Received: 26 April 2023 | Accepted: 26 June 2023

DOI: 10.1002/cdt3.85

Chronic Diseases® and Translational Medicine

META-ANALYSIS

# Efficacy and safety of different dual antiplatelet strategies in patients undergoing percutaneous coronary intervention: A systematic review and network meta-analysis

**Yuttana Wongsalap**[1,2,3] | **Kirati Kengkla**[1,2,3] | **Preyanate Wilairat**[1,2,3] | **Khemanat Ratworawong**[1,2,3] | **Surasak Saokaew**[2,3,4] | **Chaisiri Wanlapakorn**[5]

[1]Division of Clinical Pharmacy, Department of Pharmaceutical Care, University of Phayao, Phayao, Thailand

[2]Center of Health Outcomes Research and Therapeutic Safety (Cohorts), School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand

[3]Unit of Excellence on Clinical Outcomes Research and Integration (UNICORN), School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand

[4]Division of Social and Administrative Pharmacy, Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand

[5]Cardiac Centre, King Chulalongkorn Memorial Hospital, Krung Thep Maha Nakorn, Thailand

**Correspondence**

Kirati Kengkla, School of Pharmaceutical Sciences, University of Phayao, Phayao, Muang Phayao, Phayao 56000, Thailand.
Email: kirati.ke@up.ac.th

Chaisiri Wanlapakorn, Cardiac Center, King Chulalongkorn Memorial Hospital, 1873 Rama IV Rd, Wangmai, Pathumwan, Krung Thep Maha Nakorn 110330, Thailand.
Email: chaisiri.w@chula.ac.th

Edited by Yi Cui

**Funding information**
Thailand Science Research and Innovation fund; University of Phayao, Grant/Award Numbers: UoE66003, FF65-RIM100; Unit of Excellence on Clinical Outcomes Research and IntegratioN (UNICORN)

## Abstract

**Background:** Dual antiplatelet therapy (DAPT) is key for preventing ischaemic events post-percutaneous coronary intervention (PCI). Various DAPT modifications like the shortened duration or P2Y12 inhibitor (P2Y12i) de-escalation are implemented to reduce bleeding risk. However, these strategies lack direct comparative studies. This study aimed to assess the efficacy and safety of such DAPT strategies, including de-escalated and short DAPT, in patients undergoing PCI.

**Methods:** We searched PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases for relevant randomized controlled trials (RCTs). We performed a network meta-analysis (NMA) to estimate risk ratios (RRs) and 95% confidence intervals (CIs). The primary efficacy endpoint was major adverse cardiac events (MACEs), and the primary safety endpoint was major bleeding. Secondary endpoints included individual components of MACEs and net adverse clinical events (NACEs).

**Results:** A total of 17 RCTs comprising 53,156 patients (median age, 62.0 years, 24.8% female) were included. NMA suggested that de-escalation DAPT was associated with a significantly lower risk of MACEs (risk ratio [RR] = 0.79, 95% confidence interval [CI] = 0.64–0.98), bleeding (RR = 0.63, 95% CI = 0.49–0.82), and NACEs (RR = 0.69, 95% CI = 0.60–0.79) compared with standard DAPT. Short DAPT followed by P2Y12i monotherapy exhibited a significantly decreased risk of major bleeding (RR = 0.63, 95% CI = 0.46–0.86) compared with standard DAPT.

**Conclusions:** De-escalation DAPT was the most effective strategy for preventing the risk of MACEs without increasing bleeding events, while short DAPT followed by P2Y12i monotherapy was the most effective strategy for reducing the risk of bleeding among patients undergoing PCI.

KEYWORDS

de-escalation, percutaneous coronary intervention, short dual antiplatelet therapy

## Highlights

- De-escalation dual antiplatelet therapy (DAPT) is the most effective strategy to prevent ischaemic events.

- Short DAPT followed by P2Y12i is the best strategy to reduce bleeding events.
- De-escalation DAPT is the best strategy balancing ischaemic and bleeding events.

## 1 | INTRODUCTION

Dual antiplatelet therapy (DAPT) is an effective strategy to minimize the risk of stent thrombosis and ischaemic events after percutaneous coronary intervention (PCI).[1,2] According to the current DAPT guidelines, the recommended DAPT duration is at least 6–12 months after PCI for the treatment of chronic coronary syndrome (CCS) and acute coronary syndrome (ACS).[3,4] DAPT therapy has been shown to decrease ischaemic events but carries an increased risk of bleeding.[5,6] Therefore, several alternative DAPT strategies, including shorter DAPT duration or the de-escalation of P2Y12 inhibitor (P2Y12i) to reduce bleeding risk, have been developed.[7]

Several randomized clinical trials (RCTs) have shown that a shorter DAPT duration (1–3 months) followed by single antiplatelet therapy was associated with a lower risk of bleeding compared to standard DAPT.[8–15] A meta-analysis of RCTs has supported the reduction of DAPT duration.[16,17] On the basis of previous studies, current European guidelines have recommended that a shortened DAPT duration of 1–3 months should be considered in patients with a high risk of bleeding (e.g., the predicting bleeding complication in patients undergoing stent implantation and subsequent [PRECISE] DAPT ≥ 25 or academic research consortium for high bleeding risk [ARC-HBR] criteria met) after stent implantation.[1] A previous meta-analysis of RCTs demonstrated that de-escalation DAPT showed a significantly lower number of thrombotic or bleeding events than standard DAPT.[18] In a recent network meta-analysis (NMA), the de-escalation of prasugrel or ticagrelor by switching to clopidogrel or de-escalation to half dose prasugrel or ticagrelor increased the risk of major bleeding, but there was no difference in the risk of major adverse cardiac events (MACEs) compared with short DAPT.[19] However, the European Society of Cardiology guidelines only recommend consideration of the de-escalation of P2Y12i with a switch from prasugrel or ticagrelor to clopidogrel with or without platelet function testing or genetic testing in patients with a high bleeding risk.[1]

The relative efficacy and safety of shorter DAPT duration and a de-escalation DAPT strategy have yet to be examined, representing an important gap in the evidence. To provide a comprehensive synthesis of effect estimates and quality of evidence, we completed a systematic review and NMA to assess the relative efficacy and safety of de-escalation DAPT, short DAPT, and standard DAPT in patients who underwent PCI.

## 2 | METHODS

### 2.1 | Study design

This systematic review and NMA were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and the extension for NMA (PRISMA-NMA).[20] The study protocol is registered on the Prospective Register of Systematic Reviews (CRD42021258727).

### 2.2 | Search strategy and selection criteria

We searched Medline via PubMed, Embase, and Central Register of Controlled Trials for relevant studies from database inception until June 2, 2021, and updated our search on February 28, 2022. The following search terms were used: ([acute coronary syndrome] OR [percutaneous coronary intervention]) AND ([dual antiplatelet] OR [clopidogrel] OR [ticagrelor] OR [prasugrel] OR [de-escalation]). Full search strategies are provided in Supporting Information: Table S1. We did not restrict our searches by language, publication date, or status. We also searched ClinicalTrial.gov and the reference lists of relevant systematic reviews and clinical practice guidelines to identify additional relevant trials. We included RCTs that compared short-duration DAPT (≤3 months) followed by aspirin monotherapy or short-duration DAPT (≤3 months) followed by P2Y12i monotherapy or de-escalation DAPT and standard DAPT (12 months of DAPT) in patients who underwent PCI and reported MACEs, death (all-cause or cardiovascular [CV] death), nonfatal myocardial infarction (MI), nonfatal stroke, major bleeding, minor bleeding, or net adverse clinical events (NACEs) at ≥6 months. De-escalation DAPT was defined as short-duration DAPT followed by a switch from a potent P2Y12i (prasugrel or ticagrelor) to clopidogrel or reduced to half-dose of a potent P2Y12i. Studies were excluded if patients received concomitant oral anticoagulation therapy.

### 2.3 | Study selection and data extraction

Two authors (Yuttana Wongsalap and Preyanate Wilairat) independently screened all titles and abstracts of retrieved records to identify potentially eligible RCTs. Each of the potentially relevant trials was accessed in a

full-text manner and reviewed by the same two authors for eligibility. Relevant information was extracted by two investigators (any two of Yuttana Wongsalap, Kirati Kengkla, Preyanate Wilairat, or Khemanat Ratworawong) into predefined data extraction forms. The extracted data included the study name, year of publication, study type, total number of participants, inclusion criteria, exclusion criteria, study endpoint, outcome definitions, follow-up duration, and baseline characteristics. Any discrepancies were resolved by consensus with the research team.

## 2.4 | Quality assessment

Two investigators (Yuttana Wongsalap and Preyanate Wilairat) independently assessed the risk of bias for each included trial using the revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2.0 versions).[21] Five key domains of bias were assessed: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcomes; and (5) bias in selection of the reported result.[21]

## 2.5 | Outcomes

The primary efficacy outcome was MACEs, which was usually defined as a combination of either all-cause or cardiovascular mortality, nonfatal MI, and nonfatal stroke. Secondary efficacy outcomes were NACEs, stent thrombosis, and individual components of the composite MACEs outcome. NACEs were defined as a composite of death, MI, stroke, stent thrombosis, or bleeding. The primary safety outcome was major bleeding as defined by the thrombolysis in myocardial infarction (TIMI) criteria[22] or bleeding academic research consortium (BARC) criteria type 3 or 5.[23] The secondary safety outcomes were combined major and minor bleeding events. The endpoint definitions applied in each trial were incorporated. For bleeding endpoints, we prioritized using the TIMI criteria; when those criteria were unavailable, the BARC criteria were used.

## 2.6 | Data synthesis and analysis

First, a pairwise meta-analysis using a random effects model (DerSimonian and Laird) was used to estimate pooled risk ratios (RRs) with 95% confidence intervals (CIs) for each outcome for all direct treatment comparisons.[24] The Cochrane Q-statistic test, with statistical significance set at $p < 0.01$, was used to test heterogeneity in each pairwise comparison. Heterogeneity across pairwise meta-analyses was assessed using the $I^2$ statistic, with scores <25% indicating low, 25%–75% indicating moderate and >75% indicating high heterogeneity.[25] We used the random effects model NMA with a frequentist approach to simultaneously combine direct and indirect evidence of treatment effects.[26,27] We assessed the global inconsistency of the entire network by the design-by-treatment interaction model.[28,29] If global inconsistency was detected, we explored possible causes of inconsistency through sensitivity analyses. To rank the DAPT strategy, the treatment probabilities using surface under the cumulative ranking curve (SUCRA) values for each intervention were estimated. Higher SUCRA scores (range 0–100%) indicated a DAPT strategy with a greater probability of reducing the clinical endpoint.[30] We assessed small-study effects by visual inspection of comparison-adjusted funnel plots of treatments to detect the presence of any publication bias in the NMA.[26,30]

To examine the robustness of the study results, we performed sensitivity analyses by excluding (1) trials enrolling patients with CCS; (2) studies with inconsistencies in the endpoint definition; (3) nondefinite MACEs or NACEs outcomes; and (4) studies with sample sizes that were too small ($n < 1000$) to examine the robustness of the findings. We performed subgroup analyses based on race (East Asian vs. non-East Asian). A two-sided $p < 0.05$ was considered statistically significant for all analyses.

# 3 | RESULTS

Overall, 12,597 records were identified from the electronic database, and 42 records were identified through other sources (Figure 1). After removing duplicates, 7740 studies were screened for their titles and abstracts. Among the 32 potentially relevant articles based on eligibility criteria, 17 RCTs were included in the NMA.[8–15,31–36] These studies included three types of trials comparing a short DAPT strategy to standard DAPT, including (1) de-escalation DAPT, eight trials[31–38]; (2) short DAPT followed by P2Y12i monotherapy, five trials[10,12–15]; and (3) short DAPT followed by aspirin monotherapy, four trials.[8,9,11,39] The available direct comparisons and network of trials used in the present study are illustrated in Figure 2.

## 3.1 | Characteristics and quality of reviewed studies

Trial characteristics are summarized in Table 1 and Supporting Information: Tables S2–S4. The pooled cohort comprised 53,156 patients who underwent PCI. The trials involved a median of 2160 (range: 120–15,968) patients with a mean age of 62.0 ± 3.2 years. Females accounted for 16.0% (range: 7.3%–78.0%) of the participants. The

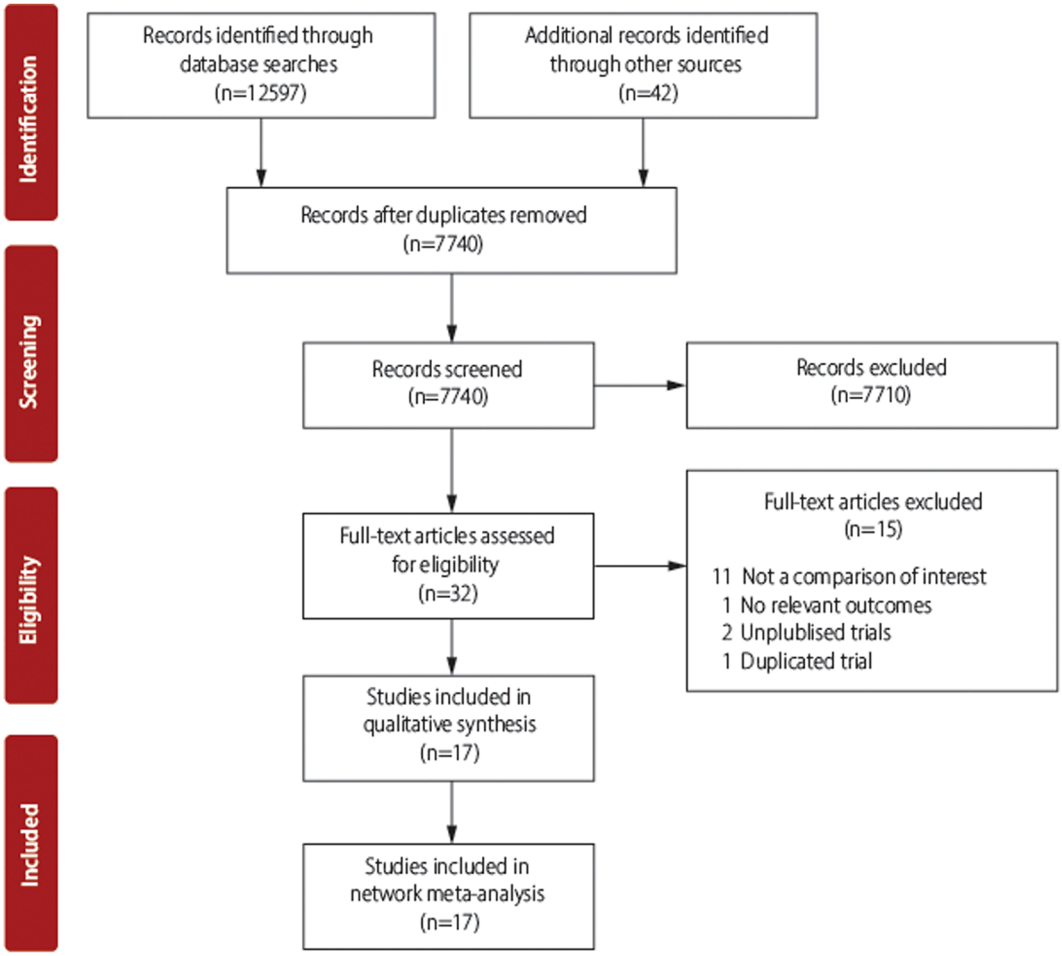


**FIGURE 1** Study flow diagram.

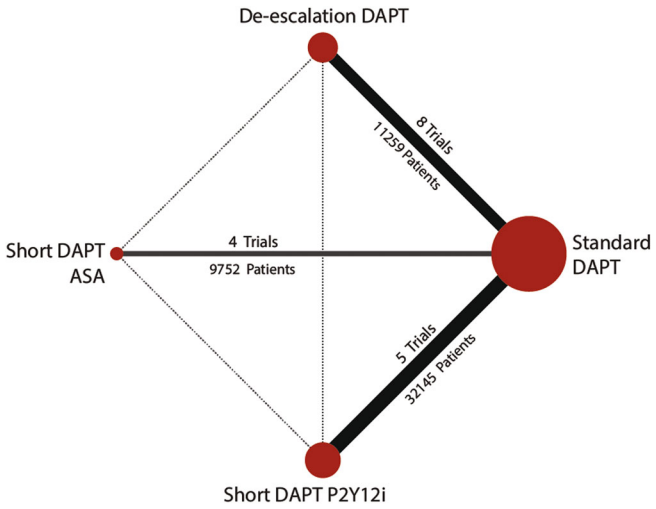


**FIGURE 2** Network comparisons of studies included in the analyses. The randomized controlled trials (RCTs) included in the network meta-analysis (NMA) are shown as solid lines, and the width of the solid line corresponds to the number of included trials. Dashed lines indicate that there are no head-to-head RCTs. Numbers above and below the lines indicate number of trials and patients respectively. ASA, aspirin; DAPT, dual antiplatelet therapy.

characteristics of patients included 75.9% ACS, 23.6% previous PCI, 13.4% previous MI, 29.1% diabetes mellitus, 60.2% hypertension, 55.5% dyslipidemia, and 32.2% smokers. The baseline characteristics of the sample are provided in Supporting Information: Table S5. In terms of the RoB of the included trials in the analysis, 14 studies were judged as low risk, whereas two studies were judged as having some concerns, and one study was judged as having a high risk of bias due to bias arising from the randomization process (Supporting Information: Figure S1).

## 3.2 | Pairwise meta-analysis

The results of pairwise meta-analysis are illustrated in Supporting Information: Figure S2. De-escalation DAPT was associated with a significantly lower MACE (RR = 0.79, 95% CI = 0.64–0.98) but showed no significant difference in the risk of major bleeding compared to standard DAPT. Short DAPT followed by P2Y12i monotherapy (RR = 0.61, 95% CI = 0.42–0.88) and short DAPT followed by aspirin monotherapy (RR = 0.66, 95%

**TABLE 1** Characteristics of included studies.

| Trial, year | Patients | Total patients | Intervention/control | *n*/*n* | Mean age (years) | Female (%) | ACS (%) | Previous MI (%) | DM (%) | HT (%) | DLP (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A-MATCH, 2021[33] | ACS | 167 | De-escalation DAPT/Standard DAPT | 82/85 | 55.8/55.1 | 11.0/7.1 | 100/100 | 0.0/3.5 | 26.8/25.9 | 63.4/57.6 | 79.3/82.4 |
| GLOBAL LEADERS, 2018[14] | ACS/CCS | 15968 | Short DAPT P2Y12i/Standard DAPT | 7980/7988 | 64.5/64.6 | 23.4/23.1 | 47.0/46.8 | 23.0/23.6 | 25.7/24.9 | 74.0/73.3 | 69.3/70.0 |
| HOST-REDUCE-POLYTECH-ACS, 2020[34] | ACS | 2338 | De-escalation DAPT/Standard DAPT | 1170/1168 | 58.7/58.9 | 10.3/11.2 | 100/100 | 3.0/4.7 | 43.8/40.9 | 62.6/63.6 | 76.1/77.8 |
| OPTIMIZE, 2013[9] | ACS/CCS | 3119 | Short DAPT ASA/Standard DAPT | 1563/1556 | 61.3/61.9 | 36.5/36.9 | 23.7/23.8 | 34.6/34.8 | 35.4/35.3 | 86.4/88.2 | 63.2/63.7 |
| POPular Genetics, 2019[31] | ACS | 2488 | De-escalation DAPT/Standard DAPT | 1242/1246 | 61.9/61.4 | 25.5/24.8 | 100/100 | 7.8/7.0 | 12.1/11.1 | 41.9/41.0 | 21.0/20.5 |
| REDUCE, 2019[8] | ACS | 1496 | Short DAPT ASA/Standard DAPT | 751/745 | 61.0/60.0 | 17.4/22.7 | 100/100 | 12.5/11.8 | 21.6/19.5 | 50.7/50.7 | 46.3/44.9 |
| RESET, 2012[11] | ACS/CCS | 2117 | Short DAPT ASA/Standard DAPT | 1059/1058 | 62.4/62.4 | 35.6/37.1 | 55.5/53.7 | 1.8/1.6 | 29.8/28.8 | 62.3/61.4 | 57.7/59.9 |
| SMART-CHOICE, 2019[10] | ACS/CCS | 2993 | Short DAPT P2Y12i/Standard DAPT | 1495/1498 | 64.6/64.4 | 27.3/25.8 | 58.2/58.2 | 4.1/4.3 | 38.2/36.8 | 61.6/61.3 | 45.1/45.5 |
| STOPDAPT-2, 2019[15] | ACS/CCS | 3009 | Short DAPT P2Y12i/Standard DAPT | 1500/1509 | 68.1/69.1 | 21.1/23.5 | 37.7/38.6 | 13.8/13.2 | 39.0/38.0 | 73.7/74.0 | 74.4/74.8 |
| TALOS-AMI, 2021[52] | ACS | 2697 | De-escalation DAPT/Standard DAPT | 1349/1348 | 60.1/59.9 | 16.1/17.6 | 100/100 | NA | 26.8/27.4 | 48.6/49.2 | 41.7/41.2 |
| TICO, 2020[12] | ACS | 3056 | Short DAPT P2Y12i/Standard DAPT | 1527/1529 | 61.0/61.0 | 21.0/20.0 | 100/100 | 4.0/3.0 | 27.0/27.0 | 50.0/51.0 | 61.0/60.0 |
| TOPIC, 2017[32] | ACS | 646 | De-escalation DAPT/Standard DAPT | 323/323 | 60.6/59.6 | 19.0/16.0 | 100/100 | 31.0/30.0 | 26.0/29.0 | 47.0/50.0 | 42.0/46.0 |
| TROPICAL-ACS, 2017[35] | ACS | 2610 | De-escalation DAPT/Standard DAPT | 1304/1306 | 59.0/58.5 | 79.0/78.0 | 100/100 | 11.0/12.0 | 11.0/22.0 | 61.0/62.0 | 42.0/41.0 |
| TWILIGHT, 2019[13] | ACS/CCS | 7119 | Short DAPT P2Y12i/Standard DAPT | 3555/3564 | 65.2/65.1 | 23.8/23.9 | 63.9/65.7 | 28.7/28.6 | 37.1/36.5 | 72.6/72.2 | 60.7/60.2 |
| One-Month DAPT 2021[39] | ACS/CCS | 3020 | Short DAPT ASA/Standard DAPT | 1507/1513 | 67.0/67.0 | 31.0/31.0 | 38.0/41.0 | 4.0/4.0 | 37.0/38.0 | 67.0/66.0 | 81.0/82.0 |
| BLESS 2016[37] | ACS | 193 | De-escalation DAPT/Standard DAPT | 98/95 | 62.2/62.2 | 14.3/13.7 | 100/100 | 17.3/25.3 | 21.4/30.5 | 57.1/57.9 | 43.9/50.5 |
| HOPE-TAILOR 2021[38] | ACS | 120 | De-escalation DAPT/Standard DAPT | 79/41 | 59.0/63.0 | 10.1/7.3 | 100/100 | 10.1/14.6 | 19.0/34.1 | 43.0/43.9 | 21.5/12.2 |

Abbreviations: ACS, acute coronary syndrome; ASA, aspirin; CCS, chronic coronary syndromes; DAPT, dual antiplatelet therapy; DLP, dyslipidemia; DM, diabetes mellitus; HT, hypertension; MI, myocardial infarction; NA, not available; P2Y12i, P2Y12 inhibitor; PCI, percutaneous coronary intervention.

CI = 0.44–0.99) exhibited a significantly reduced risk of major bleeding. De-escalation DAPT (RR = 0.68, 95% CI = 0.56–0.82) and short DAPT followed by P2Y12i monotherapy (RR = 0.71, 95% CI = 0.58–0.87) were associated with a significantly lower NACE than standard DAPT. No statistically significant difference was noted between DAPT strategies on all-cause mortality, CV death, nonfatal MI, nonfatal stroke, or stent thrombosis (Supporting Information: Table S6).

## 3.3 | Ranking of treatment strategies

NMA suggested that de-escalation DAPT was associated with the highest probability of preventing MACEs, whereas short DAPT followed by P2Y12i monotherapy was associated with the lowest probability of major bleeding. The individual rankings of treatment strategies based on SUCRAs are provided in the Supporting Information: Figure S3.

## 3.4 | NMA

De-escalation DAPT showed the greatest relative reduction in the occurrence of MACEs compared to standard DAPT (RR = 0.79, 95% CI = 0.64–0.98), but there were no significant differences found in other comparisons (Figure 3A). Short DAPT followed by P2Y12i monotherapy demonstrated the greatest relative reduction in the occurrence of major bleeding (RR = 0.63, 95% CI = 0.46–0.86) over standard DAPT, but not significantly over short DAPT followed by aspirin monotherapy (RR = 0.97, 95% CI = 0.54–1.75) and de-escalation DAPT (RR = 0.77, 95% CI = 0.46–1.28) (Figure 3B). De-escalation DAPT (RR = 0.63, 95% CI = 0.49–0.82) and short DAPT followed by P2Y12i monotherapy (RR = 0.65, 95% CI = 0.46–0.93) showed a significantly decreased risk of major and minor bleeding compared to standard DAPT, but no significant differences were found in other comparisons (Figure 3C). When considering both bleeding and ischaemic events, de-escalation DAPT (RR = 0.69, 95% CI = 0.60–0.79) and short DAPT followed by P2Y12i monotherapy (RR = 0.71, 95% CI = 0.58–0.87) were associated with a significantly lower risk of NACEs than standard DAPT. Both de-escalation DAPT (RR = 0.71, 95% CI = 0.57–0.89) and short DAPT followed by P2Y12i monotherapy (RR = 0.74, 95% CI = 0.57–0.89) demonstrated a significantly decreased risk of NACEs over short DAPT followed by aspirin monotherapy. In contrast, de-escalation DAPT showed no difference in efficacy and safety in terms of NACEs compared to short DAPT followed by P2Y12i monotherapy (Figure 3D). We observed no difference in all-cause mortality, CV death, nonfatal MI, nonfatal stroke, or stent thrombosis between treatment options (Supporting Information: Figure S4). Global inconsistencies between direct and indirect evidence are noted for some network comparisons (Supporting Information: Table S7).

## 3.5 | Sensitivity analyses, subgroup analyses, and small-study effects

The results from sensitivity analyses were unchanged in the main analysis (Supporting Information: Table S8).

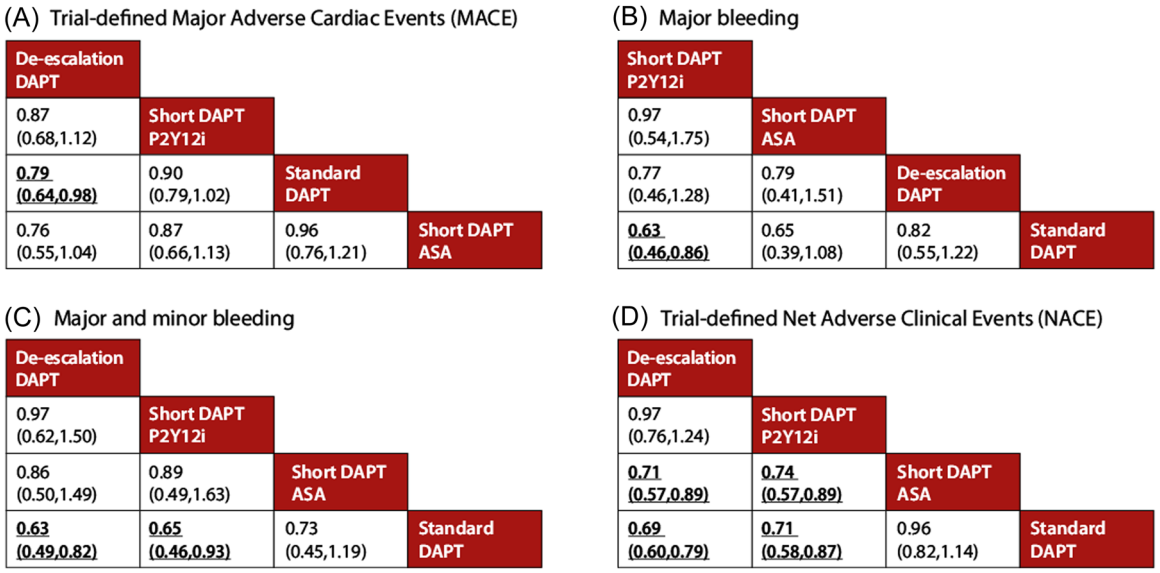


**FIGURE 3** network meta-analysis (NMA) results for (A) trial-defined major adverse cardiac events; (B) major bleeding; (C) major and minor bleeding; (D) trial-defined net adverse clinical events. Dual antiplatelet therapy (DAPT) strategies are reported in the order of ranking according to the surface under the cumulative ranking (SUCRA) curves. Comparisons should be read from left to right. The estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Significant results are in bold and underlined.

A summary of subgroup analyses for primary outcomes is shown in Supporting Information: Table S9. Subgroup analyses in East Asian versus non-East Asian populations revealed no statistically significant differences between the treatment strategy in MACEs and major bleeding due to a limited number of included RCTs in the subgroups. Comparison-adjusted funnel plots showed no signs of asymmetry (Supporting Information: Figure S5).

## 4 | DISCUSSION

This systematic review and NMA of 17 RCTs enrolling 53,156 patients who underwent PCI presented a comparative efficacy and safety analysis between different DAPT strategies, including de-escalation DAPT, short DAPT, and standard DAPT. We found that de-escalation DAPT demonstrated the greatest relative reduction in the occurrence of MACEs, while short DAPT followed by P2Y12i monotherapy was associated with the highest relative reduction in the occurrence of major bleeding. De-escalation DAPT was ranked as the most effective strategy for the prevention of ischaemic and bleeding events. However, the net clinical outcomes of de-escalation DAPT are comparable to short DAPT followed by P2Y12i monotherapy. There was no difference in ischaemic and bleeding outcomes between short DAPT followed by aspirin monotherapy and standard DAPT. We noted no significant difference in all-cause mortality, CV death, nonfatal MI, nonfatal stroke, or stent thrombosis between patients treated with different DAPT strategies.

The risk of ischaemic events is highest in the first 30 days after an ACS event, while bleeding events occur predominantly during the maintenance phase of antiplatelet treatment.[40] However, Giustino et al. showed that both bleeding and ischaemic events most often occur within the first 30 days following PCI.[41] Optimal DAPT duration is still a matter of concern, with new evidence supporting shortened DAPT, especially in patients with a high risk of bleeding.[1] Recent meta-analyses of RCTs comparing short DAPT (≤3 months) and standard DAPT (12 months) showed that short DAPT was associated with a lower risk of bleeding without a significantly increased risk of ischaemic events.[16,17] Another meta-analysis found that de-escalation DAPT with a switch from prasugrel or ticagrelor to clopidogrel after short duration DAPT compared to the standard continuation of therapy was associated with a reduction in the net clinical number of thrombotic or bleeding events similar to that which was found in our meta-analysis.[18] In addition, our meta-analysis also suggested that the de-escalation DAPT strategy minimized the risk of MACEs and major and minor bleeding compared to the standard DAPT duration. Recent large trials, including HOST-REDUCE-POLYTECH-ACS,[34] POPular Genetics,[31] TALOS-AMI,[36] and HOPE-TAILOR,[38] were included in our analysis. Our NMA found that short DAPT followed by P2Y12i monotherapy, compared with standard DAPT, reduced the risk of major bleeding in patients undergoing PCI, similar to a previous meta-analysis.[16] Another NMA concluded that an early switch from DAPT at 1–3 months to P2Y12i monotherapy was associated with a lower risk of any bleeding without a significantly increased risk of CV mortality or ischaemic outcomes compared with standard DAPT in patients undergoing PCI with a drug-eluting stent.[42]

Our results found that net clinical outcomes occurred less frequently with de-escalation DAPT and short DAPT followed by P2Y12i than standard DAPT. However, the trials considered for the analysis excluded high ischaemic risk patients and enrolled patients with a low bleeding risk.

Based on this review, although de-escalation DAPT and short DAPT followed by P2Y12i monotherapy were ranked as the most effective strategy for the prevention of ischaemic and bleeding events, further evidence regarding these strategies is needed for patients with a high ischaemic risk, and it may be reasonable to consider these strategies in patients at high risk for bleeding.

The ischaemic outcomes of patients treated with de-escalation DAPT or short DAPT were not found to be inferior to those seen with standard therapy. These results may be explained by several factors. First, many new platforms of coronary stents have proven to be compatible with short DAPT.[43–45] Second, some PCI techniques, such as intravascular imaging-guided PCI, can reduce the risk of ischaemic events.[46–50] Last, the risk of an ischaemic event was found to be highest in the early phase of the post-PCI period.[41,51]

### 4.1 | Strengths and limitations

The strengths of this meta-analysis included the comprehensive systematic search that considered trials published in languages other than English and those published only, used a prespecified protocol, and the double-checking of data extraction. This is also the first meta-analysis that compared short DAPT followed by P2Y12i monotherapy to short DAPT followed by aspirin monotherapy, and the results tended to prefer short DAPT followed by P2Y12i. However, there were several limitations. First, the study population was a mixed cohort of both ACS and CCS. Due to a lack of access to patient-level data, we could not perform any subgroup analyses in either the ACS or CCS populations. However, the sensitivity analysis that omitted studies with a mix of ACS and CCS patients showed similar results to the main analysis. Second, comparisons between the short DAPT strategy and de-escalation DAPT were generated

based on indirect evidence. We could not perform an inconsistency test since there was no trial directly comparing these therapies. In addition, given that the imbalance duration of DAPT between groups was combined, which may have introduced bias, the finding may be drawn with caution. Third, many trials had restrictive inclusion and exclusion criteria, excluding high ischaemic risk patients while enrolling patients with a low bleeding risk. Our results may be more applicable to individuals with ACS and stable CCS but not to those with a high ischaemic and bleeding risk. Additionally, the definitions of MACEs and NACEs differ between the various studies as trial-defined definitions. Any results should be considered exploratory and interpreted with caution. Last, the de-escalation DAPT protocol in each trial was not identical. Some de-escalation protocols were guided by platelet function or genetic testing, while others were not. Future studies to determine whether strategies for the de-escalation of DAPT using platelet function testing, genetic testing or even unguided as the most effective methods in patients with ACS who are at a high risk for bleeding are warranted.

## 5 | CONCLUSIONS

NMA suggested that de-escalation DAPT was associated with the highest probability of preventing MACEs, whereas short DAPT followed by P2Y12i monotherapy was associated with the lowest probability of major bleeding. When considering NACEs, de-escalation DAPT was ranked as the most effective strategy for the prevention of ischaemic and bleeding events.

### AUTHOR CONTRIBUTIONS

**Yuttana Wongsalap**: Design; data collection; analysis; interpretation; writing the manuscript; critical revision; final approval. **Kirati Kengkla**: Analysis; interpretation; writing of the manuscript; final approval. **Preyanate Wilairat**: Data collection; writing of the manuscript; final approval. **Khemanat Ratworawong**: Data collection; writing of the manuscript; final approval. **Surasak Saokaew**: Design; critical revision; final approval. **Chaisiri Wanlapakorn**: Design; interpretation; writing the manuscript; critical revision; final approval.

### ACKNOWLEDGMENTS

We are grateful to Ronpichai Chokesuwattanaskul, King Chulalongkorn Memorial Hospital, Bangkok, Thailand for the critical review. We would like to thank Chayanis Kositamongkol, Division of Ambulatory Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University for her support on full-text access. The research project was supported by the Thailand Science Research and Innovation fund and the Unit of Excellence on Clinical Outcomes Research and IntegratioN (UNICORN), the University of Phayao (grant number: UoE66003 and FF65-RIM100). The funding source had no role in the study design, collection, analysis, and interpretation of data.

### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

### DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

### ETHICS STATEMENT

This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was waived by the local Ethics Committee of the University in view of the nature of the study.

### ORCID

*Yuttana Wongsalap* http://orcid.org/0000-0003-4487-9814
*Kirati Kengkla* http://orcid.org/0000-0001-6726-5706
*Chaisiri Wanlapakorn* http://orcid.org/0000-0002-2574-3121

### REFERENCES

1. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289-1367.
2. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119-177.
3. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *JACC*. 2016;68(10):1082-1115.
4. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39(3):213-260.
5. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057.
6. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-2015.
7. Cao D, Chandiramani R, Chiarito M, Claessen BE, Mehran R. Evolution of antithrombotic therapy in patients undergoing percutaneous coronary intervention: a 40-year journey. *Eur Heart J*. 2021;42(4):339-351.
8. De Luca G, Damen SA, Camaro C, et al. Final results of the randomised evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with a new-generation stent (REDUCE trial). *EuroIntervention*. 2019;15(11):e990-e998.
9. Feres F. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA*. 2013;310(23):2510-2522. doi:10.1001/jama.2013.282183

10. Hahn JY, Song YB, Oh JH, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA*. 2019;321(24):2428-2437.
11. Kim BK, Hong MK, Shin DH, et al. A new strategy for discontinuation of dual antiplatelet therapy. *JACC*. 2012;60(15):1340-1348.
12. Kim BK, Hong SJ, Cho YH, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA*. 2020;323(23):2407-2416.
13. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without Aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381(21):2032-2042.
14. Vranckx P, Valgimigli M, Jüni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet*. 2018;392(10151):940-949.
15. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA*. 2019;321(24):2414-2427.
16. Giacoppo D, Matsuda Y, Fovino LN, et al. Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J*. 2021;42(4):308-319.
17. Kheiri B, Simpson TF, Osman M, et al. Safety and efficacy of short-term (1 to 3 months) dual antiplatelet therapy in patients undergoing percutaneous coronary interventions: a meta-analysis of randomized controlled trials. *J Thromb Thrombolysis*. 2020;50(4):867-873.
18. Kheiri B, Osman M, Abdalla A, et al. De-escalation of antiplatelet therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a meta-analysis of randomized clinical trials. *J Cardiovasc Pharmacol Ther*. 2019;24(2):153-159.
19. Laudani C, Greco A, Occhipinti G, et al. Short duration of DAPT versus de-escalation after percutaneous coronary intervention for acute coronary syndromes. *JACC Cardiovasc Intervent*. 2022;15(3):268-277.
20. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
21. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
22. TIMI Study Group. The thrombolysis in myocardial infarction (TIMI) trial. Phase I findings. *N Engl J Med*. 1985;312(14):932-936. doi:10.1056/NEJM198504043121437
23. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. *Circulation*. 2011;123(23):2736-2747.
24. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
25. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions version 6.1*; 2020. www.training.cochrane.org/handbook
26. Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One*. 2013;8(10):e76654.
27. White IR. Network meta-analysis. *Stata J Promot Commun Statis Stata*. 2015;15(4):951-985.
28. Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods*. 2012;3(2):98-110.
29. Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G. Evaluation of inconsistency in networks of interventions. *Int J Epidemiol*. 2013;42(1):332-345.
30. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *JCE*. 2011;64(2):163-171.
31. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral P2Y(12) inhibitors in primary PCI. *N Engl J Med*. 2019;381(17):1621-1631.
32. Cuisset T, Deharo P, Quilici J, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. *Eur Heart J*. 2017;38(41):3070-3078.
33. Jeong YH, Oh JH, Yoon HJ, et al. Pharmacodynamic profile and prevalence of bleeding episode in east asian patients with acute coronary syndromes treated with prasugrel standard-dose versus de-escalation strategy: a randomized A-MATCH trial. *Thromb Haemost*. 2021;121:1376-1386.
34. Kim HS, Kang J, Hwang D, et al. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. *Lancet*. 2020;396(10257):1079-1089.
35. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet*. 2017;390(10104):1747-1757.
36. Kim CJ, Park MW, Kim MC, et al. Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): an investigator-initiated, open-label, multicentre, non-inferiority, randomised trial. *Lancet*. 2021;398(10308):1305-1316.
37. Carrabba N, Parodi G, Marcucci R, et al. Bleeding events and maintenance dose of prasugrel: BLESS pilot study. *Open Heart*. 2016;3(2):e000460.
38. Jin CD, Kim MH, Song K, et al. Pharmacodynamics and outcomes of a de-escalation strategy with half-dose prasugrel or ticagrelor in east asians patients with acute coronary syndrome: results from HOPE-TAILOR trial. *J Clin Med*. 2021;10(12):2699.
39. Hong SJ, Kim JS, Hong SJ, et al. 1-month dual-antiplatelet therapy followed by aspirin monotherapy after polymer-free drug-coated stent implantation. *JACC Cardiovasc Intervent*. 2021;14(16):1801-1811.
40. Rodriguez F, Harrington RA. Management of antithrombotic therapy after acute coronary syndromes. *N Engl J Med*. 2021;384(5):452-460.
41. Giustino G, Mehran R, Dangas GD, et al. Characterization of the average daily ischemic and bleeding risk after primary PCI for STEMI. *JACC*. 2017;70(15):1846-1857.
42. Khan SU, Khan MZ, Khan MS, et al. De-escalation of antiplatelets after percutaneous coronary intervention: a Bayesian network meta-analysis of various de-escalation strategies. *Eur Heart J Cardiovasc Pharmacother*. 2021;7(3):209-215.
43. Kandzari DE, Kirtane AJ, Windecker S, et al. One-month dual antiplatelet therapy following percutaneous coronary intervention with zotarolimus-eluting stents in high-bleeding-risk patients. *Circ Cardiovasc Intervent*. 2020;13(11):e009565.
44. Mehran R, Cao D, Angiolillo DJ, et al. 3- or 1-month DAPT in patients at high bleeding risk undergoing everolimus-eluting stent implantation. *JACC Cardiovasc Intervent*. 2021;14(17):1870-1883.

45. Windecker S, Latib A, Kedhi E, et al. Polymer-based or polymer-free stents in patients at high bleeding risk. *N Engl J Med*. 2020;382(13):1208-1218.
46. Ahn JM, Kang SJ, Yoon SH, et al. Meta-analysis of outcomes after intravascular ultrasound-guided versus angiography-guided drug-eluting stent implantation in 26,503 patients enrolled in three randomized trials and 14 observational studies. *Am J Cardiol*. 2014;113(8):1338-1347.
47. Hong SJ, Mintz GS, Ahn CM, et al. Effect of intravascular ultrasound–guided drug-eluting stent implantation. *JACC Cardiovasc Intervent*. 2020;13(1):62-71.
48. Klersy C, Ferlini M, Raisaro A, et al. Use of IVUS guided coronary stenting with drug eluting stent. *Int J Cardiol*. 2013;170(1):54-63.
49. Panchal HB, Daggubati R, Zhao D, Rao SV, Paul T. Polymer-free drug-coated coronary stents in patients with stable coronary artery disease at high bleeding risk. *Curr Cardiol Rep*. 2017;19(2):12.
50. Zhang Y, Farooq V, Garcia-Garcia HM, et al. Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients. *EuroIntervention*. 2012;8(7):855-865.
51. Antman EM, Wiviott SD, Murphy SA, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. *JACC*. 2008;51(21):2028-2033.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Wongsalap Y, Kengkla K, Wilairat P, Ratworawong K, Saokaew S, Wanlapakorn C. Efficacy and safety of different dual antiplatelet strategies in patients undergoing percutaneous coronary intervention: a systematic review and network meta-analysis. *Chronic Dis Transl Med*. 2023;9:299-308. doi:10.1002/cdt3.85