitions used in the original trials and are provided in Supplementary Appendix.

Landmark analyses were pre-specified and performed to consider the potential impact of specific de-escalation timepoints on the clinical endpoints. Subgroup analyses of the primary endpoint were performed for key pre-specified clinical subgroups, which included those classified by age, sex, renal function, diabetes status, and angiographic vessel disease. The interactions between the subgroup status and the treatment effect were tested.

Data analysis

An individual participant data meta-analysis was planned with comparisons performed on an intention-to-treat basis. All patients received PCI for the treatment of ACS, and the time point 0 for the analysis was the point of randomization (after index PCI but before discharge), except for the TALOS-AMI trial in which randomization occurred 30 ± 7 days post-PCI. For the TALOS-AMI trial, we used the time of PCI as time point 0 because the trial reported all events that occurred after PCI but before randomization. Continuous variables are presented as mean $\pm$ standard deviation, while categorical variables are expressed as counts and percentages. Continuous variables were compared using Student's *t*-test, while categorical variables were compared using the χ^2 test. Adjustment for multiple hypothesis testing was not performed. Event rates were calculated using the Kaplan–Meier method, and a Cox proportional hazard regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). The HRs, 95% CIs and *P*-values were calculated by the competing risk analysis based on the Fine and Gray method. The 95% CIs for secondary endpoints were not adjusted for multiple testing. The primary analysis was based on a one-stage approach, which simultaneously included all data from the trials using a fixed-effect and random-effect Cox regression model stratified by each trial. Subsequently, a two-stage analysis of the primary endpoints was performed through a trial-level approach with an inverse-variance method, based on the DerSimonian–Laird estimator for combining the trial-level estimates. A heterogeneity analysis was performed across the included trials by testing for an interaction between the trial and the treatment effect of the primary endpoint; this analysis was performed using the two-stage fixed-effects model with the I^2 statistic and Cochran's *Q* test.

A Bayesian analysis of the co-primary endpoints at the timepoint of 12 months after randomization was also performed, assuming a non-informative prior with a uniform distribution of 0 to 1. The probabilities of absolute risk differences of 0.0%, at least 1.0%, and 2.5% in the primary endpoints between the two treatment arms were determined through Bayesian analysis. A two-sided *P*-value of <0.05 was considered significant for all tests. All analyses were performed using CRAN R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Our initial search yielded 1143 results; after applying the selection criteria, four RCTs (the TROPICAL-ACS, POPular Genetics, HOST-REDUCE-POLYTECH-ACS, and TALOS-AMI trials) were finally included in our meta-analysis (*Figure 1*). The detailed data for each trial are provided in Supplementary Appendix. Individual patient-level data were collected from all four RCTs. Among these RCTs, two evaluated guided de-escalation (the TROPICAL-ACS and POPular Genetics trials), while two evaluated unguided de-escalation (the HOST-REDUCE-POLYTECH-ACS and TALOS-AMI trials). All studies were considered to have a low bias risk (Supplementary Appendix).

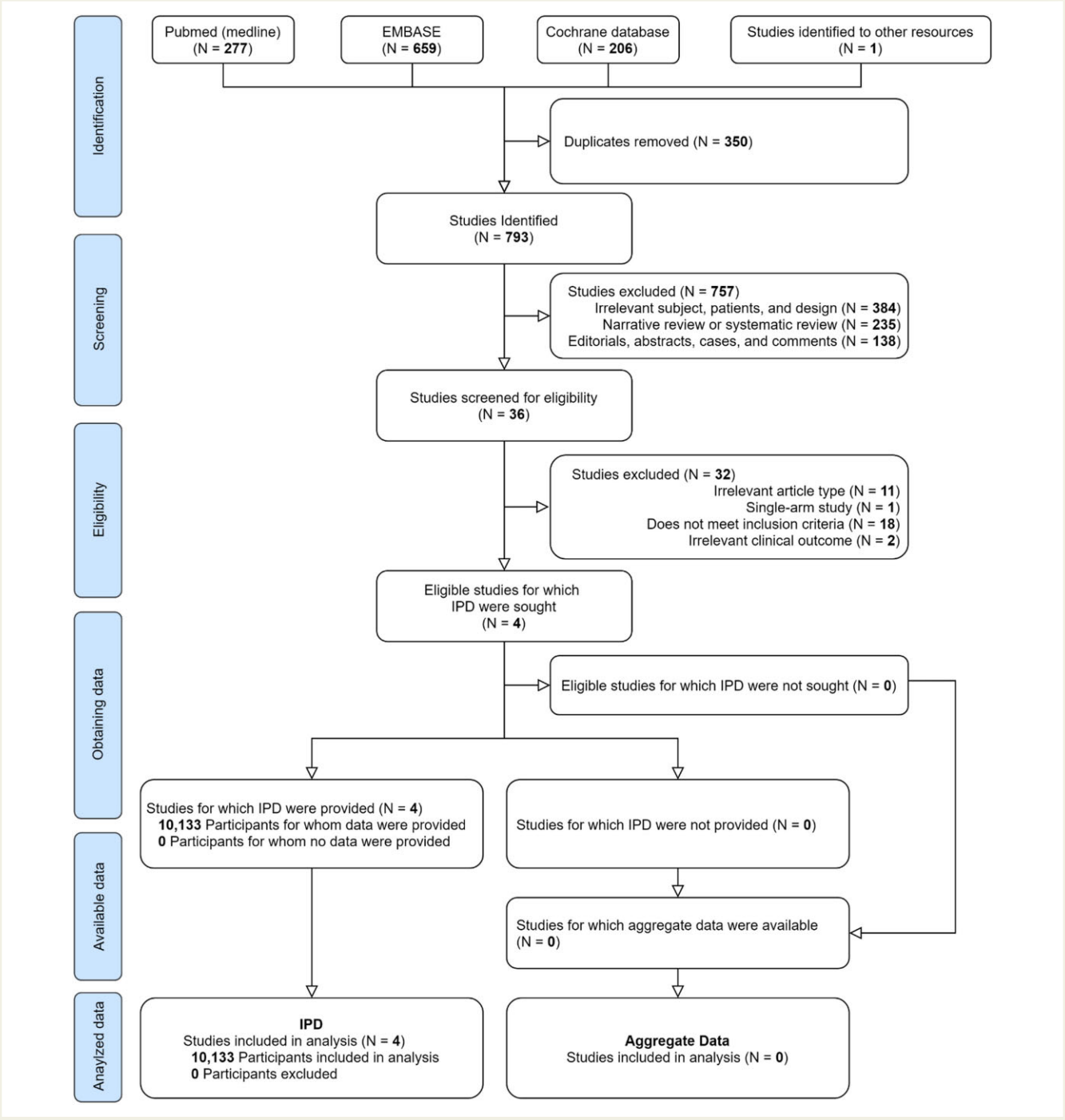


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

The baseline characteristics of the pooled total population are presented in *Table 1*. A total of 10 133 patients were analysed, among which 5065 and 5068 patients were included in the de-escalation group (de-escalation DAPT strategy implemented) and the standard group (standard DAPT strategy implemented), respectively. During the 1-year follow-up period, 140 patients (2.8%) and 146 patients (2.9%) were lost to follow-up in the de-escalation group and the standard group, respectively. Adherence to the allocated medication was marginally higher in the de-escalation group (93.1% vs. 92.1%, $P = 0.049$). The median age of the total population was 57.8 years, and 86.0% were diagnosed with acute myocardial infarction, 25.1% had diabetes mellitus, and 15.4% had a three-vessel disease. At the index PCI, the left anterior descending artery was treated in 45.8% of the patients, and 1.4 ± 0.8 stents were implanted per patient.

Clinical endpoints

During the median follow-up duration of 365 days (interquartile range [IQR]: 351–365 days), the cumulative incidence of the ischaemic endpoint was 2.3% (95% CI 1.9%–2.8%) in the de-escalation group and

Table 1 Baseline characteristics of the total population

	De-escalation ($n = 5065$)	Standard (N = 5068)
Demographics and comorbidities		
Age, years	59.9 ± 10.5	59.7 ± 10.7
Male sex	4136 (81.7%)	4108 (81.1%)
Ethnicity		
Caucasian	2486 (49.1%)	2488 (49.1%)
African	4 (0.1%)	3 (0.1%)
Arabian	14 (0.3%)	7 (0.1%)
Asian	2531 (50.0%)	2530 (49.9%)
Latin	11 (0.2%)	14 (0.3%)
Others	19 (0.4%)	26 (0.5%)
Height, cm	172 ± 9	172 ± 9
Body weight, kg	80.7 ± 14.9	80.6 ± 15.1
Body surface area, m^2	1.96 ± 0.21	1.96 ± 0.21
Diabetes mellitus	1264 (25.0%)	1272 (25.1%)
Hypertension	2702 (53.4%)	2723 (53.7%)
Dyslipidaemia	2351 (46.4%)	2356 (46.5%)
Current smoking	1168 (23.1%)	1155 (22.9%)
Chronic kidney disease	857 (16.9%)	818 (16.2%)
Previous PCI	440 (8.7%)	480 (9.5%)
Previous CABG	65 (1.3%)	79 (1.6%)
Clinical indication of PCI		
Unstable angina	689 (13.6%)	732 (14.4%)
NSTEMI	1496 (29.5%)	1494 (29.5%)
STEMI	2880 (56.9%)	5722 (56.1%)
Laboratory results		
Haemoglobin, g/dl	13.1 ± 2.8	13.0 ± 2.8
Creatinine, mg/dl	0.95 ± 0.52	0.95 ± 0.48
Antiplatelet agent at discharge		
Aspirin	5010 (99.2%)	5012 (99.2%)
P2Y12 inhibitor		
Clopidogrel	718 (14.2%)	114 (2.2%)
Prasugrel	2449 (48.4%)	2467 (48.7%)
Ticagrelor	1888 (37.3%)	2477 (48.9%)
Antiplatelet agent at the de-escalation period		
Aspirin	4980 (98.3%)	5010 (98.9%)
P2Y12 inhibitor		
Clopidogrel	2835 (56.0%)	205 (4.0%)
Prasugrel	1611 (31.8%)	2345 (46.3%)
Ticagrelor	542 (10.7%)	2486 (49.1%)
Angiographic data per patient		
Extent of CAD		
1-vessel disease	2222 (58.4%)	2220 (58.2%)
2-vessel disease	1013 (26.5%)	1004 (26.3%)
3-vessel disease	582 (15.2%)	591 (15.5%)
Left main disease	121 (2.4%)	108 (2.1%)
Total number of implanted stents	1.0 [IQR 1.0–2.0]	1.0 [1.0–2.0]
Total number of implanted stents ≥3	1545 (30.5%)	1571 (31.0%)
PCI-treated coronary artery		
Left main	90 (1.8%)	83 (1.8%)
Left anterior descending artery	2341 (46.2%)	2297 (45.3%)
Left circumflex artery	887 (17.5%)	965 (19.0%)
Right coronary artery	1740 (34.4%)	1695 (33.4%)

CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.
Data are presented as mean ± standard deviation, *n* (%), or median [interquartile range].

3.0% (95% CI 2.6%–3.5%) in the standard group (HR 0.761, 95% CI 0.597–0.972; log-rank $P = 0.029$; *Figure 2A*). Two-stage approaches yielded very similar results with no inter-trial heterogeneity observed ($I^2 = 0\%$, $\tau^2 = 0\%$, Cochran's $Q = 0.30$, and $P = 0.959$; Supplementary Appendix). The cumulative incidence of the bleeding endpoint was 6.5% (95% CI 5.8%–7.1%) in the de-escalation group and 9.1% (95% CI 8.3%–9.9%) in the standard group (HR 0.701, 95% CI 0.606–0.811; log-rank $P < 0.001$; *Figure 2B*). There was a trend for inter-trial heterogeneity, which did not reach the level of statistical significance ($I^2 = 56.6\%$, Cochran's $Q = 6.91$, and $P = 0.075$; Supplementary Appendix). The absolute risk differences at 12 months were 0.7% (95% CI 0.3%–1.1%) for the ischaemic endpoint and 2.6% (95% CI 1.9%–3.3%) for the bleeding endpoint. The cumulative incidences of the secondary endpoints are shown in *Table 2*, along with the competing risk for all endpoints except for mortality. The 1-year mortality rate was similar between the de-escalation and standard groups (1.0% [51/5065] vs. 1.1% [55/5068]; HR 0.925, 95% CI 0.632–1.354, log-rank $P = 0.687$). The incidence of ischaemic endpoints, including non-fatal myocardial infarction, cerebrovascular events, repeat revascularisation and stent thrombosis, were also similar between the de-escalation and standard groups. For major bleeding events, the incidence was numerically lower in the de-escalation group, but the difference did not reach statistical significance. No significant inter-trial heterogeneity was observed for the secondary endpoints in a two-staged approach (Supplementary Appendix).

As a sensitivity analysis, a landmark analysis was performed at the specific time point of de-escalation, which was unique for each study. Overall, the results were consistent with the original analysis. The risks

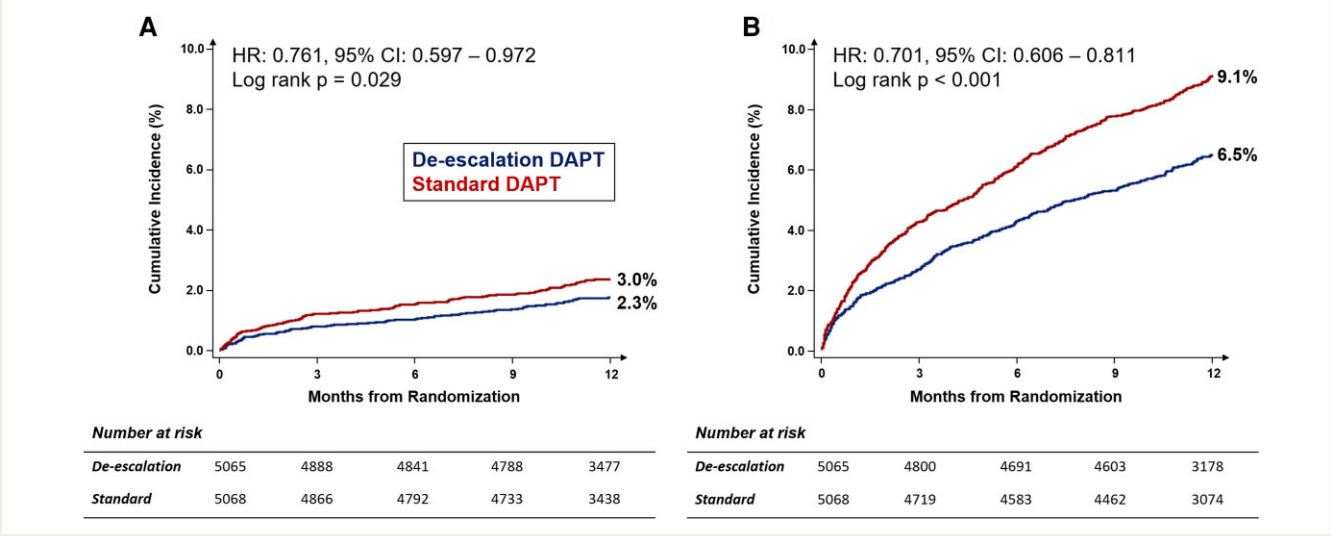


Figure 2 Cumulative analysis of the ischaemic endpoint and bleeding endpoint. The Kaplan–Meier analysis curves of patients who received de-escalation strategy and standard strategy are shown for the ischaemic endpoint (*A*) and bleeding endpoint (*B*).

Table 2 Clinical outcomes of the intention-to-treat population

	De-escalation (*N* = 5065)	Standard (*N* = 5068)	*P*-value[a]	Hazard ratio[b] (95% confidence interval)	*P*-value[b]
	*% (No. of patients)**				
Primary endpoints					
Ischaemic endpoint[c]	2.3% (114)	3.0% (149)	0.029	0.76 (0.60–0.97)	0.029
Bleeding endpoint[d]	6.5% (312)	9.1% (438)	<0.001	0.70 (0.61–0.81)	<0.001
All-cause death	1.0% (51)	1.1% (55)	0.698	0.92 (0.63–1.35)	0.687
Cardiovascular death	0.5% (26)	0.7% (38)	0.133	0.68 (0.41–1.12)	0.132
Non-cardiovascular death	0.5% (25)	0.3% (17)	0.215	1.46 (0.79–2.71)	0.222
Non-fatal myocardial infarction	1.2% (62)	1.6% (82)	0.094	0.75 (0.54–1.05)	0.089
Cerebrovascular events	0.6% (30)	0.8% (39)	0.278	0.77 (0.48–1.24)	0.273
Major bleeding[e]	1.2% (60)	1.4% (71)	0.335	0.84 (0.60–1.19)	0.314
Any revascularization	2.4% (121)	2.3% (119)	0.892	1.01 (0.79–1.31)	0.914
Stent thrombosis	0.2% (8)	0.2% (11)	0.492	0.73 (0.29–1.80)	0.486

[a]The *P* value in the fourth column are the values form the χ^2 test.
[b]The hazard ratio and *P*-values in the sixth column were calculated by the competing risk analysis based on the Fine and Gray method. The 95% confidence intervals for secondary end points have not been adjusted for multiple testing.
[c]Primary ischaemic endpoint is defined as a composite of cardiac death, non-fatal myocardial infarction, cerebrovascular events, and major bleeding events (BARC type ≥3).
[d]Primary bleeding endpoint was defined as type 2, 3, or 5 bleeding events according to the BARC criteria or minor and major bleeding according to the PLATO criteria.
[e]Major bleeding was defined as bleeding events defined as type 3 or 5 according to the BARC criteria or major bleeding according to the PLATO criteria.
*Clinical endpoints were evaluated in the intention-to-treat population at 12 months after index PCI. The percentages shown are Kaplan–Meier estimates.

of the ischaemic endpoint (HR 0.768, 95% CI 0.595–0.991; log-rank $P = 0.041$) and the bleeding endpoint (HR 0.693, 95% CI 0.596–0.807; log-rank $P < 0.001$) were significantly lower in the de-escalation group than in the standard group (Supplementary Appendix).

Bayesian analysis revealed that the absolute risk difference for the bleeding events between the two groups was 2.48% (95% credible interval: 1.47%–3.51%). The probability that the bleeding events were more common in the standard group was 99.9%. More specifically, there was a 99.8% probability that the absolute risk difference in the bleeding events was at least 1.0%, and a 48.3% probability that the absolute risk difference for the bleeding events was at least 2.5%. Furthermore, the absolute risk difference for the ischaemic events between the two groups was 0.69% (95% credible interval: 0.07%–1.31%). The probability that the ischaemic events were more common in the standard group was 98.5%, with a 16.2% probability that the absolute risk difference was at least 1.0% (*Figure 3*).

Subgroup analyses

Results of a comparison of the treatment effects between the de-escalation strategy and the standard therapy for key subgroups are presented in *Figure 4*. No statistically significant heterogeneity was observed for the ischaemic and bleeding endpoints across the clinical subgroups, including those classified by age, diabetes, hypertension, renal function, smoking, clinical presentation as ST-elevation myocardial infarction, angiographic vessel disease, stent number, and the initial P2Y12 inhibitor usage. However, the impact of bleeding risk reduction by de-escalation was numerically larger when de-escalation was performed from ticagrelor to clopidogrel as compared to de-escalation from prasugrel to clopidogrel. Also, a significant interaction was found between the bleeding endpoints and the type of de-escalation strategy used (i.e. guided or unguided; P for interaction = 0.007). Unguided de-escalation and guided de-escalation reduced the bleeding events by 50% (HR 0.50, 95% CI 0.38–0.67, $P < 0.001$) and 21% (HR 0.79, 95% CI 0.67–0.94, $P = 0.008$) of the patients, respectively.

Discussion

In this meta-analysis, we analysed individual patient-level data from four RCTs. The analysis included 10 133 patients who were randomised to either the de-escalation DAPT strategy or the standard DAPT strategy after PCI for ACS. The main findings of the current study are as follows: (i) de-escalation was associated with a significant reduction in both the ischaemic and bleeding events, (ii) there was no significant difference in mortality between the two strategies, (iii) in a landmark analysis performed from the actual timepoint of de-escalation, which was unique for each trial, the beneficial effect of de-escalation for the ischaemic and bleeding events was consistent, and (iv) compared to guided DAPT de-escalation, unguided universal DAPT de-escalation was associated with a significantly larger reduction in bleeding (*Structured Graphical Abstract*).

In patients with ACS receiving PCI, the combination of aspirin and a potent P2Y12 receptor inhibitor is one of the key components of medical therapy. Due to the heightened thrombotic risk in ACS, potent P2Y12 inhibitors, such as prasugrel and ticagrelor, are recommended due to their enhanced potency and decreased variability of platelet inhibition.[12] Although the use of potent agents significantly reduced the ischaemic events, this came at the cost of increased bleeding. Moreover, previous studies have shown that the impact of major bleeding on mortality after PCI is comparable to that of recurrent thrombotic events, further supporting the clinical necessity to reduce both ischaemic and bleeding risks.[13,14] Therefore, there is a need for novel antithrombotic strategies, where the combined risk of ischaemia and bleeding can be minimized.[15] In this regard, de-escalation of the potent P2Y12 inhibitor may be a potential solution. The concept of de-escalation is based on the hypothesis that there is a temporal change in the risk of ischaemia and bleeding after PCI over time. The risk of thrombosis is the greatest immediately after PCI. However, it rapidly decreases along with the stabilization of the patient and the lesion.[16] However, the bleeding risk is maintained or does not decline at the rate that the ischaemic risk declines. Therefore, the relative impact of the bleeding risk increases, justifying a de-escalation strategy.[17,18] The interindividual variability in the response to clopidogrel also serves to justify the requirement of de-escalation.[17] Numerous modifiable and unmodifiable factors (including the genetic polymorphisms of *CYP2C19*) may reduce the response to clopidogrel, which is associated with an increased risk of ischaemic events. These carriers of *CYP2C19* loss-of-function alleles may be the patients that need potent P2Y12 inhibitors. However, for patients that may achieve sufficient platelet inhibition with clopidogrel, prescribing a potent P2Y12 inhibitor may expose them to unnecessary bleeding risk.

Multiple RCTs have shown promising results supporting de-escalation and such a strategy is commonly adopted in clinical practice.[19] Consequently, de-escalation is backed by recent guidelines, which state that de-escalation may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition.[1,5] A few study-level analyses have addressed the outcomes of de-escalation but until now, there has been no individual patient-level analysis of de-escalation. A well-designed patient-level analysis has several advantages, such as using common definitions and time-to-event data for estimating the survival of multiple studies.[20]

In the current analysis, we obtained patient-level data from four RCTs; each RCT compared a de-escalation DAPT strategy with a standard DAPT strategy. The TROPICAL-ACS trial was the first study to evaluate the safety and efficacy of guided de-escalation. In that study, de-escalation was guided by platelet function testing (PFT); all patients were started on prasugrel for 1 week and then switched to clopidogrel. Prasugrel was re-prescribed only in those with a high platelet reactivity to clopidogrel.[21] The study showed that PFT-guided de-escalation of P2Y12 inhibitor therapy was non-inferior to standard prasugrel therapy for preventing thrombotic events, with a similar rate of bleeding. The POPular Genetics trial evaluated a *CYP2C19* genotype-guided de-escalation strategy in patients with ST-elevation myocardial infarction. In the genotype-guided strategy group, *CYP2C19* genotyping was performed; the carriers of the *CYP2C19* loss-of-function allele were treated with ticagrelor or prasugrel, while non-carriers (*CYP2C19*1/*1*) were treated with clopidogrel.[22] No significant intergroup difference was observed in the ischaemic outcome, while the bleeding outcome was significantly decreased by 22% in the genotype-guided de-escalation group. The HOST-REDUCE-POLYTECH-ACS trial evaluated an unguided prasugrel-based dose de-escalation strategy.[23] One month after the index PCI, the de-escalation group received a prasugrel daily dose de-escalated from 10 to 5 mg. The rate of ischaemic outcomes was similar between the prasugrel-based de-escalation strategy and standard strategy groups, while the de-escalation group experienced a 52% bleeding risk reduction. Finally, the TALOS-AMI trial evaluated an unguided ticagrelor-based de-escalation strategy.[24] At 1-month post-PCI, ticagrelor was switched to clopidogrel in the de-escalation group. Between the de-escalation strategy group and the standard strategy group, there was no significant difference in the composite ischaemic outcome, while bleeding occurred less frequently in the de-escalation group (relative risk reduction of 48%). Collectively, all trials showed no difference in ischaemic outcomes; however, the bleeding complications were reduced by the de-escalation strategy in three trials. Of note, the TOPIC trial also evaluated unguided de-escalation.[25] The results in this trial were mostly in line with the current analysis, reporting that switching a potent P2Y12 inhibitor to clopidogrel at 1 month after PCI reduced bleeding without a significant increase in ischaemic outcomes in ACS patients. However, the trial was a single centre study with only 646 patients enrolled and therefore was not included in the current analysis. Further, the TOPIC trial lacked data regarding clinical events that occurred within the first month after PCI.

According to the concept of de-escalation, it would seem appropriate that de-escalation would only reduce the bleeding complications and may have adverse effects on the ischaemic endpoints. However,

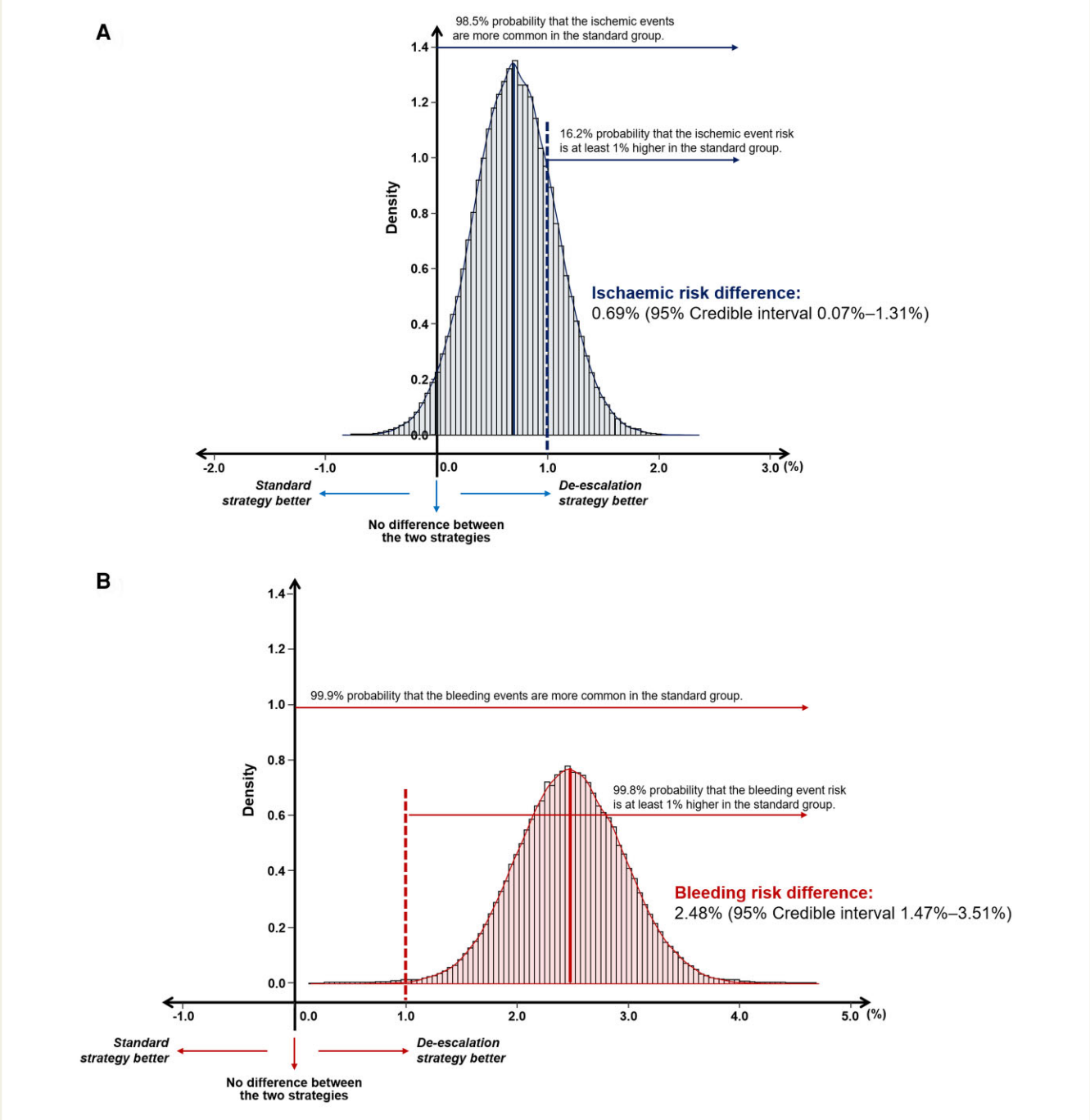


Figure 3 Density plot of the risk difference of ischaemic and bleeding endpoints. The absolute risk difference of (*A*) ischaemic risk and (*B*) bleeding risk between the two strategies was calculated using the Bayesian analysis. The risk difference for endpoints were calculated at the timepoint of 12 months post-randomization between the two treatment arms.

previous RCTs did not show that the de-escalation strategy has a hazardous effect on the ischaemic risk, while a comprehensive evaluation of the true effect of de-escalation was difficult due to the distinct definition of ischaemic endpoints. In the current analysis, to evaluate the impact of platelet-centric ischaemic endpoints, we defined ischaemic endpoints as a composite of cardiac death, myocardial infarction, and cerebrovascular events. Our analysis showed that de-escalation was associated with a significantly reduced risk of platelet-centric ischaemic endpoints. A reduction in both the bleeding and ischaemic endpoints, which seems counterintuitive theoretically, is a phenomenon that has been observed in other trials.[26,27] This can be explained in several ways. First, compliance with antiplatelet agents can be poor in those who experience bleeding events, leading to increased ischaemic endpoints. Second, various clinical factors (such as old age and chronic kidney disease) are associated with increased ischaemic and bleeding risks, therefore patients with these risk factors are at risk for various adverse events. Meticulous medical treatment in these patients would reduce both ischaemic and bleeding events. Third, cardiac death, by

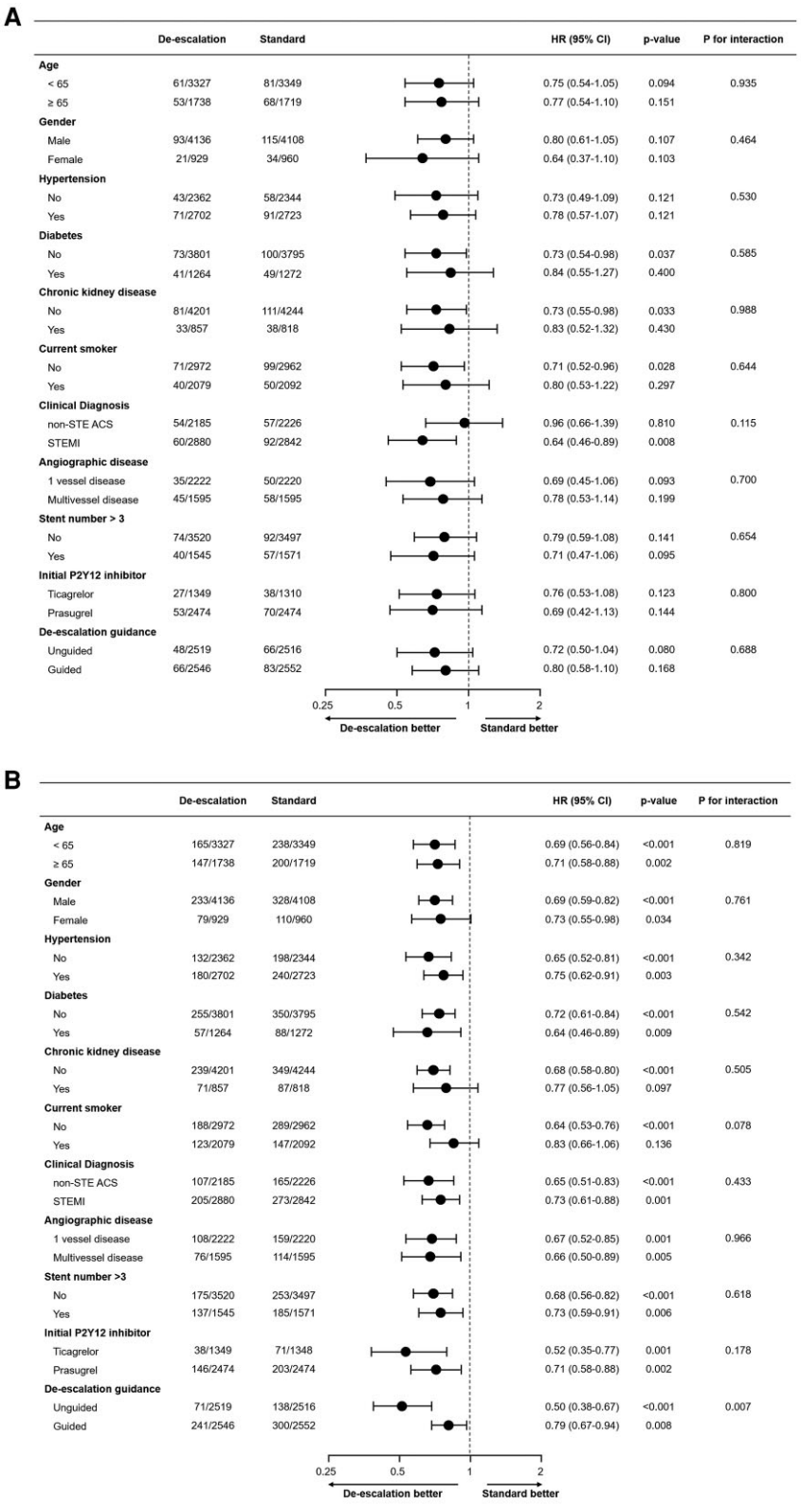


Figure 4 Subgroup analysis. Comparison of the treatment effects for the ischaemic endpoint (*A*) and the bleeding endpoint (*B*) between the de-escalation strategy and the standard therapy for the key subgroups.

definition, is an ischaemic endpoint that may originate from a bleeding complication. Therefore, reducing the risk of bleeding may be associated with a reduction in cardiac death events.

In subgroup analysis, the treatment effect was consistent between various subgroups, with no significant interaction. However, the impact of bleeding risk reduction by unguided universal DAPT de-escalation was significantly larger compared to guided DAPT de-escalation. This may be due to the fact that in the guided studies, the bleeding reduction benefit of patients that received guided de-escalation is offset by those who are deemed to be poor clopidogrel responders and continue to receive potent P2Y12 inhibitors. Also, because the two universal de-escalation studies were both conducted in Asians, who have a lower ischaemic risk, the better efficacy needs to be interpreted with caution and cannot be extrapolated to other ethnicities or to those with high ischaemic risk. Additionally, the timing of de-escalation should be considered in interpreting the results. For guided de-escalation trials, the de-escalation timing was 48 h post-PCI (POPular Genetics) and 2 weeks post-PCI (TROPICAL-ACS), while that for unguided de-escalation trials were both 1-month post-PCI (HOST-REDUCE-POLYTECH-ACS, TALOS-AMI). Although subgroup analysis showed no significant interaction between guided vs. unguided de-escalation and the ischaemic endpoint, an early unguided de-escalation may be harmful, especially in the early period after ACS, when the high ischaemic risk persists. Interestingly, bleeding risk reduction by de-escalation was numerically larger when de-escalation was performed from ticagrelor to clopidogrel as compared to de-escalation from prasugrel to clopidogrel. Such observation is in line with results from a previous trial which showed that prasugrel was associated with a lower bleeding risk than ticagrelor.[28]

Although guided and unguided de-escalation were similar with regard to ischaemic endpoints, significant improvements in the selection of patients in the guided approach could lead to better clinical outcomes. In particular, if early de-escalation is considered in patients at higher ischaemic risk, unguided de-escalation has the potential risk of increasing the risk of ischaemic adverse events. A previous study has shown that integrating clinical risk factors with genotyping could predict high on-treatment platelet reactivity, which may be used to increase the precision of selecting patients for guided de-escalation.[29]

Collectively, our findings show that compared to the standard DAPT strategy, de-escalation of the potent P2Y12 inhibitor provides clinical benefit where both ischaemic and bleeding events are decreased.

Limitations

There are important limitations that should be noted in the current study. First, our study only focused on DAPT de-escalation during the first year after index PCI. Recently, some studies have focused on potent P2Y12 inhibitor monotherapy after ultra-short-term DAPT within the first year after PCI, the so-called 'early P2Y12 monotherapy'.[26] The safety and efficacy of early P2Y12 monotherapy, with respect to those of the DAPT de-escalation therapy, are beyond the scope of the current study. Second, the definition of clinical outcomes may differ between the trials; however, the endpoints that we analysed were hard endpoints that were free from such bias. Periprocedural myocardial infarction was excluded from the primary ischaemic endpoint, and we performed a landmark analysis as a sensitivity analysis to confirm the consistency of our findings. Third, we could not analyse the impact of the procedural complexity of PCI. It is well known that patients who receive complex PCI might require a stronger antiplatelet strategy. Our database lacked specific procedural information; therefore, we could not analyse the impact of the de-escalation DAPT strategy in the complex PCI subgroup. Furthermore, we could not observe interactions between the complex PCI factors, including patients who received left main stenting, those with three-vessel disease, or those in whom more than two stents were implanted. Fourth, guided de-escalation RCTs were performed in Europe, while unguided de-escalation RCTs were performed in East Asia. Because the relative ischaemia–bleeding trade-off may be slightly different according to ethnicity, such differences may have affected the results of the analysis. As such, the generalizability of the current findings may be limited. Finally, although the concepts of guided and unguided de-escalation could be compared in the current study, a conclusion on which is the optimal de-escalation strategy cannot be drawn from the current data. This is because the individual trials used different P2Y12 inhibitors, and the timing of de-escalation was not the same. Guiding still seems to be potentially a safer strategy, particularly if considering early de-escalation or even if later in a population at higher ischaemic risk.

Conclusion

In conclusion, the de-escalation DAPT strategy compared with a standard DAPT strategy was associated with reductions in both the ischaemic and bleeding endpoints in patients with ACS who underwent PCI.

Author contributions

Han-Mo Yang (Data curation, Project administration), Hyun-Jae Kang (Resources), Doyeon Hwang (Formal analysis, Methodology), Jung-Kyu Han (Data curation, Project administration), Kiyuk Chang (Data curation, Investigation, Project administration), Bon-Kwon Koo (Investigation, Resources, Writing—review & editing), Hyo-Soo Kim (Conceptualization, Investigation, Resources, Writing—review & editing), Jur M. ten Berg (Data curation, Investigation, Resources, Writing—review & editing), Dirk Sibbing (Conceptualization, Data curation, Investigation, Resources, Writing—review & editing), Kyung Woo Park (Conceptualization, Methodology, Supervision, Writing—original draft, Writing—review & editing), Jaewook Chung (Data curation, Methodology, Visualization), Jeehoon Kang (Conceptualization, Formal analysis, Investigation, Writing—original draft, Writing—review & editing), Konstantinos D. Rizas (Conceptualization, Data curation, Writing—review & editing), Wout van den Broek (Data curation, Writing—review & editing), Dániel Aradi (Data curation, Project administration, Writing—review & editing), Steffen Massberg (Data curation, Project administration, Writing—review & editing), Daniel M.F. Claassens (Data curation, Visualization), and Eun ho Choo (Data curation, Project administration)

Acknowledgements

We would like to thank Jinseob Kim (Zarathu Co., Ltd, Seoul, Republic of Korea) for statistical advice.

Supplementary data

Supplementary data is available at *European Heart Journal* online.

Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Conflict of interest

K.W.P. reports speaker fees from Daichi Sankyo, InnoN Pharmaceutical, and DaeWoong Pharmaceutical, outside of the submitted work. All other authors declare no competing interests.

Funding

This research was supported by a grant from Seoul National University Hospital (Research ID: 30-2021-0030).

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