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ORIGINAL RESEARCH

Antiplatelet Strategy for Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention: A Systematic Review and Network Meta-Analysis

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BACKGROUND: Optimal duration and choice of antiplatelet therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention remain controversial.

METHODS AND RESULTS: Digital databases (PubMed, Cochrane, and Embase) were queried to select all randomized controlled trials on a post–percutaneous coronary intervention population with acute coronary syndrome. Dual-antiplatelet therapy (DAPT) with aspirin and clopidogrel for 12 months was compared with 4 major strategies: high-potency, high- to low-potency, low-dose, and short-duration DAPT. A network meta-analysis was performed to compare the safety and efficacy of different antiplatelet strategies. This study was the second updated manuscript under the International Prospective Register of Systematic Review registration (CRD42021286552). Thirty-two randomized controlled trials comprising 103 459 (51 750 experimental, 51 709 control) patients were included. Compared with DAPT with aspirin and clopidogrel for 12 months, high- to low-potency DAPT (risk ratio [RR], 0.69 [95% CI, 0.52–0.92]) and aspirin+prasugrel containing DAPT for 12 months (RR, 0.84 [95% CI, 0.72–0.98]) had a significantly lower, whereas DAPT for 1 month followed by clopidogrel only (RR, 1.59 [95% CI, 1.06–2.39]) had a higher, incidence of major adverse cardiovascular events at 1 year (median follow-up). Prasugrel (RR, 1.35 [95% CI, 1.09–1.66]) and ticagrelor (RR, 1.38 [95% CI, 1.17–1.62]) containing DAPT for 12 months had significantly higher rates, whereas high- to low-potency DAPT (RR, 0.85 [95% CI, 0.63–1.15]) had no significant risk of major bleeding.

CONCLUSIONS: Aspirin and ticagrelor for 3 months, followed by aspirin and clopidogrel for the remaining duration, can be considered the optimal strategy for treating post–percutaneous coronary intervention patients with acute coronary syndrome because of a significantly reduced risk of major adverse cardiovascular events without increasing the risk of bleeding.

Key Words: acute coronary syndrome ■ dual-antiplatelet therapy ■ percutaneous intervention

See Editorial by Sattar and Elgendy.

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CLINICAL PERSPECTIVE

What Is New?

- In patients with acute coronary syndrome undergoing percutaneous coronary intervention, aspirin+clopidogrel after a short period of high-potency dual-antiplatelet therapy can mitigate the risk of major bleeding while preserving the ischemic benefits.

What Are the Clinical Implications?

- Patients with acute coronary syndrome may benefit from switching from a high-potency dual-antiplatelet therapy to a low-potency dual-antiplatelet therapy; doing so has not proved a difference in the risk of major bleeding. Results from our study may bring forth a basis for further clinical trials in the future.

Nonstandard Abbreviations and Acronyms

DAPT	dual-antiplatelet therapy
HLP	high to low potency
LP	low potency
MACE	major adverse cardiovascular event
TVR	target vessel revascularization

In patients with acute coronary syndrome (ACS) who undergo coronary stenting, dual-antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 inhibitor (prasugrel, ticagrelor, or clopidogrel) for 12 months is the recommended reasonable approach to limit the risk of stent thrombosis and recurrent myocardial infarction (class I indication).[1] However, in the case of high-potency DAPT, the antithrombotic benefits are often offset by a heightened bleeding risk, which has been linked with increased morbidity and mortality.[2–5] To achieve an optimal risk/benefit ratio, several clinical trials attempted to investigate various strategies for bleeding mitigation.[6–27] These strategies include the use of aspirin in conjunction with clopidogrel, a less potent P2Y12 inhibitor (rather than ticagrelor and prasugrel), decreasing the dose of prasugrel, or switching to monotherapy after a mandated short duration of DAPT. However, these trials often yielded conflicting findings because of the selection criteria and patient population heterogeneity. A few meta-analyses also underscored the importance of deescalation strategies. Still, their applicability to the real-world cohort was hampered by major methodological limitations and the inclusion of mixed populations (eg, all patients with ACS and stable coronary artery disease).[28,29] Nonetheless, the 2021 American College of Cardiology guidelines recognize the discontinuation of aspirin after 1 to 3 months of DAPT with continued P2Y12 inhibitor as class 2a and discontinuation of P2Y12 inhibitor after 6 months of DAPT with continued aspirin as class 2b recommendations, particularly in high-bleeding risk or birisk patients (high risk of bleeding and thrombosis).[1] The current network meta-analysis uses the latest trials to determine the relative benefits and harm of deescalation strategies.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist was followed to conduct the current network meta-analysis (Table S1). This study was the second updated manuscript under the PROSPERO registration (CRD42021286552). The manuscript is limited to a population with ACS. The protocol is available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=286552. The data that support the findings of this study are available from the contributing author (Waqas Ullah, email: waqasullah.dr@gmail.com) on reasonable request.

Search Strategy

PubMed, Cochrane, and Embase databases were queried until September 2022 to identify all relevant randomized controlled trials (RCTs). Various medical subject headings were systematically combined in a 1:1 manner using Boolean operators (AND, OR, and NOT). Using an EndNote library, titles and abstracts of all items were screened, and potentially relevant studies underwent a full-text appraisal and data extraction (HS, AT). References of the included RCTs were also assessed to identify items missed on the initial screening (backward snowballing) (SG, MM, SZ). Data were extracted independently by authors, and disputes were resolved by discussion with senior authors (DF). The detailed search strategy and map are in Data S1 and Figure S1. Given the nature of the data, the article was exempted from informed consent and institutional review board approval.

Selection Criteria

The inclusion criteria included the following: (1) studies comparing the safety and efficacy of DAPT and any type of deescalation strategy; (2) in post–percutaneous coronary intervention (PCI) patients presenting with ACS, including ST-segment–elevation myocardial infarction, non–ST-segment–elevation myocardial infarction (NSTEMI), and unstable angina; (3) have at least 1 measurable safety or efficacy end point; (4) at a minimum follow-up duration of 12 months.[3,5–27,32–39] Review

articles, conference papers, case reports, studies with duplicate data, non-PCI or non-ACS patients, and trials recruiting patients on concomitant anticoagulant therapy were excluded. In addition, the trials involving short-term (<12 months) or extended (>12 to 15 months) DAPT in the control arm, use of genetics to choose the best strategy, and delayed randomization post-PCI (Prevention with TicaGrelor of Secondary Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome [PEGASUS] trial: randomization was done 1–3 years after index PCI) were excluded. The detailed reasons for trial exclusion and trial-level selection criteria are presented in Tables S2 and S3.

Study Subjects and Comparison Strategies

The included RCTs were categorized into 4 major strategies: (1) high-potency DAPT, which included aspirin (81 mg/d) in conjunction with either prasugrel (10 mg/d) or ticagrelor (90 mg twice a day) for 12 months; (2) high-potency DAPT (aspirin+prasugrel or aspirin+ticagrelor) for 1 to 3 months, which was switched to low-potency DAPT (aspirin-clopidogrel) for a total duration of 12 months (HLP-DAPT-12); (3) aspirin in combination with low-dose prasugrel (3.75 or 5 mg, instead of 10 mg) for 12 months (low-dose DAPT-12); And (4) short duration that involved discontinuing 1 antiplatelet therapy after a mandated period of DAPT. The latter group was further subdivided into 7 different strategies based on the initial duration of DAPT in months and the choice of subsequent monotherapy (aspirin, clopidogrel, prasugrel, or ticagrelor) (DAPT-1 [aspirin], DAPT-1 [clopidogrel], DAPT-3 [aspirin], DAPT-3 [clopidogrel], DAPT-3 [ticagrelor], DAPT-4 [aspirin], and DAPT-6 [aspirin]). The common control group for direct comparisons in all these strategies was 12-month aspirin-clopidogrel.

Study Outcomes

Major adverse cardiovascular events (MACEs) and major bleeding were the primary efficacy and safety end points. MACE was a composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke. Secondary end points included components of MACE, cardiovascular mortality, stent thrombosis, and target vessel revascularization (TVR). The major bleeding was mostly defined by Bleeding Academic Research Consortium >2, PLATO (Platelet Inhibition and Patient Outcomes) major, or the major class of TIMI (Thrombolysis in Myocardial Infarction). The detailed trial definitions of major outcomes are presented in Table S4.

Statistical Analysis

Statistical analysis was performed using a frequentist network meta-analysis method and a random effects model to calculate the network estimates.[30] The contribution of direct and indirect evidence in network meta-analysis was shown using split forest plots; a mixed treatment comparison indicated a mixture of direct and indirect treatment comparisons.[31] A network geometry visually illustrated the contribution of comparison strategies. An open loop indicated indirect treatment comparison, and a closed loop signified direct treatment comparison. Detailed scrutinization of trial-level methods and inclusion criteria was performed to prevent violating the network meta-analysis prerequisites (similarity and transitivity), and no gross violations were identified. The transitivity was statistically assessed by measuring the loop and global consistency of the summary estimates. The Cochran Q statistic method for assessing consistency was used, where the null hypothesis is that the treatment effectiveness in all studies is equal. It is calculated by summing the squared deviations of each study's estimate from the overall meta-analytic estimate, weighting the contribution of each study. I^2 equation and L'Abbé plots were used to assess heterogeneity in the pairwise estimates. The L'Abbé plot was used to assess inconsistency in our analysis. This graphical representation entails a scatter plot featuring 2 axes, where each data point corresponds to a pairwise comparison between 2 groups or sources. On the *x* axis, we depict the effect estimate for 1 group, whereas the *y* axis represents the effect estimate for the other group. The positioning of points on the plot is determined by the magnitude and direction of the effect estimates, facilitating a visual examination of the extent of heterogeneity or consistency among the pairwise comparisons. This approach provides a nuanced understanding of the variability in effect estimates across different comparisons, contributing to a comprehensive evaluation of inconsistency in the context of our meta-analysis.

The design- and study-level estimates were graphically illustrated using interval and network forest plots. Direct evidence plots were obtained to show the contribution of direct and indirect estimates at the level of each comparison. The number of different sources contributing to the net effect size and the net contribution of indirect evidence was visually illustrated using "minimal parallelism" and "mean path length," respectively. Ratio of odds ratios, a statistical measure, was used to compare the effect size from 2 different sources or groups. When RoR is close to 1, it suggests that the 2 sources or groups are in agreement for the effect being studied. It was particularly useful in comparing the odds of an event occurring between different interventions across multiple studies. The τ^2, serving as an estimate of between-study variance in a random-effects meta-analysis, gauged the SD of underlying effects across the studies. Multiple subgroup analyses stratified by age (<75 and >75 years), sex (male and female),

clinical presentation (ST-segment–elevation myocardial infarction and NSTEMI-ACS), and presence of diabetes, chronic kidney disease (CKD), and single-vessel and multivessel disease were also performed. A sensitivity analysis using the "leave-one-out" strategy enabled us to assess the influence of individual studies on overall results. The impact of potential effect modifiers, such as the year of publication, was assessed with sequential meta-regression analysis. The Egger regression equation and funnel plot symmetry helped determine the possibility of publication bias. Analysis was performed using STATA, version 16, and R, version 4.01 (Figure 1).

RESULTS

A systematic literature search identified a total of 3601 records, reduced to 2645 after the removal of duplicates (956). On phase 1 screening, 2460 items were excluded at the title and abstract level. The remaining 185 articles underwent full-text appraisal, and 32 RCTs qualified the selection criteria for quantitative analysis.[3,5–27,32–39] Twenty-five trials included patients with ACS, and 7 trials had subanalysis of ACS data. A total of 103 459 (51 750 experimental, 51 709 control arm) patients with ACS undergoing PCI were included in the analysis. The weighted mean age was 59 to 72 years, with 68.6% to 83.6% men. Traditional risk factors were more frequent, with the highest prevalence of hypertension. The strategy-level proportion of baseline comorbidities was comparable to that of their corresponding control group, suggesting good transitivity. In most trials, randomization occurred during index PCI, and follow-up was 12 months. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram is shown in Figure S1,

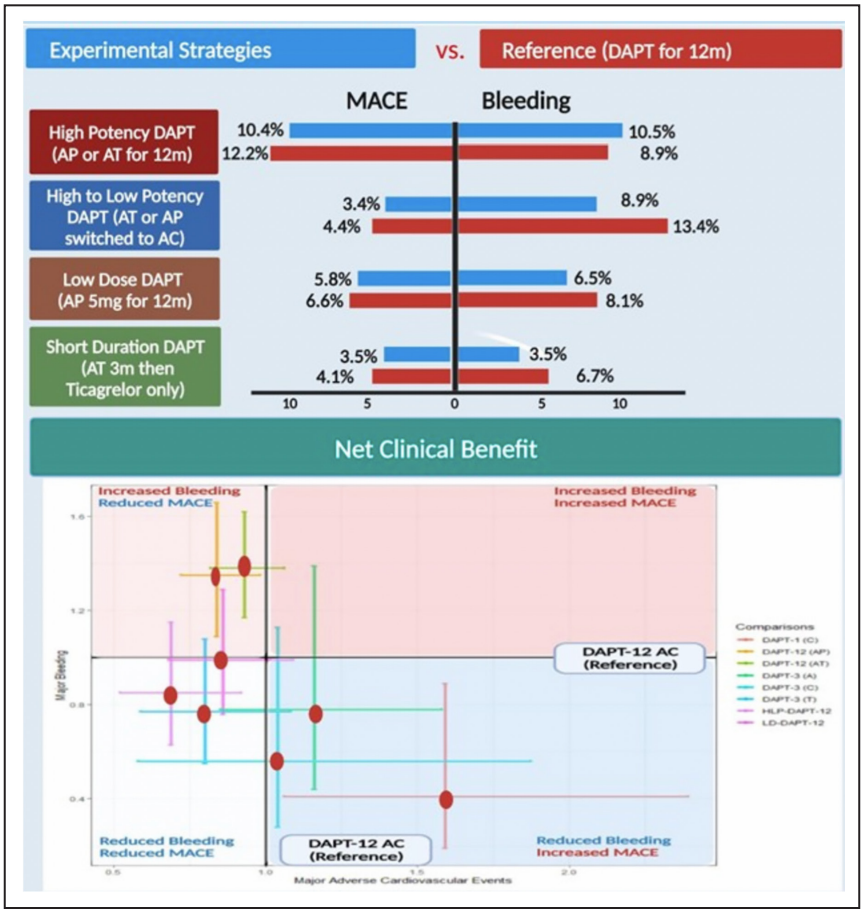

Figure 1. Optimal antiplatelet strategy in patients with acute coronary syndrome after percutaneous coronary intervention.
Top: Comparing the proportion of major adverse cardiovascular events (MACEs) and bleeding events among different experimental strategies (blue) with the reference dual-antiplatelet therapy (DAPT) with aspirin and clopidogrel for 12 months (DAPT-12-AC) (red). Bottom: Showing net clinical benefit using bivariate analysis. MACE is plotted on the *x* axis against major bleeding on the *y* axis, showing high- to low-potency (HLP) DAPT-12 as the best strategy because of the lowest MACE and no increase in bleeding. A indicates aspirin; C, clopidogrel; LD, low dose; P, prasugrel; and T, ticagrelor.

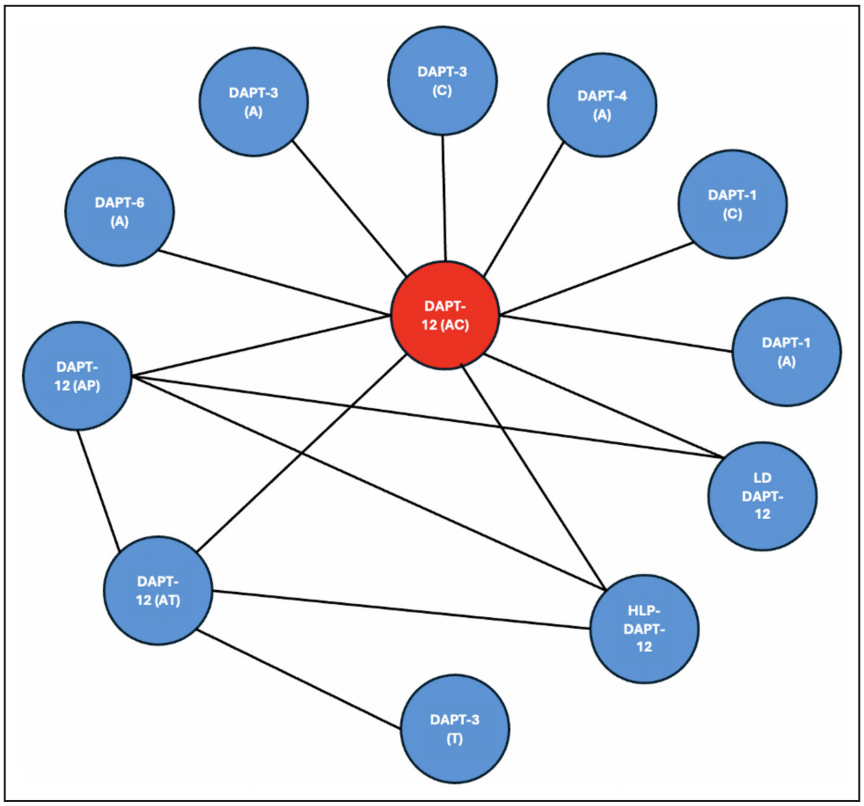

Figure 2. Network meta-analysis of different treatment strategies in post–percutaneous coronary intervention patients compared directly or indirectly with dual-antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel for 12 months (DAPT-12 [AC]).
The red node indicates control arm, and blue nodes indicate comparison strategies. HLP indicates high to low potency; LD, low dose; P, prasugrel; and T, ticagrelor.

and the details of the included trials are presented in Figure S2. The contribution of RCTs and the magnitude of relevant data in treatment regimens are displayed in the network geometry (Figure 2). Key baseline characteristics for major comparison strategies are summarized in Table 1, and trial-level demographics and clinical and procedural characteristics are shown in Tables S5 to S9.

Primary Efficacy End Point

The pairwise and network incidences of MACEs are presented in Figure 3 and Figure S3 and Table 2, respectively. On frequentist network meta-analysis, compared with standard 12-month aspirin-clopidogrel, HLP-DAPT-12 (risk ratio [RR], 0.69 [95% CI, 0.52–0.92]) and 12-month aspirin-prasugrel (RR, 0.84 [95% CI, 0.72–0.98]) had a significantly lower, whereas DAPT for 1 month followed by clopidogrel monotherapy (RR, 1.59 [95% CI, 1.06–2.39]) had a higher, incidence of MACEs at a median follow-up of 1 year after the index PCI. There was no significant difference in the rates of MACEs between all other comparison strategies.

Primary Safety End Point

The overall incidence of major bleeding was significantly lower in the deescalation regimen compared with standard 12-month aspirin-clopidogrel therapy (Figure 3). On network meta-analysis, prasugrel (RR, 1.35 [95% CI, 1.09–1.66]) and ticagrelor (RR, 1.38 [95% CI, 1.17–1.62]) containing DAPT had a significantly higher rate of major bleeding compared with 12-month aspirin-clopidogrel. Patients on 1-month DAPT, followed by clopidogrel monotherapy, had a lower rate, whereas those receiving HLP-DAPT for a total of 12 months (RR, 0.85 [95% CI, 0.63–1.15]) had a similar 1-year incidence of major bleeding compared with 12-month aspirin-clopidogrel. There was no significant difference in the risk of major bleeding between all other deescalation strategies (Table 2).

Direct Versus Nondirect Comparisons

Figure 2 shows the direct and indirect treatment comparisons. All the different antiplatelet strategies were directly and indirectly compared with the control group, 12-month aspirin-clopidogrel, except for DAPT-3 (ticagrelor), which was indirectly connected through

Table 1. Pooled Baseline Characteristics of the Patient Population Stratified Into Subgroups of Different Antiplatelet Strategies

Characteristic	HLP-DAPT 12	DAPT 12 AC	HP-DAPT 12	DAPT-12 AC	SD-DAPT 12	DAPT 12 AC	LD-DAPT	DAPT 12 AC
Size, mean, n	161	281	2277	2270	1103	1104	699	704
Age, mean, y	59	62	64.9	65	64	64	72.7	72.5
Male sex, %	83.6	74.7	72	70.8	73	71.8	68.6	69.9
Diabetes, %	39	23.8	32	30	30.4	30	33.5	31.5
Hypertension, %	51.3	57.7	64	63	65.6	68.4	75	75
Hyperlipidemia, %	3.9	3.6	58.5	56.3	58.3	63.6	61	58.5
Smoking, %	66.4	58.7	34.8	36.1	32.4	26	24.5	25
Prior PCI, %			11.6	12.28	14	13	13	11.5
CAD/prior MI, %	3.3	3.6	14.5	14	12	10	12	12
Prior CABG, %			6.58	6.26	4.5	5.11	4.5	5.5
CHF, %			7.12	6.5	6.19	5.6		
PVD, %			5.8	6.2	5.3	3.8	8	9
CVA, %			10	9.8	7.37	5.3		
LVEF, mean, %	54.7	54	57.9	57.8	60	61.6	49	48
MVD, %	83	80	53	44.3	54	52	58	61
Unstable angina, %			21.4	21.8	25.4	28.5	16.4	15
STEMI, %			37.9	37.4	31.6	26.7	45.8	45.65
NSTEMI, %			43.7	44.18	31	18	32.4	39.2

AC indicates aspirin+clopidogrel; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; DAPT 12, dual-antiplatelet therapy for 12 months; HLP, high to low potency; HP, high potency; LD, low dose; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVD, multivessel disease; NSTEMI, non–ST-segment–elevation MI; PCI, percutaneous intervention; PVD, peripheral vascular disease; SD, short duration; and STEMI, ST-segment–elevation MI.

DAPT-12 (aspirin+ticagrelor). The network estimates of MACEs and major bleeding for all comparisons were driven by the direct estimates on the split-wise interval analysis with a few exceptions. The beneficial findings of HLP-DAPT-12 in terms of lower bleeding and MACEs compared with DAPT-12 aspirin+ticagrelor were driven by indirect comparisons. On the split-wise interval estimates, the direct, indirect, and network estimates remained invariant for all strategies compared with the control group of DAPT with aspirin and clopidogrel for 12 months, except that its lower bleeding risk compared with DAPT-12 aspirin+prasugrel was driven by the indirect comparisons (Figure S4). The design-level contributions of direct and indirect evidence are presented in Figures S5 and S6.

Secondary End Points

The study- and strategy-level estimates of all secondary outcomes are given in Tables S10 to S17 and Figure S7. Compared with the standard 12-month aspirin-clopidogrel, 12-month aspirin-prasugrel appeared to have a significantly lower incidence of stent thrombosis (RR, 0.51 [95% CI, 0.39–0.65]), myocardial infarction (RR, 0.76 [95% CI, 0.65–0.89]), and need for TVR (RR, 0.68 [95% CI, 0.55–0.82]). HLP-DAPT-12 (versus 12-month aspirin-clopidogrel) also had a lower rate of myocardial infarction (RR, 0.65 [95% CI, 0.46–0.91]), but a similar risk of stent thrombosis and TVR. Among all other deescalation strategies, the 1-year rate of stent thrombosis, stroke, cardiovascular mortality, all-cause mortality, and need for TVR remained nonsignificantly different compared with 12-month aspirin-clopidogrel. However, 12-month aspirin-ticagrelor had a significantly lower incidence of stent thrombosis (RR, 0.72 [95% CI, 0.60–0.87]), cardiovascular mortality (RR, 0.82 [95% CI, 0.73–0.93]), and all-cause mortality (RR, 0.84 [95% CI, 0.75–0.94]), whereas 3-month aspirin-ticagrelor followed by ticagrelor monotherapy had lower all-cause mortality (RR, 0.57 [95% CI, 0.38–0.88]). The strategy-level contribution of direct and indirect evidence to the pooled estimates is tabulated in Table S18.

Net Clinical Benefit

The net clinical benefit was graphically illustrated with a bivariate outcome plot for primary efficacy and safety end points in Figure 4. A substantially pronounced beneficial effect was seen with HL-DAPT-12 because of a significant reduction in MACEs without increasing the risk of major bleeding, as indicated by the localization of the strategy to the left lower quadrant of the plot. The significantly lower incidence of MACEs in the 12-month aspirin-prasugrel strategy was offset by a higher risk of major bleeding. In contrast, the opposite was true in patients receiving DAPT for 1 month

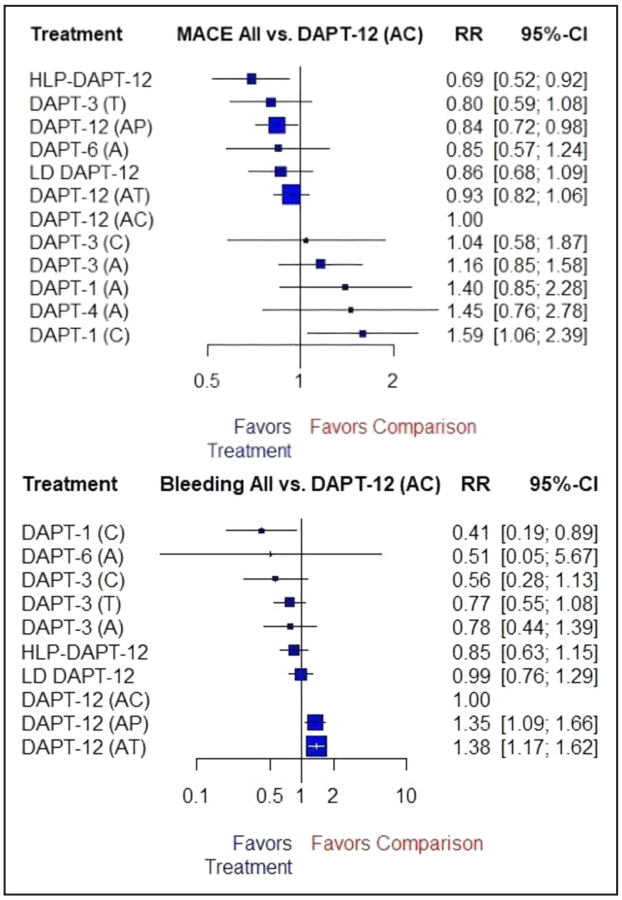

Figure 3. Network forest plot for comparison of all treatment strategies with dual-antiplatelet therapy (DAPT) with aspirin and clopidogrel for 12 months (DAPT-12 [AC]) for major adverse cardiovascular events (MACEs) (top) and bleeding (bottom).

A indicates aspirin; C, clopidogrel; HLP, high to low potency; LD, low dose; P, prasugrel; RR, risk ratio; and T, ticagrelor.

followed by clopidogrel monotherapy (DAPT-1 [clopidogrel]). Overall, the plot visually confirms a numerically lower, albeit statistically nonsignificant, decline in major bleeding with most deescalation strategies, while the tendency to reduce MACEs was heterogeneous.

Network Consistency and Heterogeneity

There was no inconsistency between direct and indirect point estimates observed. All RoRs were compatible with no inconsistency (RoR was close to 1) for all study outcomes, except for major bleeding (Tables S18 and S19). The L'Abbé plot also revealed a lack of evidence, suggesting inconsistency across the major efficacy outcome (MACEs). Data points on the plot, representing specific comparisons between groups or sources, consistently clustered together, indicating concordance in effect estimates. However, for major bleeding, the dispersion of points on the plot diverged from this pattern, indicating a potential inconsistency in effect estimates for this specific outcome (Figure S8). This could be because of the variable bleeding criteria used by the trials that were attempted to be accounted for by selecting only major bleeding events.

Subgroup Analysis

The estimates of subgroup analyses are presented in Figure 5 and Table S20. A stratified analysis based on the prespecified subgroups mirrored the network analysis findings with a few exceptions. The 12-month aspirin-clopidogrel versus deescalation strategies had a similar risk of MACEs and major bleeding among patients aged >75 years, men, and those having CKD, diabetes, or multivessel disease. Women (RR, 0.36 [95% CI, 0.14–0.90]), younger patients (RR, 0.50 [95% CI, 0.35–0.71]), nondiabetic patients (RR, 0.49 [95% CI, 0.30–0.80]), patients without CKD (RR, 0.61 [95% CI, 0.39–0.96]), and patients with single-vessel disease (RR, 0.55 [95% CI, 0.38–0.81]) had a significant reduction in MACEs with HLP-DAPT-12 (versus 12-month aspirin-clopidogrel) irrespective of the clinical presentation (both ST-segment–elevation myocardial infarction and NSTEMI-ACS). There was a substantial increase in the incidence of major bleeding with 12-month aspirin-ticagrelor in patients with CKD (RR, 1.50 [95% CI, 1.02–2.21]) and NSTEMI-ACS (RR, 1.94 [95% CI, 1.01–3.70]).

Sensitivity Influential Analyses

A leave-one-out sensitivity analysis showed no influence of any single study on pooled pairwise estimates of primary outcomes (Figure S9). Similarly, a sequential exclusion of RCTs with a mixed combination of DAPT in the control group did not influence the pooled primary end points.

Meta-Regression and Quality Assessment

The overall meta-regression model was not significant for all deescalation strategies. The year of publication of the included RCTs accounted for nonsignificant variation in net estimates of MACEs (τ^2=0.017, P=0.244) and major bleeding (τ^2=0.126, P=0.138). Overall, the publication year contributed 7.8% and 8.4% residual heterogeneity (R^2) to the observed net heterogeneity (I^2) of MACEs and major bleeding, respectively (Figure S10).

The methodological quality of the included RCTs was high on the Risk of Bias (RoB-2) tool (Figure S11). The risk of publication bias in studies assessing MACEs was minimal, as indicated by Egger nonsignificant regression (P=0.62) and the symmetrical distribution of studies on the funnel plot (Figure S12).

Discussion

The results of the current network meta-analysis, using the 12-month aspirin-clopidogrel as a common

Table 2. Net-League Comparison of Different Deescalation Strategies

MACE									
DAPT-1 (clopidogrel)*	1.59 (1.06–2.39)	1.93 (1.33– 2.79)	1.77 (1.23–2.55)	1.38 (0.87–2.18)	1.53 (0.79–2.95)	2.03 (1.32–3.12)	1.88 (1.12–3.16)	2.36 (1.53–3.66)	1.84 (1.22–2.78)
0.41 (0.19–0.89)	DAPT-12 (AC) (Reference)*	1.21 (1.12–1.32)	1.11 (1.04–1.19)	0.87 (0.65–1.15)	0.96 (0.55–1.67)	1.25 (0.92–1.69)	1.18 (0.81–1.72)	1.49 (1.16–1.90)	1.16 (0.94–1.42)
0.33 (0.16–0.68)	0.80 (0.71–0.91)	DAPT-12 (AP)*	0.92 (0.83–1.01)	0.71 (0.53–0.96)	0.79 (0.45–1.38)	1.05 (0.82–1.35)	0.98 (0.67–1.43)	1.22 (0.96–1.56)	0.95 (0.77–1.18)
0.36 (0.18–0.72)	0.86 (0.81–0.92)	1.07 (0.94–1.22)	DAPT-12 (AT)*	0.78 (0.58–1.04)	0.86 (0.49–1.50)	1.15 (0.91–1.44)	1.06 (0.73–1.55)	1.33 (0.99–1.71)	1.04 (0.84–1.29)
0.52 (0.22–1.24)	1.27 (0.76–2.10)	1.58 (0.94–2.65)	1.47 (0.88–2.45)	DAPT-3 (aspirin)*	1.11 (0.59–2.06)	1.47 (1.02–2.13)	1.36 (0.85–2.18)	1.71 (1.18–2.49)	1.33 (0.94–1.89)
0.74 (0.29–1.88)	1.77 (0.95–3.31)	2.21 (1.17–4.17)	2.06 (1.10–3.86)	1.40 (0.63–3.13)	DAPT-3 (clopidogrel)*	1.33 (0.73–2.43)	1.23 (0.63–2.40)	1.55 (0.84–2.84)	1.21 (0.67–2.17)
0.65 (0.31–1.35)	1.57 (1.27–1.95)	1.96 (1.54–2.49)	1.83 (1.49–2.24)	1.24 (0.72–2.15)	0.89 (0.46–1.71)	DAPT-3 (ticagrelor)*	0.93 (0.60–1.44)	1.16 (0.83–1.63)	0.91 (0.66–1.24)
0.82 (0.07; 9.95)	1.98 (0.18–21.73)	2.46 (0.22–27.13)	2.30 (0.21–25.27)	1.56 (0.13–18.10)	1.11 (0.09–13.27)	1.26 (0.11–13.95)	DAPT-6 (aspirin)*	1.26 (0.80–1.97)	0.98 (0.64–1.50)
0.49 (0.24–1.01)	1.18 (0.96–1.45)	1. 47 (1.22–1.77)	1.37 (1.11–1.69)	0.93 (0.54–1.61)	0.66 (0.34–1.28)	0.75 (0.56–1.01)	0.60 (0.05–6.61)	HLP-DAPT-12*	0.78 (0.57–1.07)
0.44 (0.21–0.92)	1.07 (0.88–1.30)	1.33 (1.10–1.62)	1.24 (1.01–1.53)	0.84 (0.49–1.46)	0.60 (0.31–1.16)	0.68 (0.51–0.91)	0.54 (0.05–5.99)	0.91 (0.70–1.18)	LD DAPT-12*
Major bleeding									

The risk of MACEs and major bleeding events between the coinciding treatment strategies are shown. All estimates are risk ratio with its 95% CI, and the comparisons operate left to right. AC indicates aspirin+clopidogrel; AP, aspirin+prasugrel; AT, aspirin+ticagrelor; DAPT, dual-antiplatelet therapy; HLP, high to low potency; LD, low dose; and MACE, major adverse cardiovascular event.
*There are 10 types of treatment strategies that are compared with each other.

reference group, can be summarized as follows: (1) Deescalation strategy that involves switching from high- to low-potency DAPT for a total duration of 12 months was found to be the most efficacious strategy because of a 30% to 35% relative risk reduction of composite efficacy end point (MACEs), and myocardial infarction without increasing the risk of major bleeding or secondary efficacy end points. (2) The 16% lower relative rate of MACEs in 12-month aspirin-prasugrel was offset by a significantly higher risk (35%) of major bleeding events. (3) The short-duration DAPT strategies that involved an early termination of high-potency P2Y12 inhibitor and subsequent aspirin or clopidogrel monotherapy had the worst efficacy in terms of MACEs and secondary efficacy end point reduction.

An ideal deescalation strategy would reduce the risk of clinically significant major bleeding while preserving the ischemic benefits. Evidence from a myriad of clinical trials suggests that the former is driven by both the duration as well as the potency of the P2Y12 antagonism, whereas the highest ischemic benefits are attained within the first few months after PCI.[3,35,37] This plausibly explains a significant reduction in pooled ischemic events (without increasing bleeding) with an HLP-DAPT-12 strategy that involved switching to aspirin-clopidogrel (low-potency DAPT) after a mandated initial use of aspirin-ticagrelor/prasugrel (high-potency DAPT) for 1 to 3 months compared with patients who received aspirin-clopidogrel all along.[6,13,20,27] On our subgroup analysis, the net antithrombotic benefits were invariant across both patients with ST-segment–elevation myocardial infarction and NSTEMI-ACS but were pronounced in women, younger patients, those with single-vessel disease, and those without comorbidities (CKD and diabetes), identifying the areas of maximal benefits. Overall, on the hierarchy of treatment strategies, this strategy was ranked the best for MACEs, myocardial infarction, and stroke.

Among other deescalation strategies, the use of clopidogrel monotherapy through early withdrawal of aspirin (after 1-month DAPT) showed a lower risk of major bleeding compared with both low- and high-potency 12-month DAPT, suggesting that the synergistic effect of 2 antiplatelet agents plays a key role in the safety events.[8] However, this strategy was the most unfavorable approach because of a 1.38- to 2.03-fold increase in ischemic events. By contrast, using a high-potency monotherapy (ticagrelor) after a relatively prolonged duration of high-potency DAPT (3 months) did not increase ischemic events and maintained a significant reduction in the incidence of major bleeding. Interestingly, this strategy also had the highest performance in reducing the risk of cardiovascular and all-cause mortality. These findings underscore the importance of the choice and duration of antiplatelet agents in deescalation strategies.

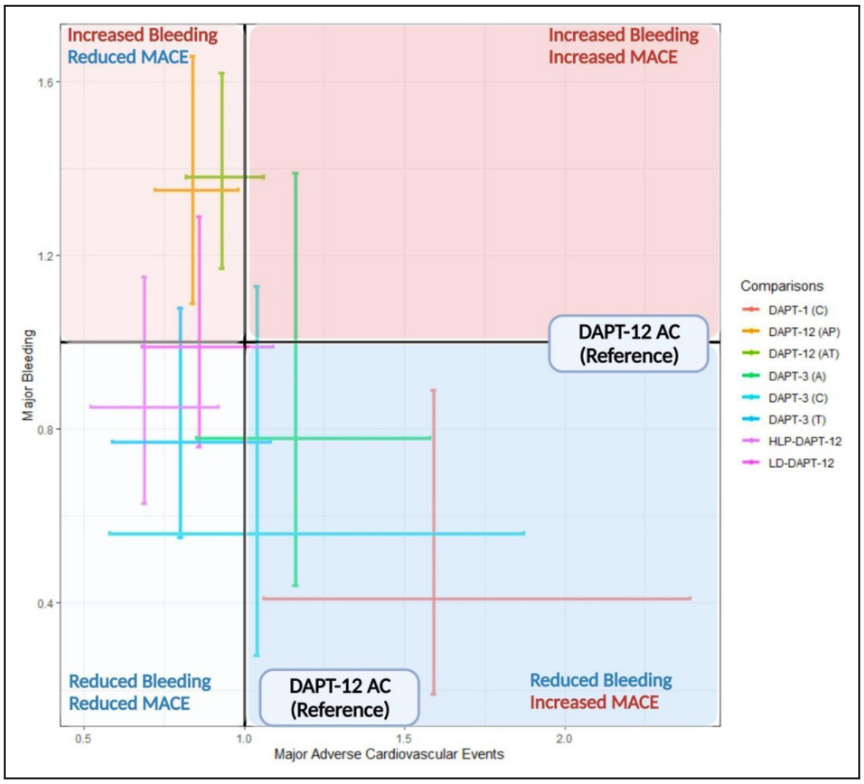

Figure 4. Bivariate plot of risk ratios of high-potency dual-antiplatelet therapy (DAPT) and deescalation DAPT strategies compared with standard 12-month DAPT with aspirin and clopidogrel (AC) with its associated 95% CIs.
Major adverse cardiovascular event (MACE) is plotted on the *x* axis against major bleeding on the *y* axis. High- to low-potency DAPT-12 was declared the best strategy (left lower quadrant) because of the lowest MACEs and no increase in bleeding, whereas DAPT-1 (clopidogrel [C]) has the highest MACEs, occupying the right quadrant (worse). LD indicates low dose; P, prasugrel; and T, ticagrelor.

These findings have important clinical implications. The foundation of the class 2a recommendation of post-PCI management is based on the use of high-potency P2Y12 inhibitors containing DAPT for 12 months (from PLATO and TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 [TRITON-TIMI-38] trials).[3,5] However, in the current study, the antithrombotic benefits of high-potency DAPT were negated mainly by an augmented risk of major bleeding. On the contrary, the aforementioned novel DAPT modulation strategies (switching high- to low-potency DAPT, or ticagrelor monotherapy) showed net clinical benefits by demonstrating no significant increase in MACEs, myocardial infarction, stent thrombosis, stroke, need for TVR, and cardiovascular and all-cause mortality, yet significantly reducing the risk of major bleeding when compared with high-potency DAPT. Hence, our findings suggest that the current class 2a recommendations could be revisited for expert discussion and to consider updates in the ranking of strategy that involves ticagrelor monotherapy after a 3-month high-potency DAPT. Moreover, contrary to the current class 2a recommendations that suggested 1- to 3-month DAPT followed by any monotherapy, our findings discourage using 1-month DAPT and clopidogrel monotherapy. This study also advocates for including the HLP-DAPT-12 strategy in the recommendations as a suitable and even better deescalation strategy.

The last deescalation strategy entailed a low-dose prasugrel use in conjunction with a standard dose of aspirin. Although the overall findings were not unfavorable, they should be interpreted with caution, as the included trials were limited to older adults or patients of South Korean origin. However, the included studies were underpowered, and extrapolating this potentially promising strategy to a Western population calls for confirmatory large-scale randomized trials.

Prior meta-analyses on the topic either included all patients (ACS+stable coronary artery disease) or had conflicting results (Table S21). More importantly, high-potency DAPT-12 was not considered for comparison with deescalation strategies. Our study differs in many

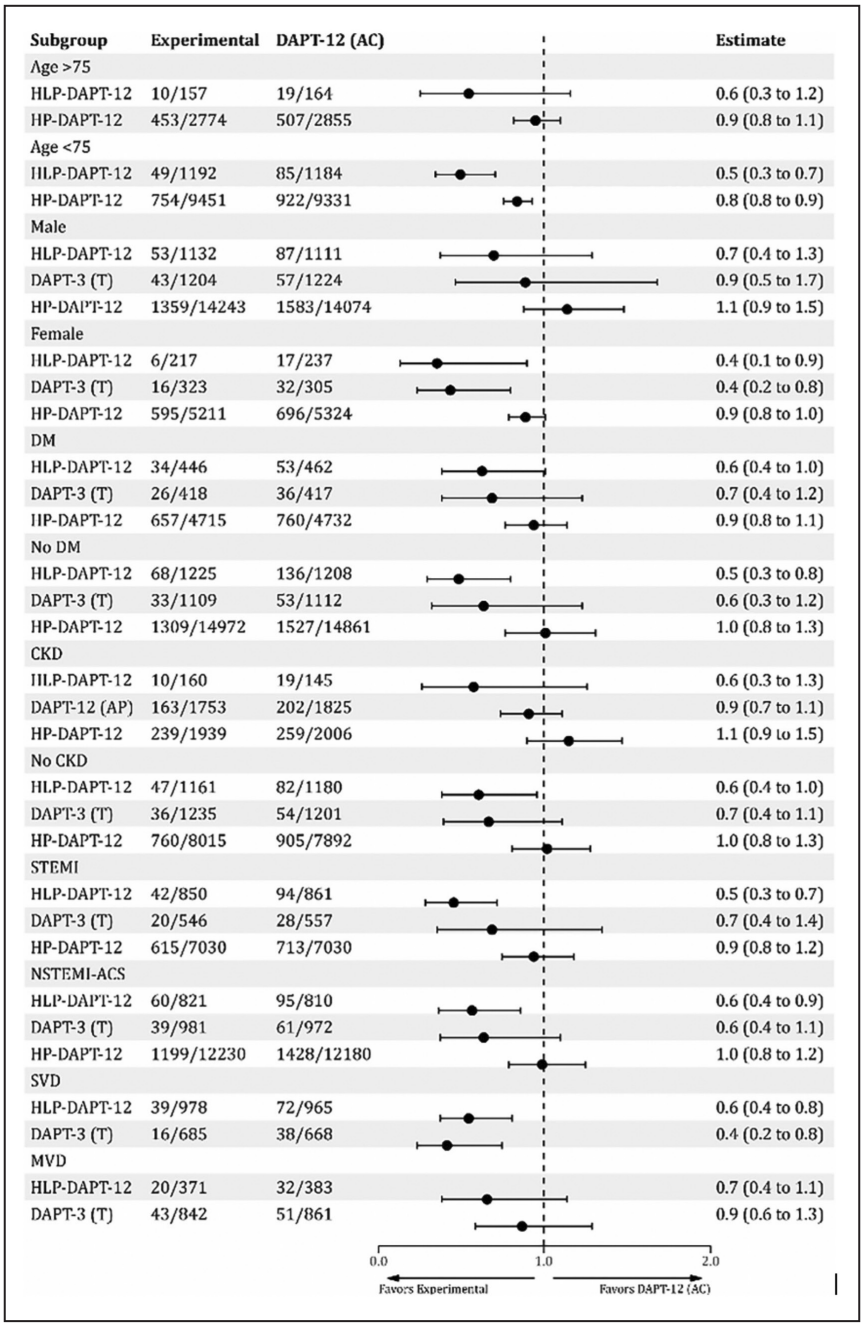

Figure 5. A subgroup analysis of major adverse cardiovascular events among high- to low-potency (HLP) dual-antiplatelet therapy for 12 months (DAPT-12) and high-potency (HP) DAPT-12 strategies in comparison with the control arm, DAPT-12 (aspirin+clopidogrel [AC]), based on age, sex, diabetes (DM), chronic kidney disease (CKD), clinical presentation (ST-segment–elevation myocardial infarction [STEMI] or non–ST-segment–elevation myocardial infarction [NSTEMI]–acute coronary syndrome [ACS]), and vessel involvement (single-vessel disease [SVD] or multivessel disease [MVD]).
P indicates prasugrel; and T, ticagrelor.

aspects, not just limited to the inclusion of a larger number of ACS trials, but the demonstration of bivariate and multiple subgroups and sensitivity analyses to identify the impact of potential confounders and identify areas of maximal benefits of deescalation strategies in post-PCI patients.

LIMITATIONS

Our findings should be interpreted with caution given the following limitations. There remained intertrial heterogeneity in the selection criteria, randomization time, stent types, follow-up duration, and bleeding criteria, and the potential impact on outcomes is uncertain. The plausible reason for within-design inconsistency in major bleeding could be the varying bleeding criteria used by the included trials. This was largely accounted for by limiting our analysis to patients who met the definition of major bleeding by all the criteria mentioned in Table S4. Lack of patient-level data precluded our ability to identify patients at a high bleeding/thrombotic risk and assess the racial impact on outcomes. Most of the deescalation trials were based on new-generation stents, limiting the external validity of our findings. We could not include some of the recent trials because of the inclusion of mixed treatment regimens and lack of stratification based on the clinical presentation by these RCTs. In some trials, the choice of DAPT in the control arm was variable, and patients with a higher percentage of aspirin plus clopidogrel were pooled into a joint group (Table S22). Some of the estimates were based on indirect comparisons that are considered inferior in the hierarchy of evidence.

CONCLUSIONS

Among all the strategies of DAPT modulation for patients with ACS undergoing PCI, switching a high-potency DAPT to a low-potency DAPT might be the optimal strategy by decreasing the risk of thrombotic events with no difference in the risk of major bleeding. Although exploratory because of its retrospective study design, our results may inform clinical decision-making, allow personalized treatment decisions, and provide a foundation for future trials.

ARTICLE INFORMATION

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None.

Supplemental Material

Data S1
Table S1–S22
Figures S1–S12
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