Efficacy and safety of dual antiplatelet therapy after percutaneous coronary drug-eluting stenting
A network meta-analysis

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Abstract
Background: To evaluate the efficacy and safety of dual antiplatelet regimens after coronary drug-eluting stenting by network meta-analysis (NMA).

Methods: PubMed, The Cochrane Library, Embase, and Web of Science databases were electronically searched to collect randomized controlled trials (RCTs) of the comparison of different dual antiplatelet regimens after coronary drug-eluting stenting from inception to September 1st, 2021. Two reviewers independently screened literature, extracted data, and assessed the risk bias of included studies. Stata 16.0 software was used for NMA.

Results: A total of 27 RCTs involving 79,880 patients were included. The results of NMA: in terms of myocardial infarction (MI), other 3 interventions were higher than the long-term dual antiplatelet therapy (L-DAPT) (the standard dual antiplatelet therapy [Std-DAPT] [odds ratio [OR] = 1.82, 95%confidence interval [CI]: 1.49-2.21], the aspirin monotherapy after short-term dual antiplatelet therapy (S-DAPT + As) [OR = 2.06, 95%CI: 1.57-2.70], the P2Y12 inhibitor monotherapy after short-term dual antiplatelet therapy (S-DAPT + P2Y12) [OR = 1.71, 95%CI: 1.29-2.28]). In terms of stent thrombosis, other 3 interventions were higher than L-DAPT (Std-DAPT [OR = 2.18, 95%CI: 1.45-3.28], S-DAPT + As [OR = 2.32, 95%CI: 1.52-3.54], S-DAPT + P2Y12 [OR = 2.31, 95%CI: 1.22-4.36]). There was no statistically significant difference among the 4 interventions in prevention of stroke and all-cause mortality (P > .05). In terms of cardiovascular and cerebrovascular adverse events, other 3 interventions were higher than L-DAPT (Std-DAPT [OR = 1.28, 95%CI: 1.12-1.45], S-DAPT + As [OR = 1.27, 95%CI: 1.09-1.48], S-DAPT + P2Y12 [OR = 1.24, 95%CI: 1.01-1.52]). In terms of safety, bleeding rate of other 3 interventions were lower than L-DAPT (Std-DAPT [OR = 0.67, 95%CI: 0.52-0.85], S-DAPT + As [OR = 0.51, 95%CI: 0.39-0.66], S-DAPT + P2Y12 [OR = 0.36, 95%CI: 0.26-0.49]). Two interventions were lower than L-DAPT (S-DAPT + As [OR = 0.77, 95%CI: 0.65-0.90], S-DAPT + P2Y12 [OR = 0.54, 95%CI: 0.44-0.66]). S-DAPT + As was higher than L-DAPT (OR = 1.42, 95%CI: 1.10-1.83).

Conclusions: S-DAPT + P2Y12 has the lowest bleeding risk, while L-DAPT has the highest bleeding risk. In the outcome of MI, stent thrombosis, and cardiovascular and cerebrovascular adverse events, L-DAPT has the best efficacy. In the outcome of stroke and all-cause mortality, the 4 interventions were equally effective.

Abbreviations: ACS = acute coronary syndrome, CI = confidence interval, DAPT = dual antiplatelet therapy, DES = drug-eluting stent, L-DAPT = long-term dual antiplatelet therapy, MI = myocardial infarction, NMA = network meta-analysis, OR = odds ratio, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, S-DAPT + As = aspirin monotherapy after short-term dual antiplatelet, S-DAPT + P2Y12 = P2Y12 inhibitor monotherapy after short-term dual antiplatelet, Std-DAPT = standard dual antiplatelet, SUCRA = surface under the cumulative ranking.

Keywords: drug-eluting stents, dual antiplatelet antiplatelets, efficacy, network meta-analysis, percutaneous coronary intervention, safety
1. Introduction
Compared with the original bare metal stent, drug-eluting stent (DES) has greatly improved the risk of in-stent restenosis and target lesion revascularization after percutaneous coronary intervention (PCI).[1–3] Concerningly, DES may be associated with the risk of late stent thrombosis,[4,5] although stent thrombosis events have become relatively rare in newer-generation DES, it still threatens the lives of patients today and cannot be ignored.

Dual antiplatelet therapy (DAPT) of aspirin combined with P2Y12 receptor inhibitors is the cornerstone of post-PCI treatment, which is crucial to prevent stent thrombosis and can effectively reduce the occurrence of ischemic events.[6] The 2016 ACC/AHA, 2016 China and 2017 ESC guidelines for PCI[7–9] all recommend that patients with acute coronary syndrome (ACS) receive standard dual antiplatelet therapy (Std-DAPT) for at least 12 months after DES implantation. Patients with stable ischemic heart disease without high bleeding risk may receive aspirin monotherapy after 1-3 months of short-term dual antiplatelet therapy. Patients with ACS without high bleeding risk may receive 6 months of dual antiplatelet therapy (S-DAPT + As).

However, in patients at higher ischemic risk for ACS, DAPT reduces ischemic events at the expense of increased bleeding risk.[10,11] In recent years, in order to balance the efficacy and safety of DAPT, some researchers recommend discontinuing aspirin after short-term dual antiplatelet and continuing to use P2Y12 inhibitor monotherapy (S-DAPT + P2Y12) to shorten the DAPT time after PCI to reduce bleeding events.[12] Some researchers have suggested that the occurrence of stent thrombosis in late ischemic event may be related to delayed coronary endothelial healing after DES implantation,[13] and premature discontinuation of DAPT treatment has been identified as a risk factor for late stent thrombosis after DES implantation.[14,15]

Long-term (more than 12 months) dual antiplatelet therapy (L-DAPT) may be recommended to reduce ischemic events if there is no high risk of bleeding.[16]

At present, there is a lack of comparison on the efficacy and safety of different DAPT regimens. This study will use network meta-analysis (NMA) to evaluate different DAPT regimens, to provide the evidence-based basis for clinical workers in the future.

2. Methods
2.1. Data sources and search strategy
Because the NMA is a secondary analysis study, it does not involve ethical approval. PubMed, The Cochrane Library, Embase, and Web of Science databases were randomized searched by computer to collect controlled trials (RCTs) on the comparison of different dual antiplatelet regimens after coronary drug-eluting stenting from the establishment of the database to September 1st, 2021. At the same time, reference literatures of published studies were traced back, and paper versions of relevant conferences were manually read to supplement (Details of our search strategy are provided in the Supplementary Appendix, http://links.lww.com/MD/H627).

2.2. Study selection
All studies must be RCTs. Patients with DES implantation who satisfied the clinical diagnostic criteria for coronary heart disease were over 18 years old. The follow-up period was at least 12 months. The experimental group and control groups were treated with different DAPT, which was aspirin combined with P2Y12 receptor inhibitors (such as clopidogrel, ticlopidine, ticagrelor, and prasugrel).

2.3. Data extraction and quality assessment
Two researchers independently screened studies, extracted data, and cross-checked them. Disputes, if any, shall be resolved through discussion or consultation with a third party. When screening studies, read the title first, then the abstract and entire text to determine whether to include it. To get information, contact the original study author by email or phone if necessary.

The RCT bias risk assessment tool recommended by Cochrane Manual 5.1.0 was used to assess the risk of bias.[17]

The following data were recorded: publication characteristics, countries or regions of the study, patient characteristics, classification of coronary heart disease, sample size, interventions, duration of follow-up, blinding, intention-to-treat analysis, efficacy and safety outcomes. The efficacy outcomes included myocardial infarction (MI), stent thrombosis, stroke, and other adverse events. The safety outcomes included bleeding events, stent thrombosis, and other adverse events.

Figure 1. Study selection flow diagram.
all-cause mortality, cardiovascular and cerebrovascular adverse events. The safety outcome included bleeding.

2.4. Data analysis

A random-effect model was constructed based on frequency theory, and Stata 16.0 software was used for direct and NMA. χ² test and I² value were used to determine heterogeneity. If there was significant heterogeneity between studies, the source of heterogeneity was analyzed first. The outcome indicators were odds ratio (OR) for dichotomous variables and mean difference for continuous variables, with a 95% confidence interval (CI) as the test level. If the number of included studies was greater than 10, a funnel plot was made to evaluate whether the intervention had a small sample effect and publication bias. The network plot represents the sample size and relationship of the interventions. When there was a closed loop, the inconsistency evaluation method was used to test the inconsistency. If the difference was not statistically significant (P > .05), and the consistency model was used for analysis. At the same time, the node-splitting method was used to test the local inconsistency. By surface under the cumulative ranking (SUCRA), the advantages and disadvantages of therapies were quantitatively compared. The larger SUCRA was, the more likely the treatment was to become the best treatment. Then, the efficacy of different therapies could be compared comprehensively.

3. Results

3.1. Study selection

A total of 10,074 related studies were obtained in the preliminary review. Twenty-six studies were eventually included, including 1 conference paper containing 2 RCTs. The 27 RCTs included a total of 79,880 patients (Study selection flow diagram in Fig. 1).

3.2. Quality evaluation and baseline characteristics

Random sequence generation, double-blind, allocation concealment, and complete outcome data were used in the majority of the studies (Quality evaluation in Table 1). A total of 4 interventions were included (Baseline characteristics in Table 2 and the network plot presented in Fig. 2). There were 13 RCTs

| Table 1
| The result of the quality evaluation. |
| Study ID | Random method | Blinding | Allocation plan hidden | Integrity of the result data | Selective reporting | Other sources of bias |
|----------|----------------|----------|------------------------|-----------------------------|--------------------|---------------------|
| ISAR-SAFE 2015[36] | Computer | Double-blind | Sealed envelope | Basically complete*, non-ITT | No | Not sure |
| OPTIMA-C 2018[16] | Computer | Open-label | Interactive-response computer system | Basically complete*, non-ITT | No | Not sure |
| RESET 2012[22] | Computer | Open-label | Interactive-response computer system | Basically complete*, ITT | No | Not sure |
| DAPT-STEMI 2018[21] | Not sure | Open-label | Interactive-response computer system | Basically complete*, ITT | No | Not sure |
| IVUS-XPL 2016[20] | Computer | Not sure | Interactive-response computer system | Basically complete*, ITT | No | Not sure |
| I-LOVE-IT 2 2010[23] | Not sure | Investigator blinding | Not sure | Basically complete*, ITT | No | Not sure |
| EXCELLENT 2012[24] | Computer | Open-label | Interactive-response computer system | Basically complete*, non-ITT | No | Not sure |
| OPTIMIZE 2013[25] | Not sure | Open-label | Interactive-response computer system | Basically complete*, non-ITT | No | Not sure |
| REDUCE 2013[26] | Computer | Open-label | Interactive-response computer system | Basically complete*, non-ITT | No | Not sure |
| SECURITY 2014[7] | Not sure | Investigator blinding | Not sure | Basically complete*, ITT | No | Not sure |
| ONE-MONTH DAPT 2021[27] | Not sure | Open-label | Center allocation | Basically complete*, ITT | No | Not sure |
| XIENCE 90 2020[28] | Not sure | Investigator blinding | Not sure | Not sure | Conference paper | Conference |
| XIENCE 28 2020[28] | Not sure | Not sure | Not sure | Not sure | Not sure | Not sure |
| TWILIGHT 2019[29] | Computer | Double-blind | Investigator blinding | Not sure | No | Not sure |
| STOP-DAPT-2 2019[30] | Computer | Investigator blinding | Center allocation | Basically complete*, ITT | No | Not sure |
| SMART-CHOICE 2019[31] | Computer | Open-label | Interactive-response computer system | Basically complete*, ITT | No | Not sure |
| GLOBAL LEADER 2019[32] | Computer | Open-label | Interactive-response computer system | Basically complete*, ITT | No | Not sure |
| TICO 2020[33] | Computer | Open-label | Interactive-response computer system | Basically complete*, ITT | No | Not sure |
| REAL-LATE and ZEST-LATE 2010[34] | Computer | Open-label | Interactive-response computer system | Basically complete*, ITT | No | Not sure |
| DAPT 2014[35] | Not sure | Open-label | Center allocation | Basically complete*, ITT | No | Not sure |
| DES-LATE 2014[36] | Computer | Open-label | Interactive-response computer system | Basically complete*, ITT | No | Not sure |
| OPTIMAL 2016[37] | Computer | Open-label | Interactive-response computer system | Basically complete*, ITT | No | Not sure |
| ARCTIC 2014[38] | Computer | Open-label | Interactive-response computer system | Basically complete*, non-ITT | No | Not sure |
| NIPPON 2017[39] | Computer | Not sure | Interactive-response computer system | Basically complete*, ITT | No | Not sure |
| SMART-DATE 2018[40] | Computer | Not sure | Interactive-response computer system | Basically complete*, ITT | No | Not sure |
| ILITALIC 2015[41] | Computer | Open-label | Interactive-response computer system | Basically complete*, non-ITT | No | Not sure |
| PRODIGY 2014[42] | Not sure | Not sure | Not sure | Basically complete*, non-ITT | No | Not sure |

*The study was lost to follow-up, but the number of lost to follow-up in each group was balanced, or the proportion of lost to follow-up was very low, which had little impact on the completeness of the result data.

ITT = intentional analysis.
comparing S-DAPT + As with Std-DAPT.[18–29] There were 5 RCTs comparing S-DAPT + P2Y12 with Std-DAPT.[30–34] There were 5 RCTs comparing L-DAPT with Std-DAPT. [35–39] There were 4 RCTs comparing S-DAPT + As with L-DAPT.[40–43]

### 3.3. Data consistency and inconsistency test

The evaluation of inconsistencies for 6 outcomes performed using loop-specific heterogeneity estimates revealed 1 triangular loop [(S-DAPT + As)-(Std-DAPT)-(L-DAPT)], all with no significant results (all $P$ values > 0.182). The node-splitting method did not yield significant results (all $P$ values > .182) (The result of direct and NMA in Table 3).

### 3.4. Network meta-analysis

#### 3.4.1. Myocardial infarction.

A total of 24 RCTs were included.[18–21,23–28,30–43] Results of NMA showed that other 3 interventions were higher than L-DAPT (Std-DAPT [OR = 1.82, 95%CI: 1.49-2.21], S-DAPT + As [OR = 2.06, 95%CI: 1.57-2.70], S-DAPT + P2Y12 [OR = 1.71, 95%CI: 1.29-2.28]). There was no statistical significance among other interventions (Table 3). SUCRA sequencing results showed that: L-DAPT (100.0) > S-DAPT + P2Y12 (52.8) > Std-DAPT (38.8) > S-DAPT + As (8.4) (Fig. 3).

#### 3.4.2. Stent thrombosis.

A total of 25 RCTs were included.[18,20–38,40–43] Results of NMA showed that other 3 interventions were higher than L-DAPT (Std-DAPT (OR = 2.18, 95%CI: 1.45-3.28), S-DAPT + As (OR = 2.32, 95%CI: 1.52-3.54), S-DAPT + P2Y12 (OR = 2.31, 95%CI: 1.22-4.36)). There was no statistical significance among other interventions (Table 3). SUCRA sequencing results showed that: L-DAPT (99.8) > Std-DAPT (99.8) > S-DAPT + P2Y12 (29.9) > S-DAPT + As (29.2) (Fig. 3).

#### 3.4.3. Stroke.

A total of 20 RCTs were included.[18,21–23,25–28,30–44] Results of NMA showed that there was no statistical significance among 4 interventions (Table 3). SUCRA sequencing results...
showed that: S-DAPT + As (70.0) > Std-DAPT (51.9) > L-DAPT (50.0) > S-DAPT + P2Y12 (28.1) (Fig. 3).

3.4.4. All-cause mortality. A total of 11 RCTs were included. Results of NMA showed that there was no statistical significance among 4 interventions (Table 3). SUCRA sequencing results showed that: S-DAPT + P2Y12 (81.6) > S-DAPT + As (54.6) > Std-DAPT (35.6) > L-DAPT (28.2) (Fig. 3).

3.4.5. Cardiovascular and cerebrovascular adverse events. A total of 27 RCTs were included. Results of NMA showed that other 3 interventions were higher than L-DAPT (Std-DAPT [OR = 1.28, 95%CI: 1.12-1.45], S-DAPT + As [OR = 1.27, 95%CI: 1.09-1.48], S-DAPT + P2Y12 [OR = 1.24, 95%CI: 1.01-1.52]). There was no statistical significance among other interventions (Table 3). SUCRA sequencing results showed that: L-DAPT (99.3) > S-DAPT + P2Y12 (41.1) > S-DAPT + As (30.4) > Std-DAPT (29.2) (Fig. 3).

3.4.6. Bleeding. A total of 27 RCTs were included. Results of NMA showed that other 3 interventions were lower than L-DAPT (Std-DAPT [OR = 0.67, 95%CI: 0.52-0.85], S-DAPT + As [OR = 0.51, 95%CI: 0.39-0.66], S-DAPT + P2Y12 [OR = 0.36, 95%CI: 0.26-0.49]). Two interventions were

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**Table 3**

The result of direct and network meta-analysis.

| Outcome                             | Interventions                              | Number of studies | Heterogeneity test | Direct meta-analysis OR (95%CI) | Network meta-analysis OR (95%CI) |
|-------------------------------------|--------------------------------------------|-------------------|--------------------|---------------------------------|---------------------------------|
| Myocardial infarction               | S-DAPT + As vs Std-DAPT                    | 10[18,21,23,28]   | 0.88               | 1.11(0.88,1.40)                | 1.13 (0.91, 1.41)                |
|                                    | S-DAPT + P2Y12 vs Std-DAPT                 | 5[30-34]          | 0.94               | 0.94 (0.76, 1.16)              | 1.13 (0.91, 1.41)                |
|                                    | Std-DAPT vs L-DAPT                         | 5[32-35]          | 1.79               | 1.79 (1.42, 2.19)              | 1.79 (1.42, 2.19)                |
|                                    | S-DAPT + As vs L-DAPT                      | 4[40-43]          | 2.40               | 2.40 (1.38, 4.19)              | 2.40 (1.38, 4.19)                |
|                                    | S-DAPT + P2Y12 vs L-DAPT                   | 0                 |                     |                                |                                |
|                                    | S-DAPT + As vs S-DAPT + P2Y12              | 0                 |                     |                                |                                |
| Stent thrombosis                    | S-DAPT + As vs Std-DAPT                    | 12[18,22-29]      | 1.22               | 1.22 (0.86, 1.74)              | 1.22 (0.86, 1.74)                |
|                                    | S-DAPT + P2Y12 vs Std-DAPT                 | 5[30-34]          | 1.06               | 1.06 (0.62, 1.80)              | 1.06 (0.62, 1.80)                |
|                                    | Std-DAPT vs L-DAPT                         | 5[35-39]          | 2.59               | 2.59 (1.77, 3.79)              | 2.59 (1.77, 3.79)                |
|                                    | S-DAPT + As vs L-DAPT                      | 4[40-43]          | 1.79               | 1.79 (1.02, 3.15)              | 1.79 (1.02, 3.15)                |
|                                    | S-DAPT + P2Y12 vs L-DAPT                   | 0                 |                     |                                |                                |
|                                    | S-DAPT + As vs S-DAPT + P2Y12              | 0                 |                     |                                |                                |
| Stroke                              | S-DAPT + As vs Std-DAPT                    | 8[18,21,23,28]    | 0.97               | 0.97 (0.65, 1.45)              | 0.97 (0.65, 1.45)                |
|                                    | S-DAPT + P2Y12 vs Std-DAPT                 | 5[30-34]          | 1.12               | 1.12 (0.65, 1.92)              | 1.12 (0.65, 1.92)                |
|                                    | Std-DAPT vs L-DAPT                         | 5[32-35]          | 1.03               | 1.03 (0.75, 1.42)              | 1.03 (0.75, 1.42)                |
|                                    | S-DAPT + As vs L-DAPT                      | 2[40-41]          | 0.35               | 0.35 (0.23, 0.64)              | 0.35 (0.23, 0.64)                |
|                                    | S-DAPT + P2Y12 vs L-DAPT                   | 0                 |                     |                                |                                |
|                                    | S-DAPT + As vs S-DAPT + P2Y12              | 0                 |                     |                                |                                |
| All-cause mortality                 | S-DAPT + As vs Std-DAPT                    | 11[18,22]         | 0.84               | 0.84 (0.66, 1.07)              | 0.84 (0.66, 1.07)                |
|                                    | S-DAPT + P2Y12 vs Std-DAPT                 | 5[30-34]          | 0.84               | 0.84 (0.66, 1.06)              | 0.84 (0.66, 1.06)                |
|                                    | Std-DAPT vs L-DAPT                         | 5[32-35]          | 0.85               | 0.85 (0.66, 1.11)              | 0.85 (0.66, 1.11)                |
|                                    | S-DAPT + As vs L-DAPT                      | 4[40-43]          | 1.26               | 1.26 (1.09, 1.44)              | 1.26 (1.09, 1.44)                |
|                                    | S-DAPT + P2Y12 vs L-DAPT                   | 0                 |                     |                                |                                |
|                                    | S-DAPT + As vs S-DAPT + P2Y12              | 0                 |                     |                                |                                |
| Cardiovascular and cerebrovascular adverse events | S-DAPT + As vs Std-DAPT | 13[18-22] | 0.99               | 0.99 (0.89, 1.10)              | 0.99 (0.89, 1.10)                |
|                                    | S-DAPT + P2Y12 vs Std-DAPT                 | 5[30-34]          | 0.97               | 0.97 (0.83, 1.14)              | 0.97 (0.83, 1.14)                |
|                                    | Std-DAPT vs L-DAPT                         | 5[32-35]          | 1.26               | 1.26 (1.09, 1.44)              | 1.26 (1.09, 1.44)                |
|                                    | S-DAPT + As vs L-DAPT                      | 4[40-43]          | 1.38               | 1.38 (1.03, 1.86)              | 1.38 (1.03, 1.86)                |
|                                    | S-DAPT + P2Y12 vs L-DAPT                   | 0                 |                     |                                |                                |
|                                    | S-DAPT + As vs S-DAPT + P2Y12              | 0                 |                     |                                |                                |
| Bleeding                            | S-DAPT + As vs Std-DAPT                    | 13[18-22]         | 0.73               | 0.73 (0.63, 0.84)              | 0.73 (0.63, 0.84)                |
|                                    | S-DAPT + P2Y12 vs Std-DAPT                 | 5[30-34]          | 0.54               | 0.54 (0.47, 0.64)              | 0.54 (0.47, 0.64)                |
|                                    | Std-DAPT vs L-DAPT                         | 5[32-35]          | 0.56               | 0.56 (0.46, 0.67)              | 0.56 (0.46, 0.67)                |
|                                    | S-DAPT + As vs L-DAPT                      | 4[40-43]          | 0.74               | 0.74 (0.68, 0.80)              | 0.74 (0.68, 0.80)                |
|                                    | S-DAPT + P2Y12 vs L-DAPT                   | 0                 |                     |                                |                                |
|                                    | S-DAPT + As vs S-DAPT + P2Y12              | 0                 |                     |                                |                                |

L-DAPT = Long-term dual antiplatelet therapy, S-DAPT + As = aspirin monotherapy after short-term dual antiplatelet, S-DAPT + P2Y12 = P2Y12 inhibitor monotherapy after short-term dual antiplatelet, Std-DAPT = standard dual antiplatelet.

※The difference was statistically significant.
lower than L-DAPT (S-DAPT + As [OR = 0.77, 95%CI: 0.65-0.90], S-DAPT + P2Y12 [OR = 0.54, 95%CI: 0.44-0.66]). S-DAPT + As was higher than L-DAPT (OR = 1.42, 95%CI: 1.10-1.83) (Table 3). SUCRA sequencing results showed that: S-DAPT + P2Y12 (99.9) > S-DAPT + As (66.8) > Std-DAPT (33.3) > L-DAPT (0.0) (Fig. 3).

3.5. Risk assessment of bias
The funnel plot was drawn for publication bias test for the outcome index of cardiovascular and cerebrovascular adverse events. The results showed that the distribution of each study point was roughly symmetrical on both sides of the funnel plot, suggesting that there was little possibility of publication bias (The funnel plot in Fig. 4).

4. Discussion
As P2Y12 receptor inhibitors show extensive individual differences among different individuals, especially clopidogrel,
about one-third of patients receiving clopidogrel will develop platelet resistance. At the same time, platelet resistance may be associated with higher cardiogenic death and ischemic events. Thus, aspirin is still the best choice for antiplatelet therapy. In recent years, despite the deepening understanding of the pathogenesis of coronary artery disease and the continuous optimization of PCI technology, there is still controversy about how to balance ischemia and bleeding after surgery and the choice of the best antithrombotic regimen. In clinical practice, the severity of bleeding is often underestimated relative to the risk of ischemia, and the bleeding risk of discharged patients after PCI may be greater than the ischemic risk of MI, and is bleeding directly related to death. Std-DAPT does reduce the risk of late thrombosis after PCI, but it also brings about safety of bleeding, so the duration of DAPT has been the focus of attention. Current European, American and Chinese guidelines all recommend that patients with high bleeding risk should receive S-DAPT + As due to the bleeding problems caused by Std-DAPT and L-DAPT. Our study showed that the bleeding risk of S-DAPT + As was significantly lower than Std-DAPT and L-DAPT. There was no statistical significance in the efficacy of S-DAPT + As, Std-DAPT and S-DAPT + P2Y12. In the outcome of MI, stent thrombosis, and cardiovascular and cerebrovascular adverse events, the efficacy of S-DAPT + As was inferior to L-DAPT. More than two decades ago, the addition of the P2Y12 receptor inhibitor clopidogrel to initial aspirin monotherapy treatment was shown to reduce the risk of ischemia in patients with non-ST-segment elevation ACS, but also to increase the risk of major bleeding. In recent years, the efficacy of aspirin has been greatly challenged. Armstrong demonstrated that in the presence of an effective P2Y12 receptor inhibitor, aspirin had little additional inhibitory effect on thromboxane A2-mediated platelet aggregation. Studies have shown that the effect of P2Y12 receptor inhibitor monotherapy to the coagulation system is similar to that of DAPT. The MATCH trial confirmed that in high-risk stroke patients, clopidogrel monotherapy may reduce ischemic risk as much as DAPT, with a lower risk of bleeding. Our study showed that S-DAPT + P2Y12 had the least bleeding risk. There was no statistical significance in the efficacy of S-DAPT + P2Y12, S-DAPT + As, Std-DAPT. In the outcome of MI, stent thrombosis, and cardiovascular and cerebrovascular adverse events, the efficacy of S-DAPT + P2Y12 was inferior to L-DAPT. ACS patients with particularly complex coronary lesions, especially those with diabetes, have a high risk of ischemia after PCI, and 10% of ischemic events still occur after Std-DAPT therapy. The optimal duration of DAPT has been controversial since the advent of DES. Initially in patients following rapamycin DES implantation, a minimum duration of 3 months of DAPT was recommended. DAPT was recommended for a minimum duration of 6 months after implantation of paclitaxel DESs. Afterwards, regardless of the type of DES, an extension of the DAPT duration to 1 year or more was recommended to reduce the risk of thrombosis as reported in some observational studies. Therefore, it is necessary for meta-analysis to comprehensively evaluate L-DAPT treatment regimen. Our study showed that L-DAPT had the greatest bleeding risk. In the outcome of MI, stent thrombosis, and cardiovascular and cerebrovascular adverse events, L-DAPT had the best efficacy. In the outcome of stroke and all-cause mortality, there was no statistical significance among 4 interventions. Some limitations of this study exist. First, there are many types of P2Y12 receptor inhibitors, and their efficacy varies greatly. Due to the limitations of the included studies, subgroup analysis cannot be performed, which may affect the reliability of the conclusion. Second, the subtypes, complications and intervention procedural of coronary heart disease in the included patients were different, which may affect the conclusions. Lastly, most of the included studies were not blinded, and there may be biases in implementation and measurement. Due to the influence of indirectness of evidence and sample size, it is hoped that there will be more RCTs in the future to verify the relationship between its efficacy and safety. 5. Conclusions The available evidence suggests that S-DAPT + P2Y12 has the lowest bleeding risk, while L-DAPT has the highest bleeding risk. In the outcome of MI, stent thrombosis, and cardiovascular and cerebrovascular adverse events, L-DAPT has the best efficacy. In the outcome of stroke and all-cause mortality, the 4 interventions were equally effective. Author contributions Conceptualization: Lin Luo, Shenglin Wang, Kai Tang. Data curation: Lin Luo, Shenglin Wang, Kai Tang, Liqiong Xu. Formal analysis: Lin Luo, Shenglin Wang, Kai Tang, Jianli Wu, Liqiong Xu. Funding acquisition: Shenglin Wang, Kai Tang, Jianli Wu, Liqiong Xu. Investigation: Shenglin Wang, Kai Tang, Tao Feng, Dejin Li. Methodology: Shenglin Wang, Kai Tang, Tao Feng, Jiuju Ran. Project administration: Shenglin Wang, Kai Tang, Xu Yang, Tao Feng, Li Zhang. Resources: Shenglin Wang, Kai Tang, Dan Wang, Dan Zhao. Software: Shenglin Wang, Kai Tang, Xu Yang, Dan Zhao. Supervision: Shenglin Wang, Kai Tang, Xu Yang, Debo Li. Validation: Lin Luo, Shenglin Wang, Kai Tang, Debo Li. Visualization: Lin Luo, Shenglin Wang, Kai Tang. Writing – original draft: Lin Luo. Writing – review & editing: Lin Luo. References [1] Stone GW, Moses JW, Ellis SG, et al. 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