# Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: Meta-analysis of randomized controlled trials

Yue FEI[1], Man Fung TSOI[2], Tommy Tsang CHEUNG[3], Bernard Man Yung CHEUNG[4]

[1] Division of Clinical Pharmacology and Therapeutics, Department of Medicine, The University of Hong Kong, Pokfulam, Hong Kong, China.
This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

[2] Division of Clinical Pharmacology and Therapeutics, Department of Medicine, The University of Hong Kong, Pokfulam, Hong Kong, China.
This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

[3] [a]Division of Clinical Pharmacology and Therapeutics, Department of Medicine, The University of Hong Kong, Pokfulam, Hong Kong, China.
[b] Partner State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Pokfulam, Hong Kong, China.
This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

[4] [a]Division of Clinical Pharmacology and Therapeutics, Department of Medicine, The University of Hong Kong, Pokfulam, Hong Kong, China.
[b] Partner State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Pokfulam, Hong Kong, China.
[c] Research Centre of Heart, Brain, Hormone and Healthy Aging, The University of Hong Kong, Pokfulam, Hong Kong, China.
[d] Institute of Cardiovascular Science and Medicine, The University of Hong Kong, Pokfulam, Hong Kong, China.

**Correspondence:**

Prof Bernard Cheung,

University Department of Medicine, Queen Mary Hospital,

102 Pokfulam Road, Hong Kong, China.

Email: mycheung@hku.hk

Tel: +85222554347

Fax: +85228186474

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## Abstract

**Objective** After implantation of drug-eluting stents (DES), patients usually receive 6-12 months of dual antiplatelet therapy (DAPT). However, the optimal duration of DAPT is controversial. Therefore, we performed a meta-analysis of randomized controlled trials to assess the risks and benefits of different DAPT durations.

**Methods** We searched the literature using MEDLINE, Scopus, EMBASE, ISI Web of Science, Cochrane Library, ClinicalTrials.gov and recent conference proceedings, and included those trials randomizing patients to receive different durations of DAPT after DES implantation and reporting frequencies of cardiovascular and bleeding events. Data from eleven trials were analyzed using RevMan.

**Results** Compared to 12-month DAPT treatment, extended DAPT significantly reduced the frequencies of myocardial infarction (OR 0.54 95%CI: 0.43-0.66; $p<0.00001$) and stent thrombosis (OR 0.36 95%CI: 0.24-0.55; $p<0.00001$), but the risks of major bleeding (OR 1.54 95%CI 1.22-1.96) and all-cause mortality (OR 1.43 95%CI 1.14-1.81) were substantially increased. There was no significant difference in stroke, cardiovascular mortality or repeat revascularization. Compared to short-term DAPT, 12-month DAPT or longer was associated with increased major bleeds (OR 1.98 95%CI: 1.26-3.11). No significant differences were found in the risk of other primary outcomes.

**Conclusion** 12-month DAPT appears to be a pragmatic compromise between preventing stent thrombosis and increasing bleeding risk. Patients at high bleeding risk should have shorter duration DAPT while those with low bleeding risk can be considered for DAPT beyond 12 months.

**Keywords** Drug-eluting stent; Dual antiplatelet therapy; Bleeding; Meta-analysis

## 1 Introduction

Drug-eluting stents (DES)[5] have been widely used in percutaneous coronary intervention in combination with medical treatment for relieving angina. Although DES cause less restenosis than bare metal stents, delayed endothelial healing may increase the risk of late stent thrombosis. To prevent this, dual antiplatelet therapy (DAPT)[6] is given for a certain period of time [1,2]. Current clinical guidelines recommend 6-12 months DAPT after DES implantation. However, they are largely based on observational data and small randomized controlled trials [3,4]. Recent trials with newer generation DES have suggested that short-term DAPT is safe, and can therefore replace 12 months' therapy [5-11]. Whether extended duration of DAPT over 12 months is superior has also been questioned; inconsistent results were found in clinical trials comparing different durations of DAPT [12-16]. In general, short-term DAPT (<12 months) is associated with a lower frequency of major bleeding, but early discontinuation of DAPT could increase the risk of late stent thrombosis [17-19]. A recent large randomized controlled trial showed a significant reduction of myocardial infarction and stent thrombosis with extended DAPT [15]. However, the potential superiority of extended DAPT duration has been challenged recently [16]. The optimal

[5] DES, drug-eluting stents.
[6] DAPT, dual antiplatelet therapy.

duration of DAPT is controversial, and needs to be re-examined in the light of recent trial evidence to guide clinical practice. Therefore, we conducted a meta-analysis comparing either short-term DAPT or extended DAPT with 12 months' therapy in patients receiving DES implantation, aiming to find out the efficacy and safety of different DAPT durations.

## 2 Methods

We searched the literature written in English on randomized trials comparing different DAPT durations after DES implantation up to 28 January 2016. MEDLINE, EMBASE, Scopus, ISI Web of Science, Cochrane Library, ClinicalTrials.gov, recent meta-analyses and cardiology conference abstracts were searched using the terms "dual antiplatelet therapy", "DAPT", "$P2Y_{12}$", "clopidogrel", "drug-eluting stent", "myocardial infarction", "stent thrombosis", and "bleeding". The inclusion criteria for this meta-analysis were: (1) a randomized controlled trial of different durations of DAPT; (2) participants had to be over 18 years of age; (3) the trial had to report the incidence of cardiovascular and bleeding events; and (4) patients receiving percutaneous coronary intervention with DES. Two investigators conducted the literature assessment, risk of bias assessment and data extraction independently; divergences were resolved to reach a consensus. Selected trials were stratified according to the durations of DAPT into three groups: (1) >12 months DAPT vs. 12 months DAPT; (2) >12 months DAPT vs. <12 months DAPT; (3) <12 months DAPT vs. 12 months DAPT.

Primary outcomes were frequencies of myocardial infarction, definite/probable stent thrombosis and stroke. Secondary outcomes were frequencies of cardiovascular mortality, all-cause mortality, major bleeding and repeat revascularization. Statistical analysis was performed using RevMan version 5.3.4. Odds ratios (OR) and 95% confidence intervals (95% CI) were used as summary statistics; summary OR for categorical variables were calculated using random effects model. Heterogeneity among studies was assessed by $I^2$ statistics. We also conducted sensitivity analysis to evaluate the effect of the inclusion or exclusion of trials. Potential publication bias and selection bias were examined using funnel plots, Begg's, Egger's and trim-and-fill tests. $P < 0.05$ was considered statistically significant. The reporting of meta-analysis was performed in compliance with the PRISMA Statement. The protocol for our meta-analysis has been registered on PROSPERO (http://www.crd.york.ac.uk/prospero, registration number: CRD42016037587).

## 3 Results

A summary of the screening and selection process is described in the PRISMA flowchart (Supplementary Fig.1). Eleven randomized controlled trials (n = 33520) were included in the meta-analysis. Their characteristics and results for risk of bias assessment are shown in Table 1, Supplementary Tables S1 and S2.

**Table 1 Summary of design for studies included in meta-analysis**

| Studies (ClinicalTrials.gov Identifier) | Number of participants | Treatment durations (months) | Stent type | DAPT drugs | Primary endpoints | Bleeding criteria |
|---|---|---|---|---|---|---|
| RESET 2012 [9] (NCT01145079) | 2,117 | 12 vs. 3 | SES[a], EES[b], E-ZES[b], R-ZES[b] | Clopidorgrel + ASA | Composite of cardiac death, MI, ST, ischemia-driven TVR or bleeding | TIMI |
| EXCELLENT 2012 [6] (NCT00698607) | 1,443 | 12 vs. 6 | SES[a], EES[b] | Clopidorgrel + ASA | Composite of cardiac death, MI or ischemia-driven TVR | TIMI |
| PRODIGY 2012 [5] (NCT00611286) | 1,970 | 24 vs. 6 | BMS, PES[a], ZES[b], EES[b] | Clopidorgrel + ASA | Death, MI or CVA | TIMI |
| OPTIMIZE 2013 [10] (NCT01113372) | 3,119 | 12 vs. 3 | E-ZES[b] | Clopidorgrel + ASA | Death, MI, CVA or major bleeding | REPLACE-2, GUSTO |

| | | | | | | |
|---|---|---|---|---|---|---|
| DES-LATE 2014 [13] (NCT01186146) | 5,045 | 24 vs. 12[c,d] | SES[a], PES[a]; ZES[b], EES[b] | Clopidorgrel + ASA | Composite of cardiac death, MI, stroke | TIMI |
| ARCTIC-Interruption 2014 [14] (NCT00827411) | 1,259 | 18–30 vs. 12[c] | DES | Thienopyridine + ASA | Composite of death, MI, ST, stoke or urgent TVR | STEEPLE |
| OPTIDUAL 2014 [16] (NCT00822536) | 1,385 | 30 vs. 12 | SES[a], PES[a]; ZES[b], EES[b] | Clopidorgrel + ASA | Composite of death, MI, stoke or major bleeding | ISTH |
| SECURITY 2014 [8] (NCT00944333) | 1,399 | 12 vs. 6 | DES[b] | Clopidorgrel + ASA | Composite of cardiac death, MI, stoke, ST, or bleeding | BARC |
| ITALIC 2014 [7] (NCT01476020) | 1,822 | 24 vs. 6[e] | EES[b] | Clopidorgrel, prasugrel or ticagrelor + ASA | Composite of death, MI, stoke, urgent TVR, stroke or major bleeding | TIMI |

| | | | | | | |
|---|---|---|---|---|---|---|
| ISAR-SAFE 2014 [11] (NCT00661206) | 4,000 | 12 vs. 6 | BES, SES[a], EES[b], ZES[b] | Clopidogrel + antiplatelet drug (not specified) | Composite of Death, MI, ST, stoke or major bleeding | TIMI |
| DAPT 2014 [15] (NCT00977938) | 9,961 | 30 vs. 12 | SES[a], PES[a]; ZES[b], EES[b]; BMS[f] | Thienopyridine + ASA | Composite of death, MI, stroke, ST or bleeding | BARC, GUSTO |

Abbreviations used in this table: ASA = aspirin; ST = stent thrombosis; MI = myocardial infraction; CVA = cerebrovascular accident; TVR = target vessel revascularization; DES = drug-eluting stent; BES = biolimus-eluting stent; BMS = bare metal stent; EES = everolimus-eluting stent; ZES = zotarolimus-eluting stent; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent; E-ZES = endeavor zotarolimus-eluting stent; R-ZES = resolute zotarolimus-eluting stent, DAPT = dual antiplatelet therapy.

[a] First-generation DES: PES SES;

[b] Second-generation DES: ZES EES.

[c] Patients in ARCTIC-Interruption and DES-LATE study had previous DAPT.

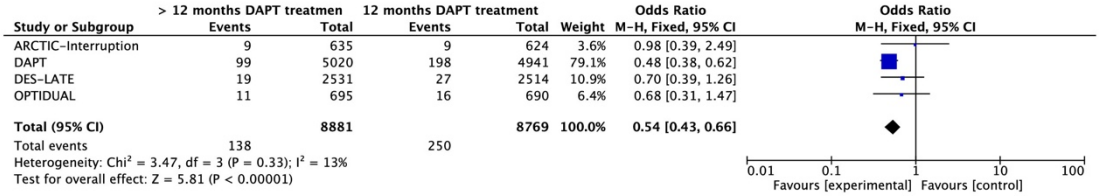
[d] DES-LATE study allowed patient enrolment with 1 year or longer after percutaneous coronary intervention.

[e] First year data of ITALIC study has been published. In the extended DAPT arm, 5.4% patients discontinued treatment before 24 months.

[f] DAPT study allowed enrolment of patients with BMS but they were not included in statistical analysis.

Four studies comparing extended DAPT (>12 months) versus 12 months' regimen and seven studies comparing short-term DAPT (<12 months) versus 12 months' regimen were included. Clopidogrel and aspirin was the most frequent drug combination in dual antiplatelet therapy. Compared to 12-month DAPT, extended DAPT beyond 12 months [13-16] yielded a very significant reduction in the frequencies of myocardial infarction (OR 0.54 95% CI: 0.43-0.66; $p < 0.00001$) (Fig. 1A) and definite/probable stent thrombosis (OR 0.36 95% CI: 0.24-0.55; $p < 0.00001$) (Fig. 2A). There was no significant difference in the risk of cardiovascular mortality (OR 1.03 95% CI: 0.75-1.40) (Supplementary Fig. S2A), stroke (OR 0.93 95% CI: 0.67-1.29) (Supplementary Fig. S3A) or repeat revascularization (OR 1.13 95% CI: 0.87-1.47) (Supplementary Fig. S4A). However, a significant increase in the risk of all-cause mortality (OR 1.43 95% CI 1.14-1.81, $p = 0.002$) (Fig. 3A) and major bleeding (OR 1.54 95% CI: 1.22 to 1.96, $p = 0.0004$) (Fig. 4A) was also observed.

**A)**




**B)**

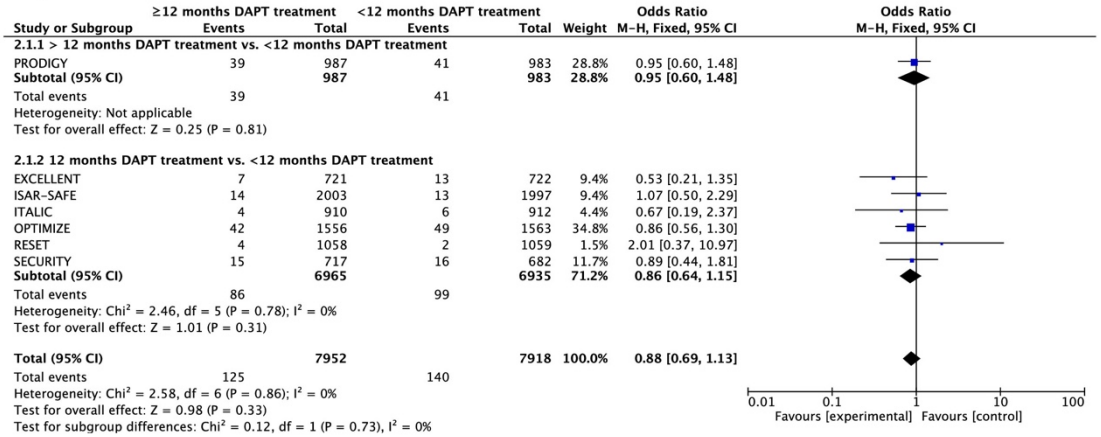
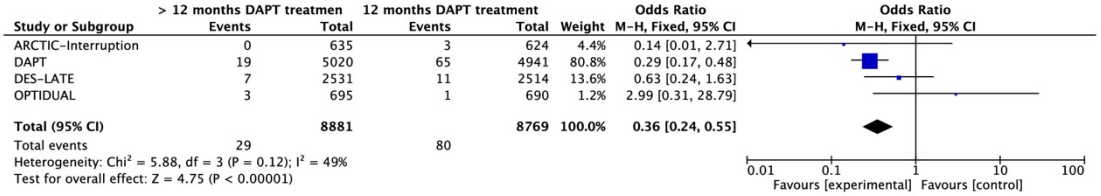



**Fig. 1** (A) The effect of extending the duration of dual antiplatelet therapy to more than 12 months on frequency of myocardial infarction in patients after drug-eluting stent implantation. (B) The effect of shortening the duration of dual antiplatelet therapy to less than 12 months on the frequency of myocardial infarction in patients after drug-eluting stent implantation.

**A)**




**B)**

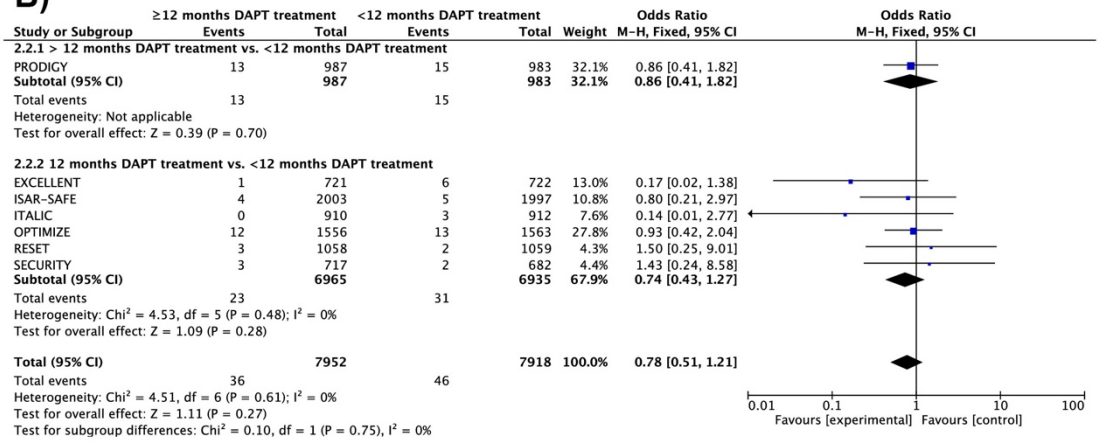
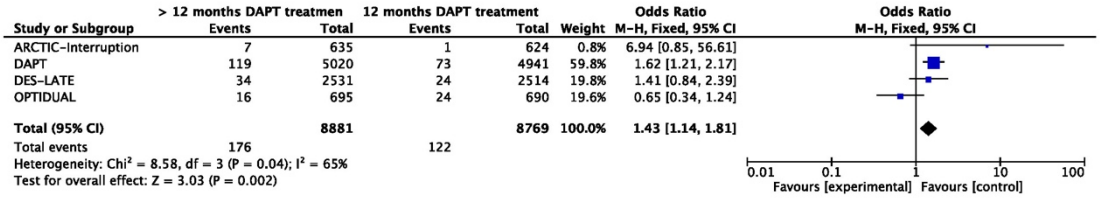



**Fig. 2** (A) The effect of extending the duration of dual antiplatelet therapy to more than 12 months on frequency of definite or probable stent thrombosis in patients after drug-eluting stent implantation. (B) The effect of shortening the duration of dual antiplatelet therapy to less than 12 months on the frequency of definite or probable stent thrombosis in patients after drug-eluting stent implantation.

**A)**




**B)**

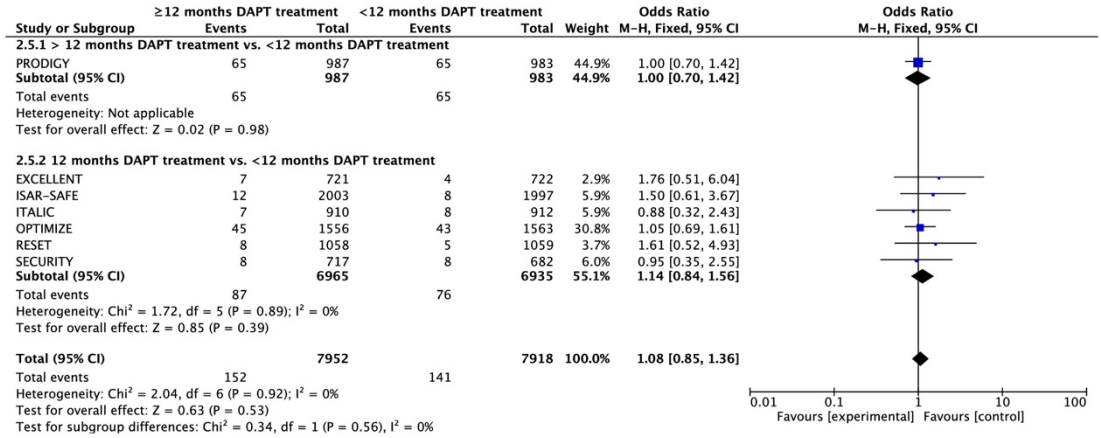
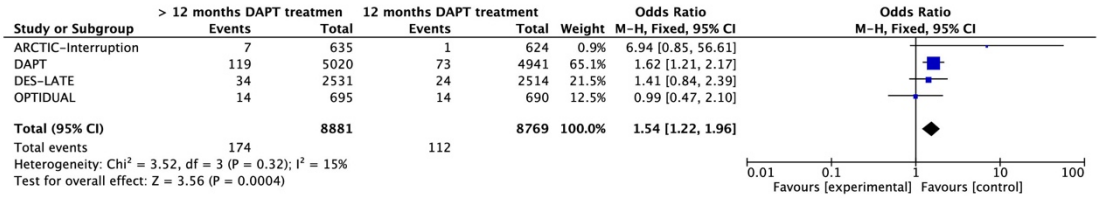



**Fig. 3** (A) The effect of extending the duration of dual antiplatelet therapy to more than 12 months on all-cause mortality rate in patients after drug-eluting stent implantation. (B) The effect of shortening the duration of dual antiplatelet therapy to less than 12 months on all-cause mortality rate in patients after drug-eluting stent implantation.

**A)**




**B)**

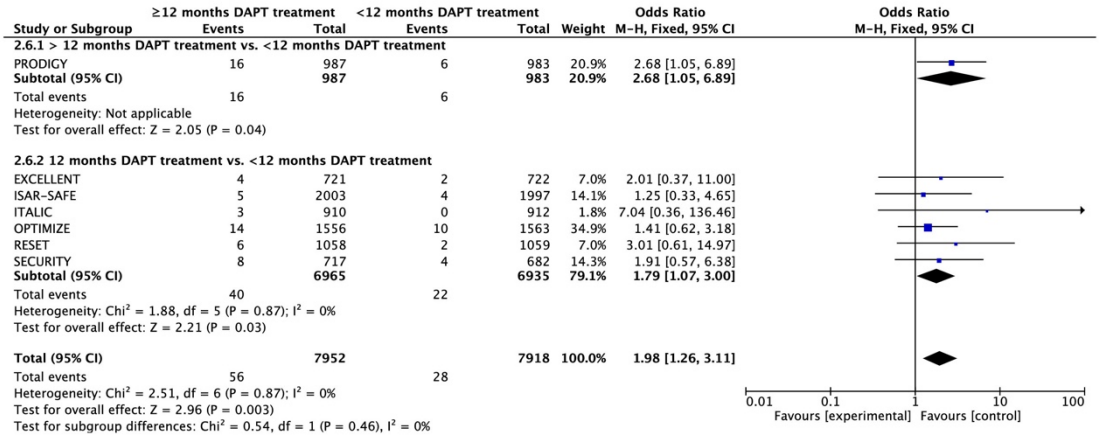



**Fig. 4** (A) The effect of extending the duration of dual antiplatelet therapy to more than 12 months on frequency of major bleeding in patients after drug-eluting stent implantation. (B) The effect of shortening the duration of dual antiplatelet therapy to less than 12 months on the frequency of major bleeding in patients after drug-eluting stent implantation.

Compared to short-term DAPT, 12 months' regimen [6-11] and extended DAPT [5] showed no significant alteration in the risk of myocardial infarction (OR 0.88 95% CI: 0.69-1.13) (Fig. 1B), definite or probable stent thrombosis (OR 0.78 95% CI: 0.51-1.21) (Fig. 2B), cardiovascular mortality (OR 0.98 95% CI: 0.72-1.35) (Supplementary Fig. S2B) stroke (OR 1.16 95% CI: 0.77-1.76) (Supplementary Fig. S3B), all-cause mortality (OR: 1.08; 95% CI:

0.85-1.36) (Fig. 3B), or repeat revascularization (OR 0.87 95% CI: 0.71-1.07) (Supplementary Fig. S4B), but the risk of major bleeding was significantly increased (OR 1.98 95% CI: 1.26-3.11, p = 0.003) (Fig. 4B).

No significant heterogeneity across the trials was found in the effect on stroke or repeat revascularization in all groups ($I^2 = 0$). In trials comparing short-term and ≥12 months DAPT, no significant heterogeneity was found in the effect on myocardial infarction, stent thrombosis, cardiovascular mortality, all-cause mortality, and major bleeding. In the trials comparing extended DAPT and 12-month DAPT, insignificant heterogeneity was found in the effect on myocardial infarction, cardiovascular mortality and major bleeding ($I^2$ = 13%, 17%, 15%; p = 0.33, 0.30, 0.32, respectively). Significant heterogeneity was found in the effect on stent thrombosis and all-cause mortality across the trials comparing extended DAPT versus 12-month DAPT ($I^2$ = 49% and 65% respectively). Therefore, sensitivity analysis comparing extended and 12-month DAPT was performed in both outcomes. OR and $I^2$ of sensitivity analysis showing the effect of including and excluding each trial are summarized in Supplementary Tables S3 and S4. The heterogeneity in the risk of all-cause mortality was due to the OPTIDUAL trial. $I^2$ could be reduced to 5% with a non-significant OR after excluding it. The heterogeneity in the risk of stent thrombosis was due to the DAPT and OPTIDUAL trials. Excluding either one of the studies resulted in a non-significant OR;

excluding the DAPT trial reduced $I^2$ to 28% while excluding the OPTIDUAL trial reduced $I^2$ to 18%. No significant publication bias or small study effects were suggested by the funnel plots (Supplementary Figs S5A–S11B, Supplementary Table S5).

## 4 Discussion

The present meta-analysis comparing the efficacy and safety of three different durations of DAPT in patients receiving DES implantation shows two main findings: (1) compared to 12-month DAPT, extended regimen reduced the incidence of myocardial infarction and definite/probable stent thrombosis, but at the price of more major bleeding as well as all-cause mortality, driven by non-cardiovascular deaths; (2) compared to 12-month DAPT, short-term therapy showed no significant difference in the frequency of stent thrombosis or myocardial infarction, but a reduction in the risk of major bleeding.

Short-term DAPT definitely reduces the number of major bleeds, and appears to have similar efficacy to 12-month regimen, especially with new-generation DES and modern interventional techniques. Our finding is consistent with previous meta-analyses comparing short-term and extended DAPT, confirming the non-inferiority of short-term regimen [20-23]. Previous registry studies and some trials had suggested the benefits of extended DAPT, but they were criticized for being underpowered due to the bias from observational data or relatively small sample size [24-26]. The DAPT trial [15] was the largest randomized

controlled trial comparing the efficacy and safety of extended versus 12-month DAPT. The decrease in myocardial infarction and stent thrombosis with extended DAPT was further confirmed in this trial. However, extended DAPT was not favored in previous meta-analyses without DAPT study, which showed no apparent ischemic benefits and no significant increase in all-cause mortality with extended DAPT, but a significant increase in the frequency of major bleeding [20-23].

As the most recent OPTIDUAL trial showed no significant difference in primary outcomes between 12 months' therapy and extended DAPT [16], it was of great interest to see if a meta-analysis would settle the issue of the optimal duration of DAPT and guide clinical decision. Our meta-analysis included both the DAPT trial and OPTIDUAL trial, and yielded new conclusions, in that extended DAPT showed extremely significant protection against myocardial infarction and stent thrombosis ($p < 0.00001$), but with a concurrent increase in major bleeding and all-cause, although not cardiovascular, mortality. The excess death was possibly driven by non-cardiovascular events including bleeding. Recent meta-analyses that included the DAPT trial also showed this trend [27-29]. For every stent thrombosis being prevented, about one major bleeds will occur [27,29]. This highlights the importance of balancing the risks and benefits in the individual patient before making any treatment decision. No decrease was found in the incidence of repeat revascularization. The reason

might be that it was not an endpoint in DAPT, the largest trial, so there was not enough statistical power for this outcome.

Our meta-analysis and other recent meta-analyses [27-29] have provided evidence that extended DAPT can significantly lower the incidence of myocardial infarction and stent thrombosis. There is no effective alternative to DAPT for preventing stent thrombosis after DES implantation, but there are ways of reducing bleeding risk, such as risk stratification, blood pressure control and prophylaxis with proton pump inhibitor. Therefore, extended DAPT could be considered for selected patients with low bleeding risk or those who tolerate it without gastrointestinal adverse effects. The results of our meta-analysis also suggested that the 12-month DAPT may be a reasonable compromise rather than the optimal duration. DAPT duration should be individualized for each patient after considering the thrombotic and bleeding risk. Duration of less than 12 months after DES implantation may be more widely offered, especially for those at high bleeding risks. Extended duration may be an option for low bleeding risk population.

Our meta-analysis was not without limitations. Inevitably, there were differences among the trials with regard to patient characteristics and definitions of primary endpoints and major bleeding [30]. Patients in the trials and their outcomes may not be representative of real-world patients because of better compliance and follow-up, and exclusions of high-risk

patients. ARCTIC-Interruption, DES-LATE and DAPT excluded patients with major bleeding in the first year therapy. Different $P2Y_{12}$ antagonists (clopidogrel, prasugrel, and ticagrelor) and different types of DES were used across and within clinical trials; all of these may differ in the benefit-risk ratio in the setting of DAPT after DES. There is scope for more clinical studies comparing different stents and different DAPT drug regimens. The relatively low heterogeneity across trials in the pooled analysis and consistent results in the sensitivity analyses suggested that our conclusions were robust. Nevertheless, the availability of patient-level data would allow a variety of subgroup analyses and add further insights.

## 5 Conclusions

This meta-analysis demonstrates the potential benefits in extending DAPT beyond 12 months in reducing the risk of myocardial infarction and stent thrombosis after DES implantation. However, there is a substantial increase in the risk of all-cause mortality and major bleeding. Short-term DAPT less than 12 months decreases the incidence of major bleeding without apparent alteration in other primary outcomes. Continuing DAPT beyond 12 months can be considered after a careful consideration of the risks and benefits in selected patients with low bleeding risk and very high ischemic risk. Physicians have to explain the increased risk of major bleeding to patients and take measures to minimize the risk. The increase in the rate of

all-cause mortality but not cardiovascular mortality resulted from extended DAPT requires further investigation.

**Author responsibility information**

FY designed the study, interpreted the data and wrote the first draft. FY and MFT performed statistical analysis. TTC and BMYC contributed to the interpretation of the data and the final version of the manuscript. All authors have read and approved the final version of the manuscript and its conclusions. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

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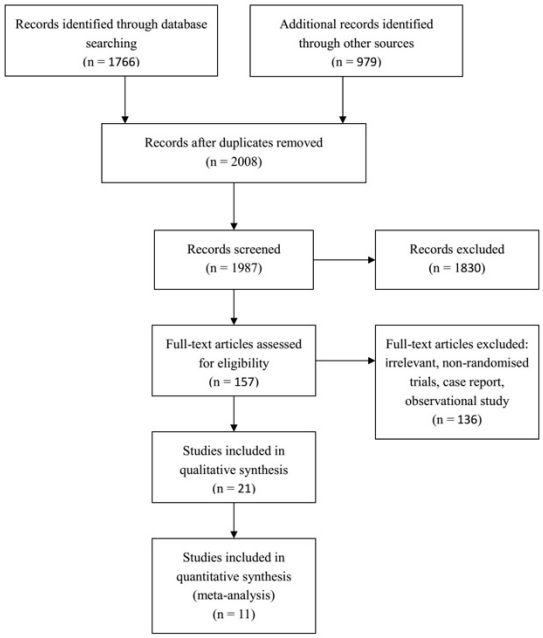
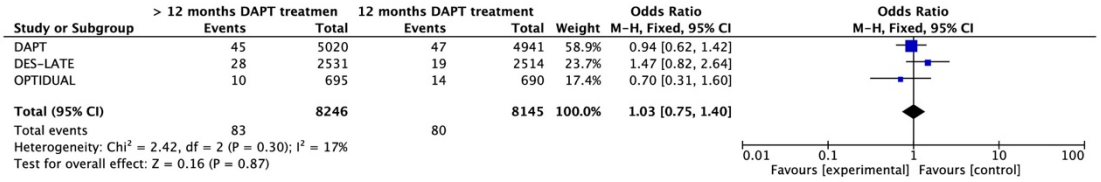
## E-component

The following are the supplementary data related to this article.

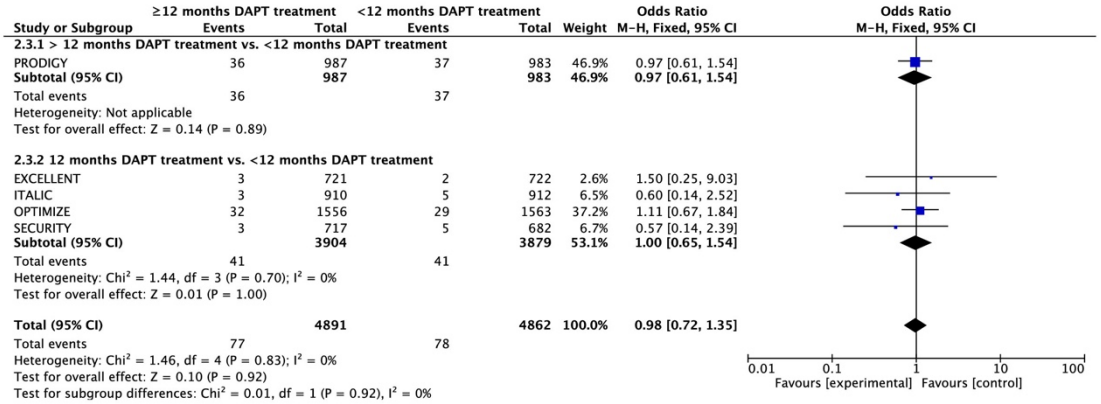



**Supplementary Fig. S1** Flow diagram of scientific literature search and study selection.

**A)**

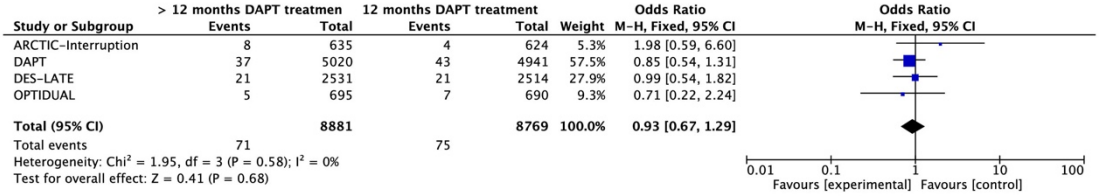



**B)**




**Supplementary Fig. S2** (A) The effect of extending the duration of dual antiplatelet therapy to more than 12 months on cardiovascular mortality rate in patients after drug-eluting stent implantation. (B) The effect of shortening the duration of dual antiplatelet therapy to less than 12 months on cardiovascular mortality rate in patients after drug-eluting stent implantation.

**A)**

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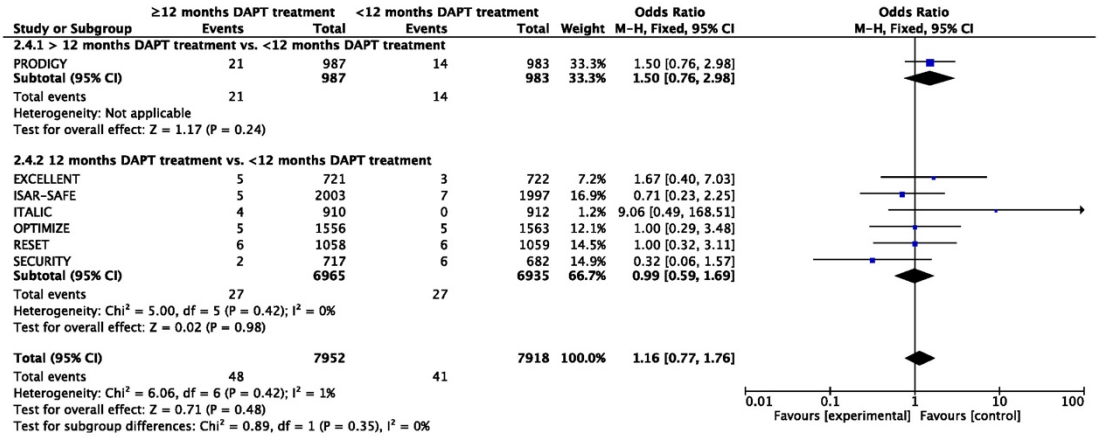
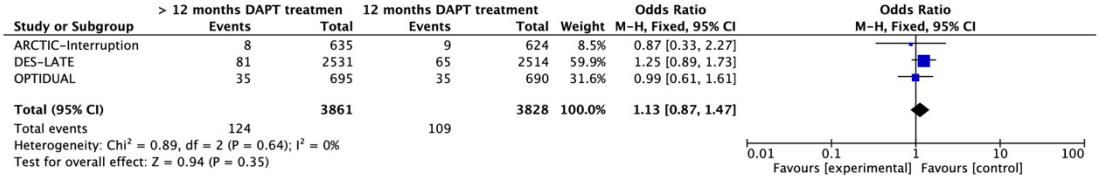



**Supplementary Fig. S3** (A) The effect of extending the duration of dual antiplatelet therapy to more than 12 months on frequency of stroke in patients after drug-eluting stent implantation. (B) The effect of shortening the duration of dual antiplatelet therapy to less than 12 months on frequency of stroke in patients after drug-eluting stent implantation.

**A)**

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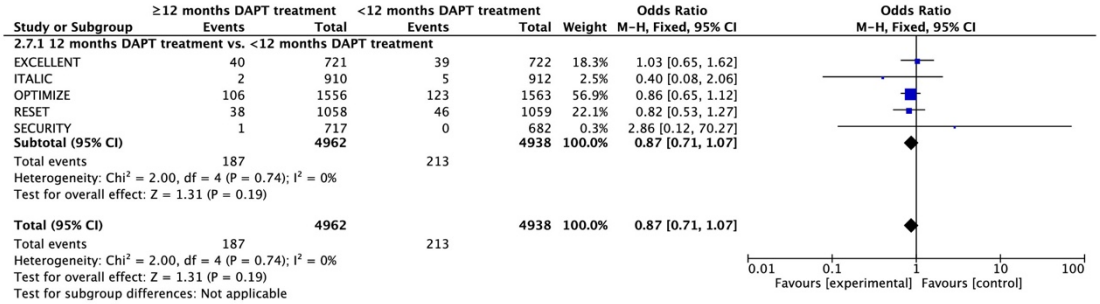
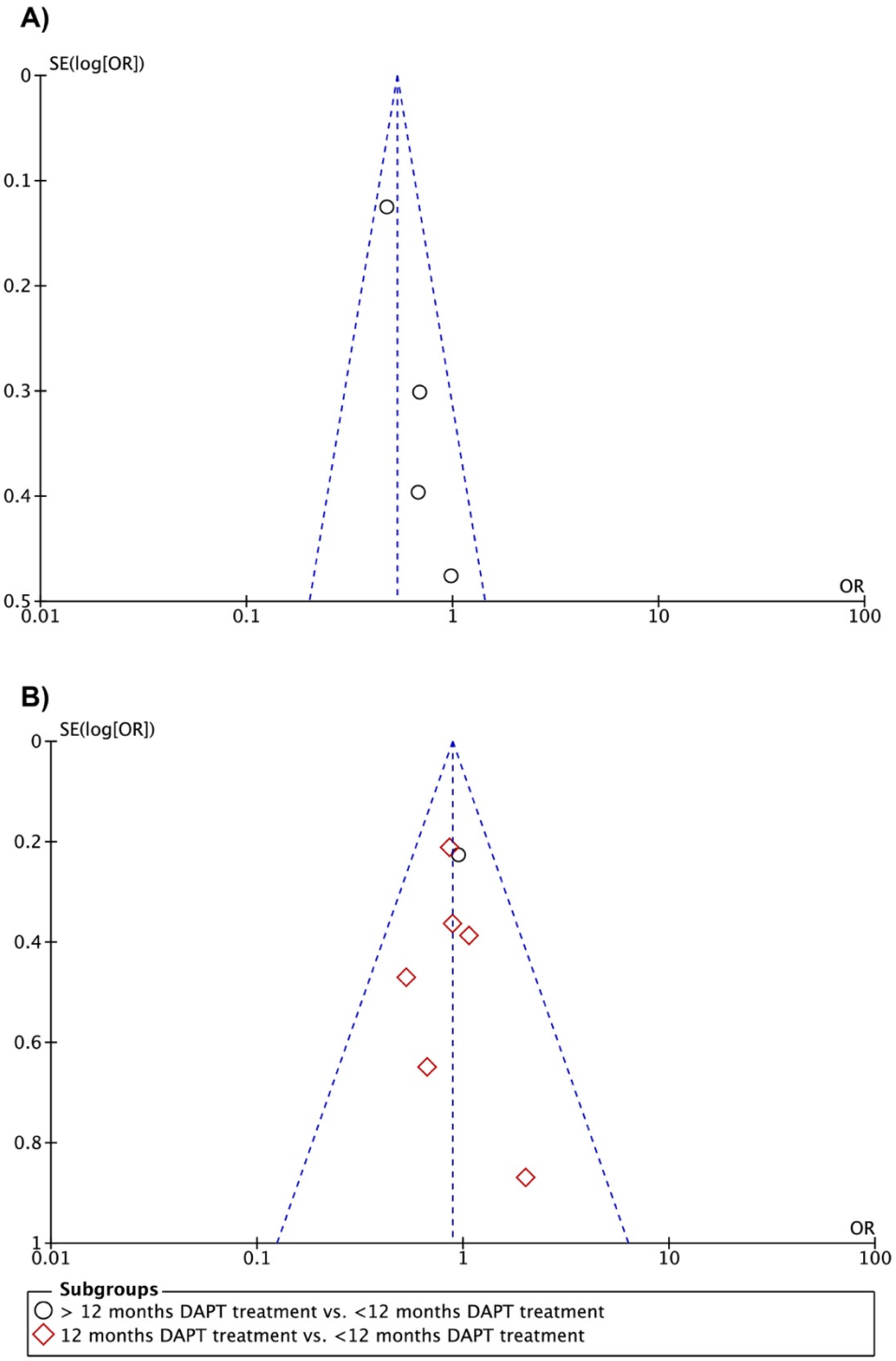
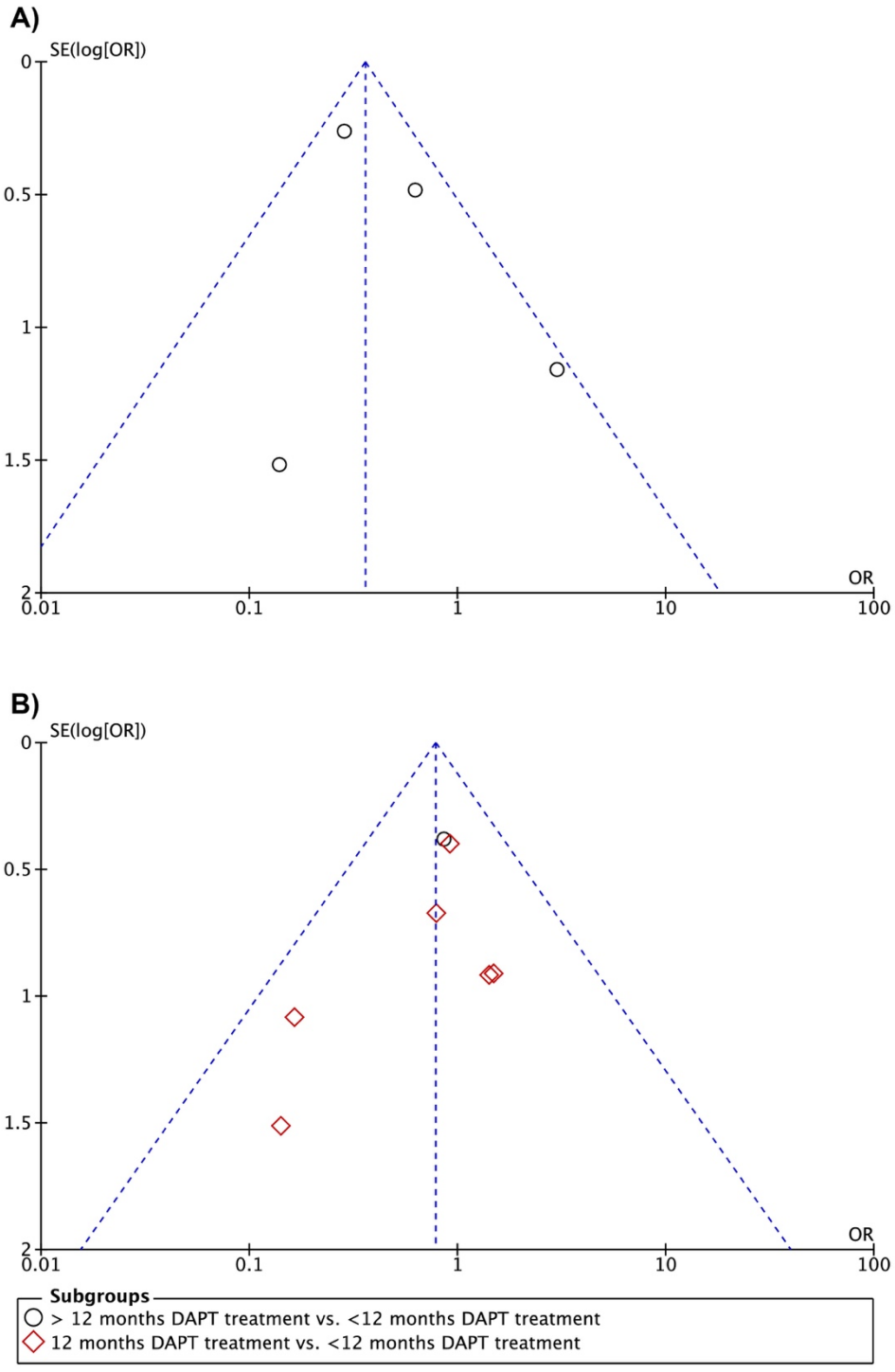


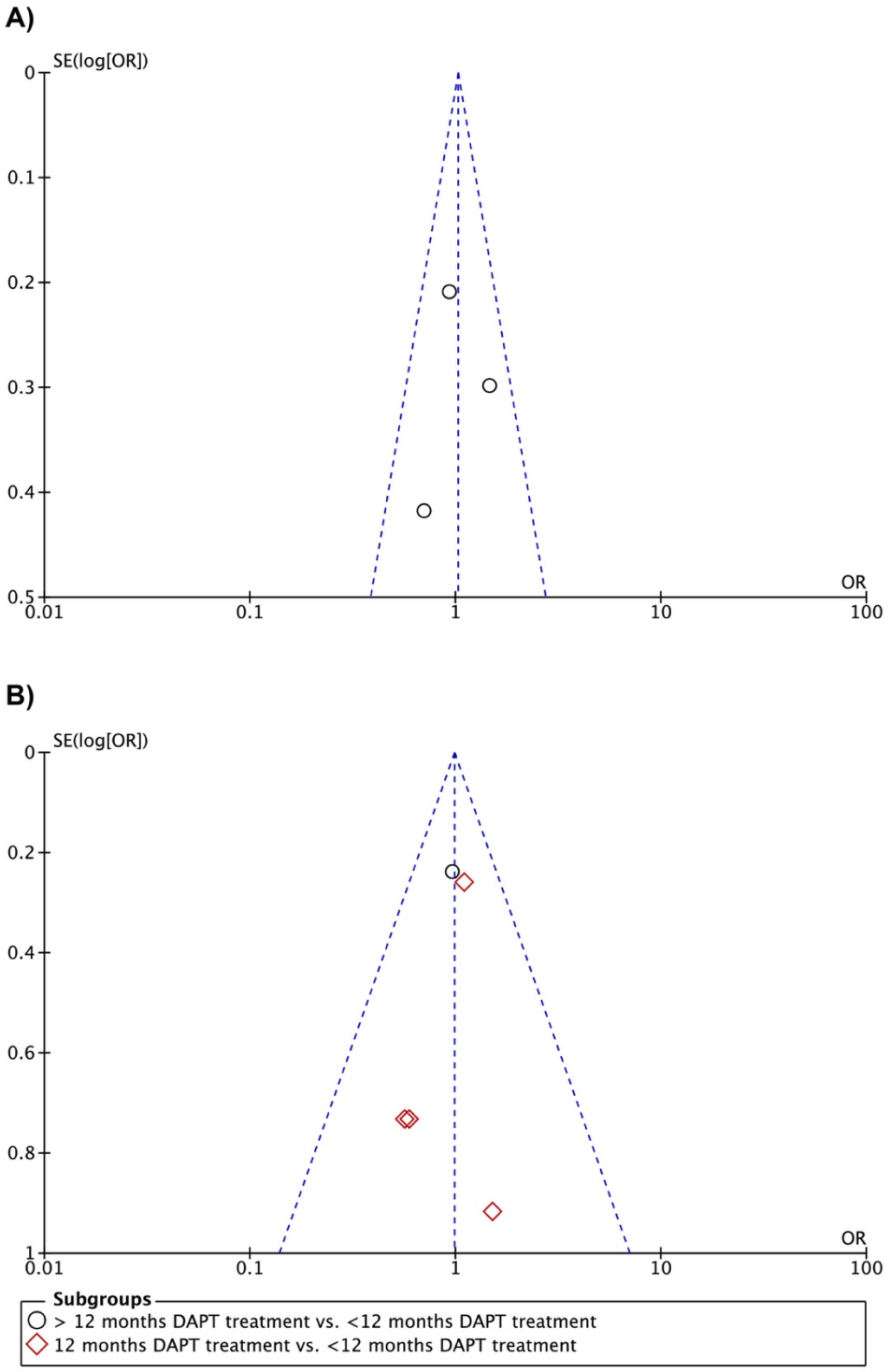

**Supplementary Fig. S4** (A) The effect of extending the duration of dual antiplatelet therapy to more than 12 months on frequency of repeat revascularization in patients after drug-eluting stent implantation. (B) The effect of shortening the duration of dual antiplatelet therapy to less than 12 months on frequency of repeat revascularization in patients after drug-eluting stent implantation.



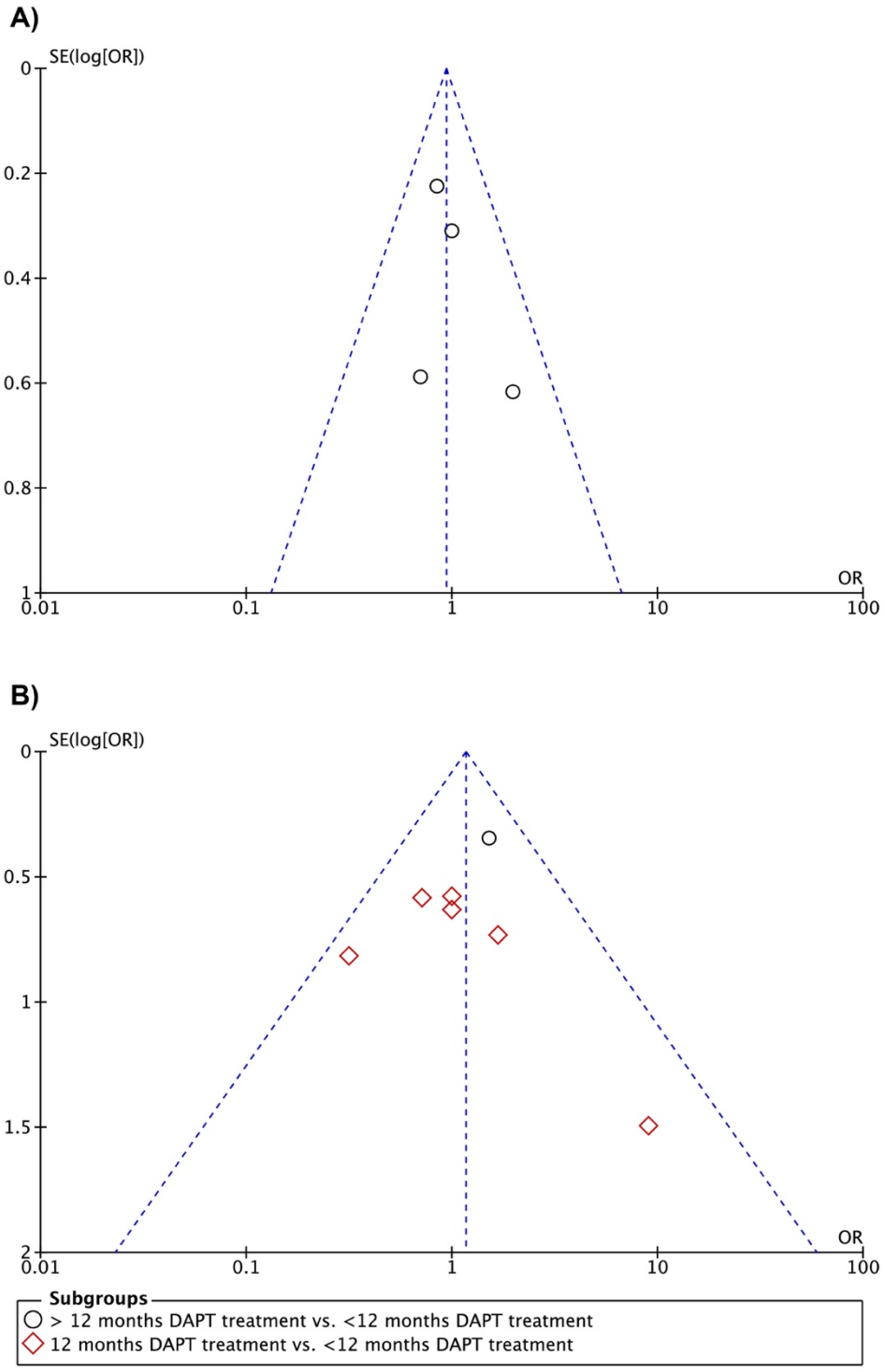

**Supplementary Fig. S5** (A) Funnel plot showing publication bias for the effect of prolonging the duration of dual antiplatelet therapy to more than 12 months on frequency of myocardial infarction in patients after drug-eluting stent implantation. (B) Funnel plot showing publication bias for the effect of shortening the duration of dual antiplatelet therapy to less than 12 months on frequency of myocardial infarction in patients after drug-eluting stent implantation.



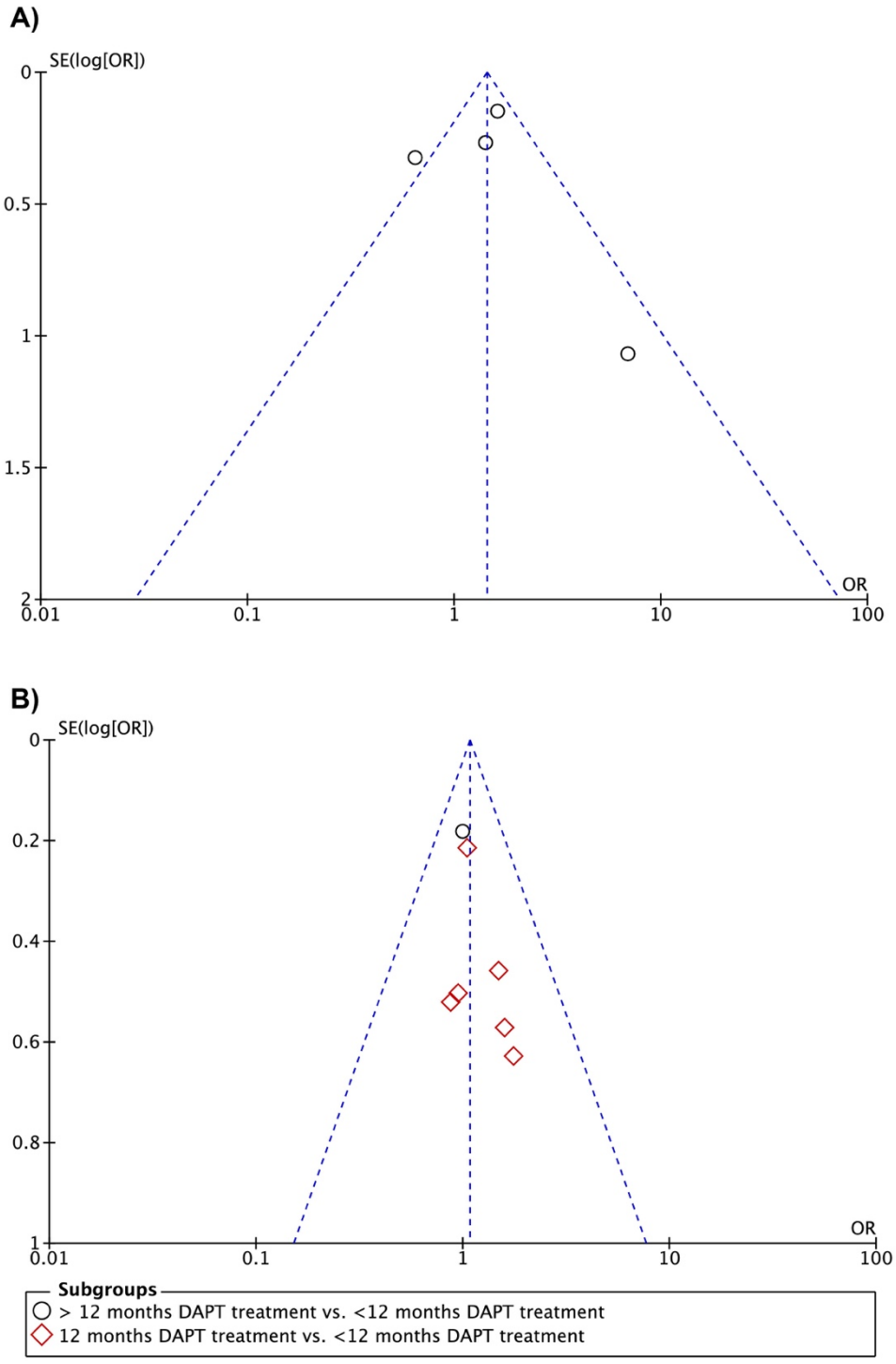

**Supplementary Fig. S6** (A) Funnel plot showing publication bias for the effect of prolonging the duration of dual antiplatelet therapy to more than 12 months on frequency of definite or probable stent thrombosis in patients after drug-eluting implantation. (B) Funnel plot showing publication bias for the effect of shortening the duration of dual antiplatelet therapy to less than 12 months on frequency of definite or probable stent thrombosis in patients after drug-eluting implantation.



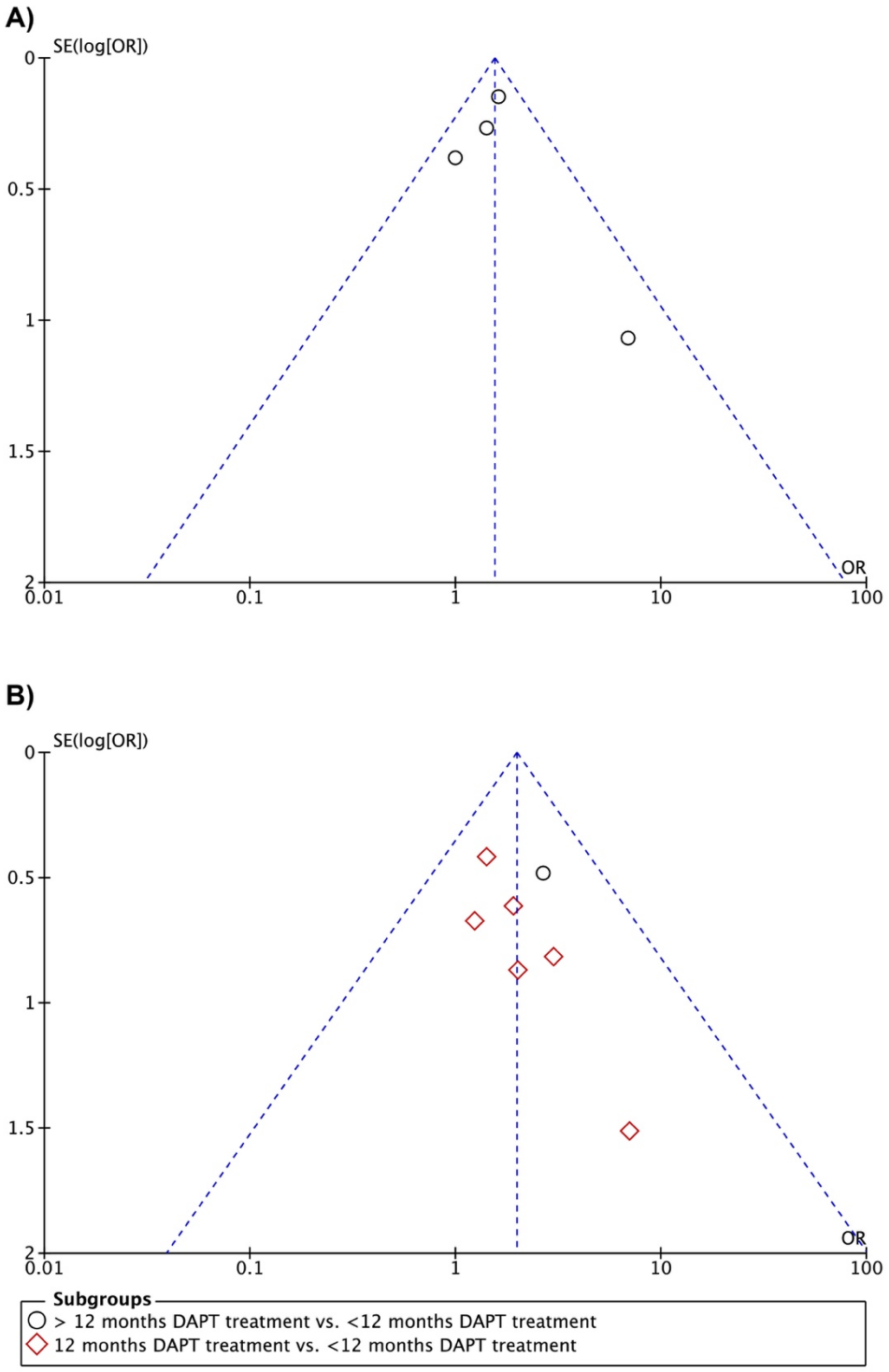

**Supplementary Fig. S7** (A) Funnel plot showing publication bias for the effect of prolonging the duration of dual antiplatelet therapy to more than 12 months on frequency of cardiovascular mortality in patients after drug-eluting stent implantation. (B) Funnel plot showing publication bias for the effect of prolonging the duration of dual antiplatelet therapy to more than 12 months on frequency of cardiovascular mortality in patients after drug-eluting stent implantation.



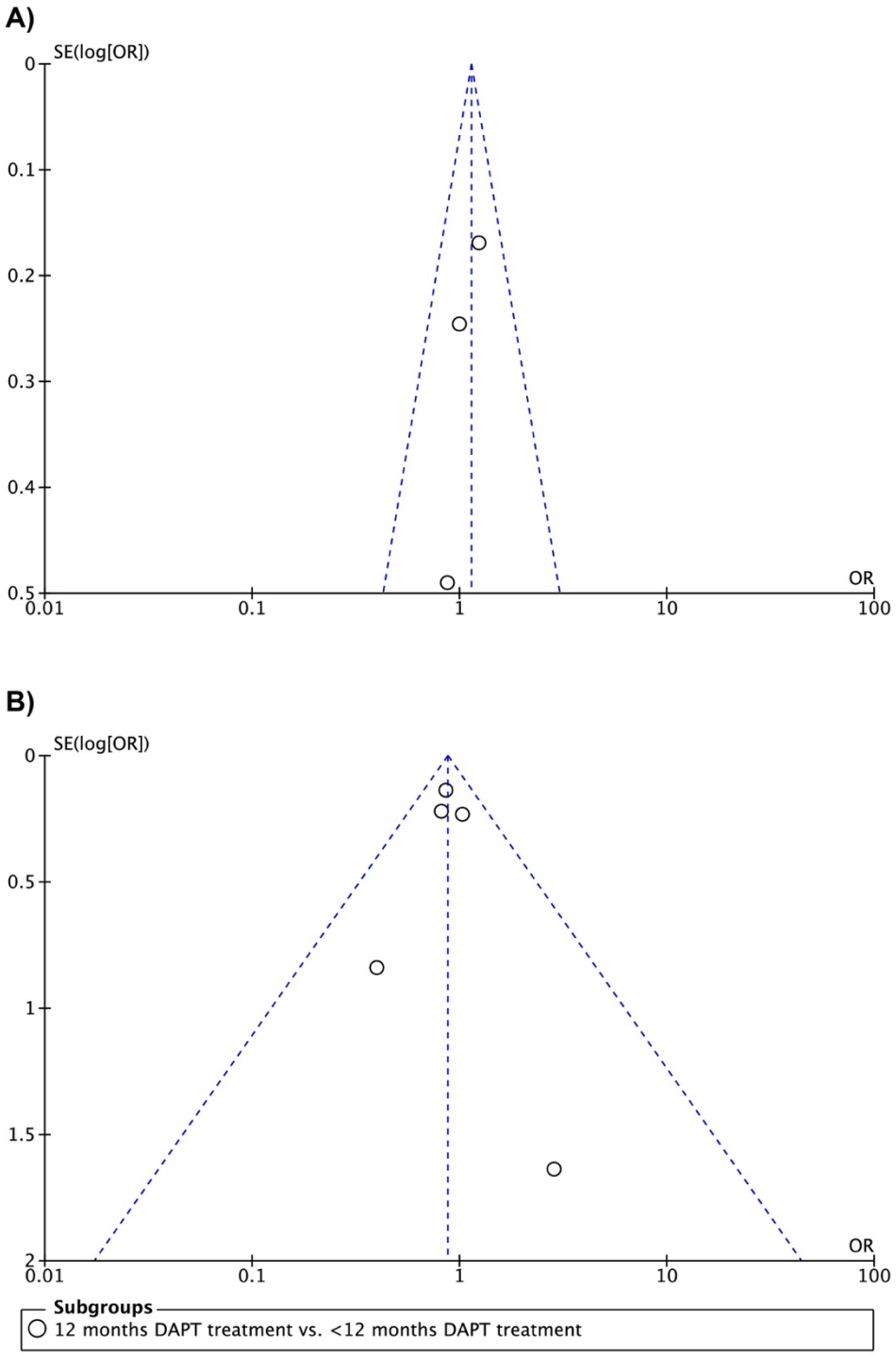

**Supplementary Fig. S8** (A) Funnel plot showing publication bias for the effect of prolonging the duration of dual antiplatelet therapy to more than 12 months on frequency of stroke in patients after drug-eluting stent implantation. (B) Funnel plot showing publication bias for the effect of shortening the duration of dual antiplatelet therapy to less than 12 months on frequency of stroke in patients after drug-eluting stent implantation.




**Supplementary Fig. S9** (A) Funnel plot showing publication bias for the effect of prolonging the duration of dual antiplatelet therapy to more than 12 months on all-cause mortality rate in patients after drug-eluting stent implantation. (B) Funnel plot showing publication bias for the effect of shortening the duration of dual antiplatelet therapy to less than 12 months on all-cause mortality rate in patients after drug-eluting stent implantation.




**Supplementary Fig. S10** (A) Funnel plot showing publication bias for the effect of prolonging the duration of dual antiplatelet therapy to more than 12 months on frequency of major bleeding in patients after drug-eluting stent implantation. (B) Funnel plot showing publication bias for the effect of shortening the duration of dual antiplatelet therapy to less than 12 months on frequency of major bleeding in patients after drug-eluting stent implantation.




**Supplementary Fig. S11** (A) Funnel plot showing publication bias for the effect of prolonging the duration of dual antiplatelet therapy to more than 12 months on frequency of repeat revascularization in patients after drug-eluting stent implantation. (B) Funnel plot showing publication bias for the effect of shortening the duration of dual antiplatelet therapy to less than 12 months on frequency of repeat revascularization in patients after drug-eluting stent implantation.

## Multimedia Component 1

**Supplementary Table S1. Summary for blinding, randomization and placebo control of studies**

| Study | Blinding | Randomization assignment | Presence of Placebo | Time of randomization |
|---|---|---|---|---|
| ARCTIC-Interruption | Open-labelled | Assignments were made by using an interactive voice response system with a 1:1 ratio stratified by study site. | No placebo control | 1 year after DES implantation |
| DAPT | Double-blinded | Assignments were made with a computer-generated randomization schedule and stratified according to the type of stent received (DES vs. BMS), hospital site, study sites. | With placebo control | 12 months after DES implantation |
| DES-LATE | Open-labelled | Assignments were made according to a pre-established, computer-generated randomization scheme on the basis of the site and the type of drug in the DES. | No placebo control | 12-18 months after DES implantation |
| EXCELLENT | Open-labelled | Randomization was performed with a Web-based response system and stratified by the study sites and lesion length. | No placebo control | Before DES implantation |

| | | | | |
|---|---|---|---|---|
| ISAR-SAFE | Double-blinded | Randomization was conducted in a 1:1 ratio via sealed opaque envelopes containing a computer-generated sequence with randomly permuted block lengths. | With placebo control | 6 months after DES implantation |
| ITALIC | Open-labelled | Assignments were made by centralized randomization using an interactive web-based system into ratio of 1:1. | No placebo control | 6 months after DES implantation |
| OPTIDUAL | Open-labelled | Randomization was stratified with interactive voice response system. | No placebo control | At 12±3 months after DES implantation |
| OPTIMIZE | Open-labelled | Randomization was conducted in a 1:1 ratio with the use of a block size of 8 and stratified by study sites. | No placebo control | Before DES implantation |
| PRODIGY | Open-labelled | Both randomizations for received stent type and DAPT duration were performed with a computer-generated sequence produced in coordinating center with random | No placebo control | Stent randomization: before DES implantation; Randomization of DAPT |

| | | | | |
|---|---|---|---|---|
| | | block size of 4, 8 and 12. | | duration: 30 ±5 days after DES implantation |
| RESET | Open-labelled | Randomization was performed by using an interactive web-based response system into a 1:1 ratio and stratified by study sites and clinical or lesion characteristics. | No placebo control | Before DES implantation |
| SECURITY | Open-labelled | Randomization was performed by electronic case report, according to a 1:1 scheme, balanced within the center by blocks of 4. | No placebo control | After DES implantation |

Abbreviations used in Supplementary Table S1: DAPT: Dual Anti-platelet therapy; DES: Drug-eluting stent; BMS: Bare-meta stent.

**Supplementary Table S2. Risk of Bias Reporting**

| Study | Sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome | Incomplete outcome data | Free from other bias |
|---|---|---|---|---|---|---|
| >12 months treatment vs. 12 months treatment | | | | | | |
| ARCTIC-Interruption | Low | Low | Unclear | Low | Low | Low |
| DES-LATE | Low | Low | Unclear | Low | Low | Low |
| OPTIDUAL | Low | Low | Unclear | Low | Low | Low |
| DAPT | Low | Low | Low | Low | Low | Low |
| >12 months treatment vs. <12 months treatment | | | | | | |
| PRODIGY | Low | Low | Unclear | Low | Low | Low |
| 12 months treatment vs. <12 months treatment | | | | | | |
| EXCELLENT | Low | Low | Unclear | Low | Low | Low |

| | | | | | | |
|---|---|---|---|---|---|---|
| RESET | Low | Low | Unclear | Low | Low | Low |
| OPTIMIZE | Low | Unclear | Unclear | Low | Low | Low |
| ISAR-SAFE | Low | Unclear | Low | Low | Low | Low |
| ITALIC | Low | Low | Low | Low | Low | Low |
| SECURITY | Low | Low | Unclear | Low | Low | Low |

Each domain of risk was assigned “Low” for low risk, “Unclear” for unclear risk and “High” for high risk.

**Supplementary Table S3. Sensitivity analysis of the effect of prolonging the duration of dual antiplatelet therapy to more than 12 months on frequency of all-cause mortality in patients after drug-eluting stent implantation**

| STUDY | Before excluding study | | | | | After excluding study | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OR | p-value | $I^2$ | $Chi^2$ | P-value | OR | p-value | $I^2$ | $Chi^2$ | P-value |
| ARCTIC-Interruption | 1.43 | 0.04 | 65% | 8.58 | 0.002 | 1.39 | 0.04 | 68% | 6.35 | 0.006 |
| DAPT | 1.43 | 0.04 | 65% | 8.58 | 0.002 | 1.16 | 0.04 | 69% | 6.40 | 0.46 |
| DES-LATE | 1.43 | 0.04 | 65% | 8.58 | 0.002 | 1.44 | 0.01 | 77% | 8.59 | 0.006 |
| OPTIDUAL | 1.43 | 0.04 | 65% | 8.58 | 0.002 | 1.62 | 0.35 | 5% | 2.11 | 0.0002 |

**Supplementary Table S4. Sensitivity analysis of the effect of prolonging the duration of dual antiplatelet therapy to more than 12 months on frequency of definite or probable stent thrombosis in patients after drug-eluting stent implantation**

| STUDY | Before excluding study | | | | | After excluding study | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OR | p-value | $I^2$ | $Chi^2$ | P-value | OR | p-value | $I^2$ | $Chi^2$ | P-value |
| ARCTIC-Interruption | 0.36 | 0.12 | 49% | 5.88 | <0.00001 | 0.37 | 0.06 | 63% | 5.48 | <0.00001 |
| DAPT | 0.36 | 0.12 | 49% | 5.88 | <0.00001 | 0.67 | 0.25 | 28% | 2.76 | 0.32 |
| DES-LATE | 0.36 | 0.12 | 49% | 5.88 | <0.00001 | 0.32 | 0.12 | 53% | 4.22 | <0.00001 |
| OPTIDUAL | 0.36 | 0.12 | 49% | 5.88 | <0.00001 | 0.33 | 0.30 | 18% | 2.44 | <0.00001 |

**Supplementary Table S5. Analysis of funnel plots in supplementary figures 2 to 6 to assess publication bias**

| | Begg's rank correlation test | | Egger's regression intercept | Trim and fill | | |
|---|---|---|---|---|---|---|
| Suppl. | | | | Before trimming | | After trimming |
| Figure | τ without continuity correction | p-value | p-value | Observed Point estimate (LL-UL) | Trimming direction | Adjusted Point estimate (LL-UL) |
| S2A | 0.667 | 0.174 | 0.029 | 0.563 (0.432-0.734) | Left | 0.508 (0.380-0.679) |
| S2B | 0.143 | 0.652 | 0.924 | 0.886 (0.693-1.132) | Not Applicable | 0.886 (0.693-1.132) |
| S3A | 0.333 | 0.497 | 0.480 | 0.464 (0.196-1.098) | Left | 0.353 (0.135-0.925) |
| S3B | -0.238 | 0.453 | 0.291 | 0.833 (0.531-1.306) | Not Applicable | 0.833 (0.531-1.306) |
| S4A | -0.333 | 0.602 | 0.925 | 1.027 (0.720-1.464) | Right | 1.105 (0.791-1.546) |
| S4B | -0.200 | 0.624 | 0.460 | 0.986 (0.716-1.358) | Right | 1.015 (0.742-1.388) |
| S5A | 0.667 | 0.174 | 0.499 | 0.930 (0.670-1.292) | Not Applicable | 0.930 (0.670-1.292) |

| | | | | | | |
|---|---|---|---|---|---|---|
| S5B | 0.048 | 0.881 | 0.958 | 1.135 (0.733-1.756) | Not Applicable | 1.135 (0.733-1.756) |
| S6A | 0.000 | 1.000 | 0.996 | 1.324 (0.792-2.215) | Left | 1.219 (0.716-2.075) |
| S6B | 0.428 | 0.176 | 0.159 | 1.076 (0.851-1.360) | Left | 1.056 (0.838-1.330) |
| S7A | 0.000 | 1.000 | 0.786 | 1.503 (1.121-2.015) | Not Applicable | 1.503 (1.121-2.015) |
| S7B | 0.429 | 0.176 | 0.204 | 1.919 (1.213-3.037) | Left | 1.778 (1.150-2.752) |
| S8A | -0.333 | 0.602 | 0.334 | 1.134 (0.872-1.474) | Right | 1.246 (0.996-1.558) |
| S8B | 0.000 | 1.000 | 0.957 | 0.874 (0.713-1.071) | Not Applicable | 0.874 (0.713-1.071) |

Abbreviations used in Supplementary Table S5: LL: Lower limit; Suppl. Figure: Supplementary Figure; UL: Upper limit