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Dual antiplatelet therapy after percutaneous coronary intervention in patients at high bleeding risk: A systematic review and meta-analysis

Yan Han et al., Short DAPT in HBR patients

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Abstract

Background: To date, it has not been ascertained whether shortening the duration of dual antiplatelet therapy (DAPT) can benefit high bleeding risk (HBR) patients. This systematic review and meta-analysis was performed to investigate the safety and efficacy of short (≤ 3 months) DAPT in HBR patients after percutaneous coronary intervention (PCI).

Methods: The PubMed, Embase, and Clinical Trials databases were searched from inception until November 2021 to identify studies that evaluated the safety and efficacy of short DAPT in HBR patients implanted with new-generation drug-eluting stents (DES). Primary endpoints included major bleeding, definite or probable stent thrombosis (ST), and myocardial infarction (MI), while secondary endpoints included all-cause death and ischemic stroke. Based on the fixed and random effect model, the risk ratio (RR) and 95% confidence interval of each endpoint were measured.

Results: Five observational studies and one randomized controlled trial were included, involving 15,432 HBR patients. Short DAPT for HBR patients undergoing PCI had a lower incidence of major bleeding in comparison with standard (> 3 months) DAPT (2.3% vs. 3.2%, RR 0.64 [0.44, 0.95], p = 0.03), while short DAPT was comparable to standard DAPT with regard to definite or probable ST (0.4% vs. 0.3%, RR 1.31 [0.77, 2.23], p = 0.32) and MI (2.4% vs. 2.0%, RR 1.17 [0.95, 1.45], p = 0.14).
Conclusions: Among HBR patients implanted with new-generation DES, short DAPT was associated with reduced risk of major bleeding without significantly increasing the risk of definite or probable ST and MI in comparison with standard DAPT.
Key words: duration, dual antiplatelet therapy, new-generation stent, high bleeding risk, percutaneous coronary intervention

Introduction

Dual antiplatelet therapy (DAPT), the mainstream antithrombotic strategy in patients undergoing percutaneous coronary intervention (PCI), has significantly reduced the risk of stent thrombosis (ST) since its introduction [1]. However, prolonged duration of DAPT and potent $P2Y_{12}$ inhibitors increase the risk of bleeding while improving ischemic protection [2, 3]. The adverse prognosis of bleeding complications after PCI is comparable to that of thrombotic events, and more than one-third of post-PCI patients showed clinical and comorbid conditions associated with an increased bleeding risk [4, 5]. Especially for elderly and more vulnerable populations, DAPT seems to be a double-edged sword with both benefit and damage. Therefore, how to balance the relationship between ischemic protection and hemorrhagic prevention has always been a topic of debate and research.

As the concept of precision medicine gains popularity, antithrombotic strategy after PCI tends to be more refined and individualized. According to the definition of the Academic Research Consortium for High Bleeding Risk (ARC-HBR), patients with high bleeding risk (HBR) have > 4% risk of major bleeding as defined by the Bleeding Academic Research Consortium (BARC) and > 1% risk of intracranial hemorrhage within one year after PCI and require more cautious and targeted antiplatelet therapy [6].

For HBR patients undergoing PCI with a drug-eluting stent (DES), the current international guidelines recommended shorter DAPT for 6 months in acute coronary syndrome and for 1–3 months in stable coronary syndrome, but the recommended strengths were weak or moderate (Class IIb or IIa) due to the lack of valid clinical data [7, 8]. Generally, the risk of ST is highest soon after DES implantation, and neointimal coverage of second- and later-generation DES could be completed within 3–6 months, which provided supporting evidence to shorten the duration of DAPT [9, 10]. However, there is a lack of sufficient studies to provide clinical validation for the optimal DAPT duration in HBR patients.

Recently, several studies have produced comparative data on the selection of DAPT duration for HBR patients undergoing PCI, and this study performed a meta-analysis of them to verify the efficacy and safety of short (≤ 3 months) DAPT duration for HBR patients undergoing PCI with DES, by comparing with standard (> 3 months) DAPT duration.

Methods

Literature search and selection criteria

This systematic review and meta-analysis was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [11]. Because of the statistical nature of these analyses, ethical committee approval and patient consent were not required.

Two investigators (Y. Han and X.H. Yuan) independently performed the literature search by using the PubMed, Embase, and Clinical Trials databases from inception to November 27, 2021. The search was carried out using relevant search terms: “percutaneous coronary intervention,” or “drug-eluting stents,” and “dual anti-platelet therapy” or “aspirin,” or “clopidogrel,” or “ticagrelor,” or “prasugrel,” or “$P2Y_{12}$ inhibitor” or “platelet aggregation inhibitors,” and “high bleeding risk” without language restrictions. References to all retrieved articles were reviewed to avoid potential literature omissions. Studies were excluded if they were duplicative or used a crossover design. Two independent investigators (Y. Han and X.H. Yuan) screened the articles from the three levels of title, abstract, and full-text, respectively, based on the prespecified

selection criteria. Conflicts between investigators were resolved by discussion or the opinion of a third author (L. Gao).

The inclusion criteria were as follows: (1) clinical studies with fully available data published in a peer-reviewed journal; (2) studies (or subgroup analysis of a study) that compared the short-term DAPT with standard-term DAPT in HBR patients undergoing PCI with DES; (3) follow-up duration ≥ 6 months after the index PCI; and (4) reported incidence of the primary efficacy and safety outcomes of interest. The exclusion criteria included review articles, case reports, and studies that did not report the baseline and outcome data for HBR patients.

Data extraction and quality assessment

The data of studies and patients was extracted and cross-checked by 2 reviewers (Y. Han and X.H. Yuan) independently, and any discrepancy was resolved through negotiation (L. Gao). We abstracted data on the characteristics of the trials, sample sizes, the baseline features and therapeutic options of the participants, such as stent type, $P2Y_{12}$ inhibitor type and the duration of DAPT, and the outcomes. The primary endpoints included major bleeding, definite or probable ST, and myocardial infarction (MI); the secondary endpoints included all-cause death and ischemic stroke.

Statistical analysis

Statistical analyses were conducted using Review Manager Version 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark). and Stata version 14.0 software (Statacorp LP, College Station, Texas, USA). I^2 statistics were used to evaluate the heterogeneity of the included studies. After excluding literature with high risk of bias, in case of substantial heterogeneity ($I^2 \geq 50\%$), a random effects model was used, otherwise a fixed effects model was applied to calculate the pooled risk ratios (RRs). The efficacy and safety in each study were reported as RRs with 95% confidence intervals (CIs). Sensitivity analysis was conducted using the “one-study removed” method to find the causes of heterogeneity. In addition, two other researchers (M.T. Jiang and Y. Fang) independently assessed the risk of bias in observational studies using the Newcastle-Ottawa Scale (NOS) [12], and in randomized controlled trials using the Cochrane Bias

Risk Tool [13]. The publication bias was assessed by funnel plot, and Begg's and Egger's tests. All estimated p values were two sided, with $p < 0.05$ considered significant.

Results

Search results and study characteristics

A total of 327 articles were retrieved from PubMed, Embase, and Clinical Trials, 47 of which were reviewed in detail. Finally, 5 articles met the inclusion and exclusion criteria [14–18], including one randomized controlled trial [15] and 5 observational studies [14, 16–18]. Among the observational studies, 2 studies reported the data of HBR patients in the subgroup cohorts [14, 17]. The flowchart of literature screening and study selection is exhibited in Figure 1. The included studies mainly applied the second- and new-generation DES; the key features of the studies are summarized in Table 1. All studies (or subgroups of studies) enrolled HBR patients, but the definition of HBR was not identical (**Suppl. Table S1**). Only 2 studies [14, 17] enrolled patients based on ARC-HBR criteria [19]. In 3 studies, patients in the short-term DAPT group received DAPT for one month, while in other studies, those in the corresponding group received DAPT for 3 months. For the standard DAPT group, patients received DAPT for 6, 12, and 15 months, respectively. In addition, DES types, $P2Y_{12}$ inhibitor types, and monotherapy strategies (dosage and type of medication) showed heterogeneity in the studies (Table 1).

In this study, major bleeding was defined as BARC 3 or 5 [6]. ST was reported as Academic Research Consortium definite or probable definition [20]. In total, BARC 3 or 5, definite or probable ST, MI, all-cause death, and ischemic stroke occurred in 405 (2.7%), 54 (0.4%), 340 (2.2%), 781 (5.1%), and 97 (6.0%) patients, respectively.

A total of 15,432 patients were divided into the short-DAPT group (7854 patients, 50.9%) and the standard-DAPT group (7578 patients, 49.1%). The baseline characteristics of patients and procedures are shown in Table 2 and **Supplementary Table S2**. Overall, the mean age of the patients ranged from 71.7 to 76.1 years, 64.3% of the patients were 75 years or older, 65.9% of the patients were men, 84.5% had hypertension, 37.6% had diabetes, and 21.6% were receiving concomitant oral anticoagulation. The patient demographic information was mostly well balanced across studies, including the distributions of age, sex, and presentation.

According to NOS, all 5 observational studies had scores ≥ 7, which were considered to be of high quality (Table 1). According to the Cochrane Bias Risk Tool, the MASTER DAPT trial had low risk of bias for random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and high risk of bias for blinding of participants and personnel.

The primary endpoints

The incidence of major bleeding was reflected in all studies (14,838 patients). In comparison with standard DAPT, short DAPT followed by aspirin or $P2Y_{12}$ inhibitor monotherapy in HBR patients after PCI with DES appeared to have lower risk of major bleeding (2.3% vs. 3.2%, RR 0.64 [0.44, 0.95], p = 0.03) (Fig. 2A, **Suppl. Table S3**). Of note, significant heterogeneity (p = 0.006, I^2 = 70%) across studies was observed, and the difference analyses above were performed based on random effect models. After removing the MASTER DAPT trial, which is the only randomized controlled trial among the 6 studies and the standard DAPT duration is diverse (14.1% of patients had less than 3 months duration of DAPT), the statistical difference in the incidence of major bleeding was consistent with the above, but the heterogeneity did not decrease (2.2% vs. 3.5%, RR 0.57 [0.35, 0.94], p = 0.03; I^2 = 73%, $p_{heterogeneity}$ = 0.006) (Fig. 3A).

Definite or probable ST as the primary efficacy endpoint was reported in each study (15,274 patients). Compared with standard DAPT, no significant difference (0.4% vs. 0.3%, RR 1.31 [0.77, 2.23], p = 0.32; I^2 = 0%, $p_{heterogeneity}$ = 0.89) was observed with short DAPT followed by aspirin or $P2Y_{12}$ inhibitors (Fig. 2B, **Suppl. Table S3**). After removing the MASTER DAPT trial, the sensitivity analysis (0.3% vs. 0.3%, RR 1.08 [0.55, 2.13], p = 0.82; I^2 = 0%, $p_{heterogeneity}$ = 0.93) further confirmed that the incidence of definite or probable ST was basically constant in either short or standard DAPT (Fig. 3B).

Myocardial infarction as the primary efficacy endpoint was reported in each study (15,274 patients), and there was no significant difference (2.4% vs. 2.0%, RR 1.17 [0.95, 1.45], p = 0.14; I^2 = 0%, $p_{heterogeneity}$ = 0.68) in the incidence of MI between short DAPT and standard DAPT (Fig. 2C, **Suppl. Table S3**). After removing the MASTER DAPT

trial, the sensitivity analysis (2.3% vs. 2.0%, RR 1.12 [0.87, 1.44], p = 0.39; I^2 = 0%, $p_{heterogeneity}$ = 0.61) was consistent with the above result (Fig. 3C).

The secondary endpoints

All-cause death was also reported in all 6 studies (15,274 patients), which showed no significant difference between the 2 DAPT strategies (3.0% vs. 2.9%, RR 1.05 [0.88, 1.27], p = 0.57; I^2 = 0%, $p_{heterogeneity}$ = 0.61) (Fig. 2D, **Suppl. Table S3**). This finding was consistent in sensitivity analysis after removing the MASTER DAPT trial (3.0% vs. 2.6%, RR 1.13 [0.90, 1.41], p = 0.29; I^2 = 0%, $p_{heterogeneity}$ = 0.64) (Fig. 3D).

Ischemic stroke, which was mentioned in the 6 studies (15,274 patients), did not differ statistically between the short-DAPT and standard-DAPT cohorts (0.7% vs. 0.5%, RR 1.37 [0.59, 3.17], p = 0.47) (Fig. 2E, **Suppl. Table S3**). Due to significant heterogeneities (p = 0.01, I^2 = 66%), random effects models were applied to estimate the overall effect of all studies. After removing the MASTER DAPT trial, the sensitivity analyses confirmed the result with a slight improvement in heterogeneity (0.8% vs. 0.5%, RR 1.73 [0.66, 4.52], p = 0.26; I^2 = 61%, $p_{heterogeneity}$ = 0.04) (Fig. 3E).

Subgroup analysis

Subgroup analyses were performed according to the different durations of short-term DAPT (1-month short DAPT and 3-month short DAPT), which showed no significant difference in the incidence of major bleeding, definite or probable ST, MI, and all-cause death between the two strategies. However, the results of ischemic stroke were inconsistent in the subgroup analyses; 3-month short DAPT was inferior to standard DAPT (1.0% vs. 0.3%, RR 3.18 [1.55, 6.51], p = 0.002) but 1-month short DAPT was not (0.4% vs. 0.7%, RR 0.61 [0.34, 1.09], p = 0.10) (**Suppl. Fig. S1**).

Publication bias

No significant evidence of publication bias (p = 0.452 and 0.143 for major bleeding, p = 1.000 and 0.614 for definite or probable ST, p = 0.707 and 0.882 for MI, p = 1.000 and 0.807 for all-cause death, p = 0.452 and 0.474 for ischemic stroke) were observed on

the basis of Begg's and Egger's tests, respectively. The funnel plots are shown in **Supplementary Figure S2**.

Discussion

In this meta-analysis based on 6 clinical studies with 15,432 patients, despite some heterogeneity, short DAPT followed by aspirin or $P2Y_{12}$ inhibitors for HBR patients undergoing PCI had a lower incidence of major bleeding in comparison with standard DAPT, while short DAPT was comparable to standard DAPT with regard to definite or probable ST and MI. The preliminary results suggest that it appears feasible to shorten the duration of DAPT before switching to monotherapy in HBR patients.

In the context of the increased risk of ST caused by delayed endothelialization, hypersensitivity reaction, and inflammation of first-generation DES [21], new-generation DES came into being. For the latter, the application of newer antiproliferative drugs with new polymers resulted in less inflammation [22], and the development of the cobalt-chromium platform implemented a thin stent structure to improve flexibility and deliverability [23, 24]. A recent meta-analysis showed that the risk for ST was higher with first-generation DES compared with new-generation DES when short-term DAPT was compared to long-term DAPT (p for interaction = 0.008) [25]. In the current study, almost all patients underwent PCI with new-generation DES, which may be the rationale for the reduced risk of major bleeding without an increase in the risk of MI and definite or probable ST after short DAPT.

Benefitting from the development of stent design, alloy, polymer, and drug, shortening DAPT to balance the risk of major bleeding and ischemic complications is increasingly recommended. To date, several studies [26–33] as well as meta-analyses of multiple studies [34–37] have explored the safety and efficacy of short DAPT after PCI with DES. The prior evidence mostly indicates that short DAPT enhances the prevention of bleeding events for the general population without compromising the protection against ischemic events. Furthermore, the TALOS-AMI study showed that a de-escalation strategy of DAPT from ticagrelor to clopidogrel after acute MI significantly reduced the risk of net clinical events for up to 12 months, mainly by reducing the bleeding events [38]. However, eligibility criteria of several studies have limited the

inclusion of HBR patients who may benefit more from a shorter duration or de-escalation of DAPT. In our study, the overall tests of the included studies confirmed the correlation between short DAPT and a reduced risk of major bleeding in the HBR population, with a reduction of approximately 29% compared with standard DAPT.

With concerns about the lack of enough evidence from high-risk populations and the controversy over existing trials, the current guidelines in Europe and the USA are cautious about using 1- to 3-month DAPT after PCI with DES [7, 8]. In 2 randomized controlled trials involving patients undergoing PCI with a zotarolimus-eluting stent [30, 31], 3-month short DAPT was noninferior to 12-month standard DAPT with regard to a composite endpoint of cardiovascular and bleeding events. However, the pooled analysis of the above 2 studies suggested that 3-month short DAPT was associated with an increased risk of definite or probable ST and MI in patients with acute coronary syndrome [39], similarly to another trial involving patients undergoing PCI with sirolimus-eluting stents [32]. In our meta-analysis, in terms of definite or probable ST, MI, all-cause death, and ischemic stroke, HBR patients undergoing PCI did not benefit more from standard DAPT than the short DAPT regimen.

There were limited data available to compare the efficacy and safety of 1-month DAPT with standard DAPT. The GLOBAL LEADERS study showed that 1-month DAPT followed by ticagrelor monotherapy was not superior to 12-month DAPT in terms of all-cause death and Q-wave MI [27]. Conversely, the STOPDAPT-2 study suggested a significantly reduced risk of a composite of cardiovascular and bleeding events associated with 1-month DAPT followed by clopidogrel monotherapy compared with 12-month DAPT [28]. The treatment effects of 1-month DAPT are controversial for all patients, but what about HBR patients? This meta-analysis included a subgroup analysis of different short DAPT regimens (1- and 3-month). Due to heterogeneity, a numerical rather than statistical reduction in the incidence of major bleeding was observed both in HBR patients with 1-month and 3-month DAPT. Nevertheless, the incidences of definite or probable ST and MI were comparable between 1- or 3-month DAPT and standard DAPT without heterogeneity. This further confirmed that 1-month DAPT could still provide effective ischemic protection for HBR patients after PCI, although the duration was further shortened. The impetus of shorter DAPT derives from the continuous

modification of stents and drugs, and our preliminary results provide more evidence of the effective ischemic protection of 1-month DAPT with the assistance of new-generation DES.

Limitations of the study

To our knowledge, this is the first review of the current available data of HBR patients receiving DAPT after PCI with the following limitations. First, in view of the few current studies on HBR patients, and only from the past 2 years, although the quantitative tests found low bias of publication, the potential bias remained. Second, certain clinical endpoints had high heterogeneity, which was mainly due to different study designs. Of the 6 included studies, only one qualified for a randomized controlled trial, and 3 had patients with standard DAPT from historical controls. In addition, inconsistency and complexity of HBR criteria, as well as the particularity of the population, added to the uneven patient enrollment. Third, subgroup analyses were only conducted for the duration of short DAPT (1- and 3-month). In fact, clopidogrel monotherapy is more likely to benefit patients after PCI with DES than acetylsalicylic acid monotherapy [40], but it was not possible to further verify whether the optimal DAPT duration was affected by monotherapy strategy due to the heterogeneity of antiplatelet therapies in this study. Finally, it is increasingly clear that short DAPT appears to be the optimal DAPT regimen in HBR patients, whereas the optimal regimen in patients at high ischemic risk remains “terra incognita” and warrants further investigation in the future.

Conclusions

This systematic review and meta-analysis indicated that, among HBR patients after implantation of new-generation stents, short DAPT was associated with reduced risk of major bleeding without significantly increasing the risk of MI or ST in comparison with standard DAPT. Given the limited available data of HBR patients, further research on larger sample sizes is needed to increase confidence in the findings.

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Conflict of interest: None declared

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Figure 1. Flow diagram of literature search.

Figure 2. Comparison of primary and secondary endpoints between short dual antiplatelet therapy (DAPT) and standard DAPT cohorts; **A.** Major bleeding; **B.** Definite or probable stent thrombosis; **C.** Myocardial infarction; **D.** All-cause death; **E.** Ischemic stroke.

Figure 3. Sensitivity analyses of primary and secondary endpoints; **A.** Major bleeding; **B.** Definite or probable stent thrombosis; **C.** Myocardial infarction; **D.** All-cause death; **E.** Ischemic stroke.

Table 1. Baseline characteristics of the included studies.

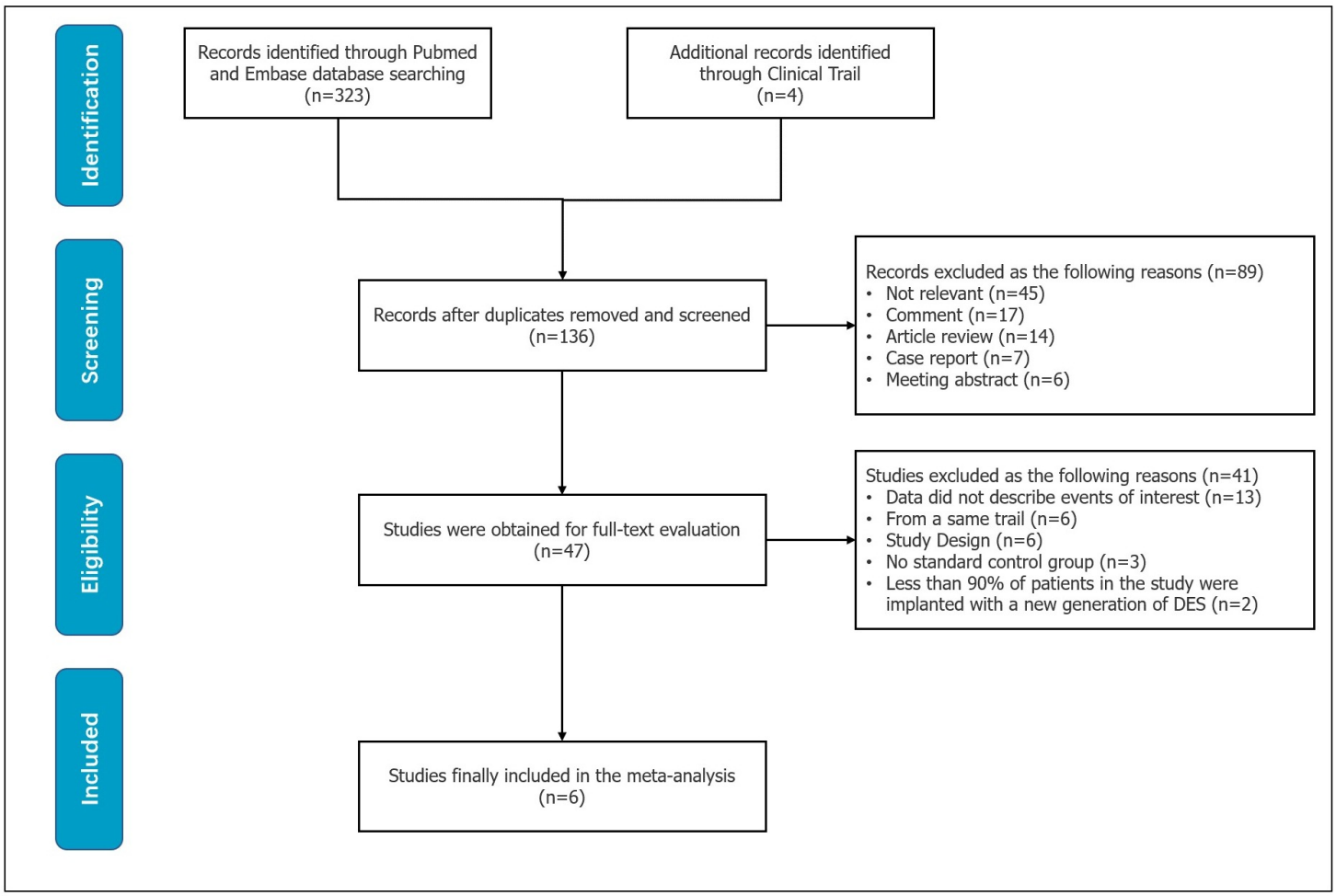
Study	Design	Publica-tion year	Comparison of DAPT duration [months]	HBR cohort size	Stent type	DAPT strategy	SAPT strategy	Follow up [months]	NOS score
XIENCE 28	Observational	2021	1 vs. 6	2803	Cobalt-chromium everolimus DES	ASA + $P2Y_{12}$ inhibitor	ASA	6	7
XIENCE 90	Observational	2021	3 vs. 12	2973	Cobalt-chromium everolimus DES	ASA + $P2Y_{12}$ inhibitor	ASA	12	7
TWILIGHT-HBR	Observational	2021	3 vs. 15	1064	DES	ASA + ticagrelor	Ticagrelor	12	8
EVOLVE Short DAPT	Observational	2021	3 vs. 12	2959	Bioabsorbable polymer-coated everolimus DES	ASA + $P2Y_{12}$ inhibitor	ASA	12	7
MASTER DAPT	Randomized Control Trial	2021	1 vs. 6	4579	Biodegradable polymer sirolimus DES	ASA + $P2Y_{12}$ inhibitor	ASA and $P2Y_{12}$ inhibitor (53.9% clopidogrel)	12	NA
STOPDAPT-2	Observational	2019	1 vs. 12	1054	Cobalt-chromium everolimus DES	ASA + $P2Y_{12}$ inhibitor	$P2Y_{12}$ inhibitor (clopidogrel)	12	8

ASA — acetylsalicylic acid; DAPT — dual antiplatelet therapy; DES — drug-eluting stent; HBR — high bleeding risk; NOS — Newcastle-Ottawa scale; SAPT — single antiplatelet therapy

Clinical characteristics	XIENCE 28	XIENCE 90	TWILIGHT-HBR	EVOLVE Short DAPT	MASTER DAPT	STOPDAPT-2
Sample size	1392/1411	1693/1280	521/543	1457/1502	2295/2284	496/558
Age (mean)	75.97/72.56	75.25/72.70	71.7/72.0	75.2/74.8	76.1/76.0	75.8/75.8
≥ 75 years of age (%)	68.2/54.9	66.5/55.3	50.9/48.1	67.5/66.5	68.9/68.8	67.1/67.2
Men (%)	67.5/59.2	64.8/59.1	67.9/65.6	65.2/64.9	69.3/69.2	70.0/69.7
BMI [kg/mm^2]	28.32/29.53	30.13/29.52	28.5/28.8	29.1/29.1	27.25/27.44	23.5/23.5
Hypertension (%)	84.7/91.5	89.5/91.7	81.4/81.2	88.2/87.9	76.9/78.2	79.2/82.8
Diabetes (%)	37.0/42.3	39.2/42.9	45.9/48.6	32.9/33.0	32.9/34.3	45.6/43.0
Anemia (%)	14.4/16.2	15.0/16.3	67.8/67.2	–	–	–
Dyslipidemia (%)	67.5/90.7	82.8/90.7	65.6/68.3	–	67.2/68.1	73.2/72.0
Current smoker (%)	–	–	10.0/10.7	7.6/8.2	10.0/8.1	16.3/11.5
Previous MI (%)	16.4/30.3	15.8/30.1	28.0/29.5	20.6/21.5	18.9/18.8	16.9/14.3
Previous PCI (%)	28.0/37.9	30.7/38.8	44.5/46.2	–	25.9/26.0	45.2/43.0
Previous CABG (%)	8.0/14.8	12.1/14.1	15.5/16.2	13.6/13.9	7.4/7.5	1.8/4.7
Chronic kidney disease (%)	47.4/44.0	40.2/44.3	59.1/62.7	–	18.2/20.1	74.8/69.9
Peripheral vascular disease (%)	–	–	12.7/12.2	12.9/12.8	10.6/10.6	12.9/12.5
Previous bleeding (%)[a]	3.3/2.6	2.9/2.7	5.2/5.0	–	7.2/6.8	3.4/4.5
Oral anticoagulants (%)[b]	44.3/13.0	41.6/12.5	NA	NA	37.0/35.9	NA
Acute coronary syndrome	34.1/35.8	34.7/33.9	61.8/62.4	26.2/22.6	–	28.8/29.8
Chronic coronary syndrome	65.9/64.2	65.3/66.1	38.2/37.6	73.8/77.4	–	71.2/70.2

Data are shown as groups with short/standard dual antiplatelet therapy. [a]In XIENCE 28, XIENCE 90 and TWILIGHT-HBR trials, only previous major bleeding was reported in previous bleeding records; [b]In TWILIGHT-HBR, EVOLVE Short DAPT and STOPDAPT-2 studies, patients receiving oral anticoagulants were not included; BMI — body mass index; CABG — coronary artery bypass graft; MI — myocardial infarction; PCI — percutaneous coronary intervention

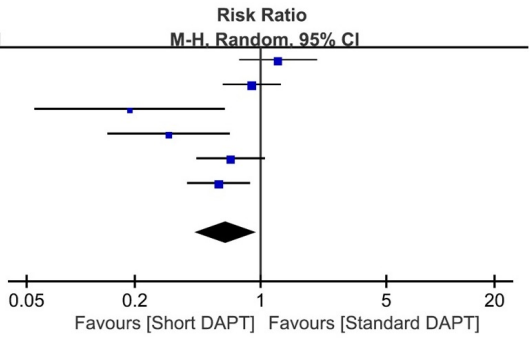
Table 2. Baseline characteristics of the included participates.


Identification
Screening
Eligibility
Included
Records identified through Pubmed and Embase database searching (n=323)
Additional records identified through Clinical Trail (n=4)
Records after duplicates removed and screened (n=136)
Records excluded as the following reasons (n=89)
• Not relevant (n=45)
• Comment (n=17)
• Article review (n=14)
• Case report (n=7)
• Meeting abstract (n=6)
Studies were obtained for full-text evaluation (n=47)
Studies excluded as the following reasons (n=41)
• Data did not describe events of interest (n=13)
• From a same trail (n=6)
• Study Design (n=6)
• No standard control group (n=3)
• Less than 90% of patients in the study were implanted with a new generation of DES (n=2)
Studies finally included in the meta-analysis (n=6)

A

Study or Subgroup	Short DAPT Events	Short DAPT Total	Standard DAPT Events	Standard DAPT Total	Weight	Risk Ratio M-H, Random, 95% CI
EVOLVE Short DAPT 2021	30	1032	31	1333	18.4%	1.25 [0.76, 2.05]
MASTER DAPT 2021	53	2295	59	2284	21.2%	0.89 [0.62, 1.29]
STOPDAPT-2 2019	3	496	18	558	7.4%	0.19 [0.06, 0.63]
TWILIGHT -HBR 2021	8	521	27	543	12.8%	0.31 [0.14, 0.67]
XIENCE 28 2021	33	1392	49	1411	19.7%	0.68 [0.44, 1.05]
XIENCE 90 2021	41	1693	53	1280	20.5%	0.58 [0.39, 0.87]
Total (95% CI)		**7429**		**7409**	**100.0%**	**0.64 [0.44, 0.95]**
Total events	168		237			

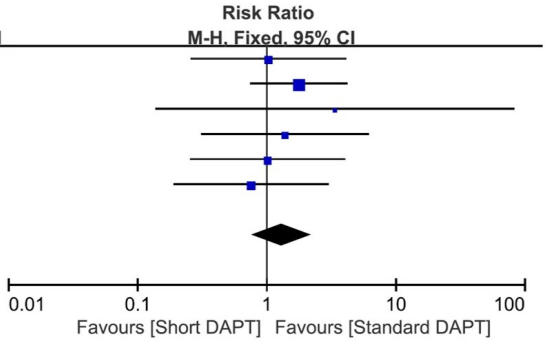
Heterogeneity: Tau² = 0.15; Chi² = 16.51, df = 5 (P = 0.006); I² = 70%
Test for overall effect: Z = 2.22 (P = 0.03)



B

Study or Subgroup	Short DAPT Events	Short DAPT Total	Standard DAPT Events	Standard DAPT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
EVOLVE Short DAPT 2021	4	1457	4	1502	16.5%	1.03 [0.26, 4.11]
MASTER DAPT 2021	14	2204	8	2230	33.4%	1.77 [0.74, 4.21]
STOPDAPT-2 2019	1	496	0	558	2.0%	3.37 [0.14, 82.64]
TWILIGHT -HBR 2021	4	516	3	535	12.4%	1.38 [0.31, 6.15]
XIENCE 28 2021	4	1392	4	1411	16.7%	1.01 [0.25, 4.05]
XIENCE 90 2021	4	1693	4	1280	19.1%	0.76 [0.19, 3.02]
Total (95% CI)		**7758**		**7516**	**100.0%**	**1.31 [0.77, 2.23]**
Total events	31		23			

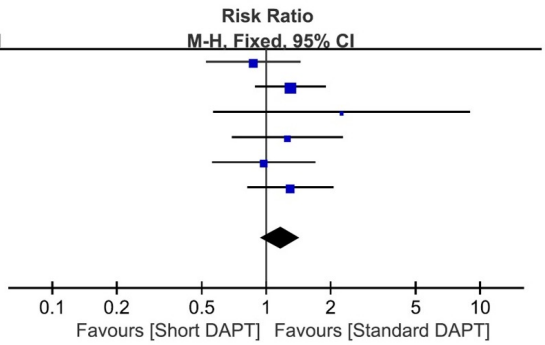
Heterogeneity: Chi² = 1.66, df = 5 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)



C

Study or Subgroup	Short DAPT Events	Short DAPT Total	Standard DAPT Events	Standard DAPT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
EVOLVE Short DAPT 2021	27	1457	32	1502	20.3%	0.87 [0.52, 1.44]
MASTER DAPT 2021	59	2204	46	2230	29.4%	1.30 [0.89, 1.90]
STOPDAPT-2 2019	6	496	3	558	1.8%	2.25 [0.57, 8.95]
TWILIGHT -HBR 2021	23	516	19	535	12.0%	1.26 [0.69, 2.28]
XIENCE 28 2021	24	1392	25	1411	16.0%	0.97 [0.56, 1.70]
XIENCE 90 2021	48	1693	28	1280	20.5%	1.30 [0.82, 2.05]
Total (95% CI)		**7758**		**7516**	**100.0%**	**1.17 [0.95, 1.45]**
Total events	187		153			

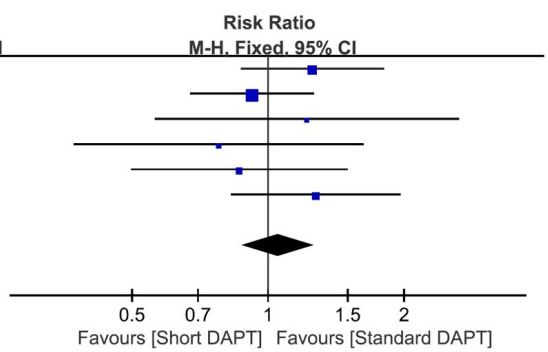
Heterogeneity: Chi² = 3.13, df = 5 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)



D

Study or Subgroup	Short DAPT Events	Short DAPT Total	Standard DAPT Events	Standard DAPT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
EVOLVE Short DAPT 2021	62	1457	51	1502	22.9%	1.25 [0.87, 1.80]
MASTER DAPT 2021	72	2204	79	2230	35.9%	0.92 [0.67, 1.26]
STOPDAPT-2 2019	13	496	12	558	5.2%	1.22 [0.56, 2.65]
TWILIGHT -HBR 2021	12	516	16	535	7.2%	0.78 [0.37, 1.63]
XIENCE 28 2021	23	1392	27	1411	12.2%	0.86 [0.50, 1.50]
XIENCE 90 2021	54	1693	32	1280	16.6%	1.28 [0.83, 1.96]
Total (95% CI)		**7758**		**7516**	**100.0%**	**1.05 [0.88, 1.27]**
Total events	236		217			

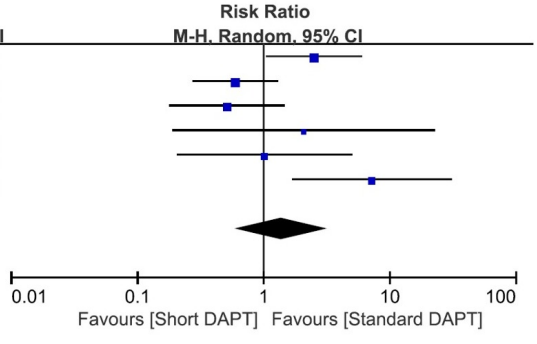
Heterogeneity: Chi² = 3.61, df = 5 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.57 (P = 0.57)



E

Study or Subgroup	Short DAPT Events	Short DAPT Total	Standard DAPT Events	Standard DAPT Total	Weight	Risk Ratio M-H, Random, 95% CI
EVOLVE Short DAPT 2021	17	1457	7	1502	21.1%	2.50 [1.04, 6.02]
MASTER DAPT 2021	10	2204	17	2230	22.2%	0.60 [0.27, 1.30]
STOPDAPT-2 2019	5	496	11	558	19.2%	0.51 [0.18, 1.46]
TWILIGHT -HBR 2021	2	516	1	535	8.5%	2.07 [0.19, 22.80]
XIENCE 28 2021	3	1392	3	1411	13.8%	1.01 [0.20, 5.01]
XIENCE 90 2021	19	1693	2	1280	15.1%	7.18 [1.68, 30.78]
Total (95% CI)		**7758**		**7516**	**100.0%**	**1.37 [0.59, 3.17]**
Total events	56		41			

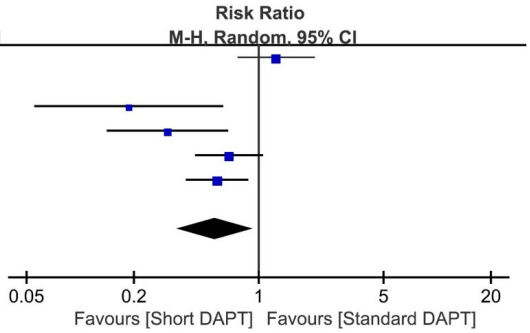
Heterogeneity: Tau² = 0.68; Chi² = 14.70, df = 5 (P = 0.01); I² = 66%
Test for overall effect: Z = 0.72 (P = 0.47)



A

Study or Subgroup	Short DAPT Events	Short DAPT Total	Standard DAPT Events	Standard DAPT Total	Weight	Risk Ratio M-H, Random, 95% CI
EVOLVE Short DAPT 2021	30	1032	31	1333	23.0%	1.25 [0.76, 2.05]
MASTER DAPT 2021	53	2295	59	2284	0.0%	0.89 [0.62, 1.29]
STOPDAPT-2 2019	3	496	18	558	10.6%	0.19 [0.06, 0.63]
TWILIGHT -HBR 2021	8	521	27	543	17.1%	0.31 [0.14, 0.67]
XIENCE 28 2021	33	1392	49	1411	24.3%	0.68 [0.44, 1.05]
XIENCE 90 2021	41	1693	53	1280	25.0%	0.58 [0.39, 0.87]
Total (95% CI)		**5134**		**5125**	**100.0%**	**0.57 [0.35, 0.94]**
Total events	115		178			

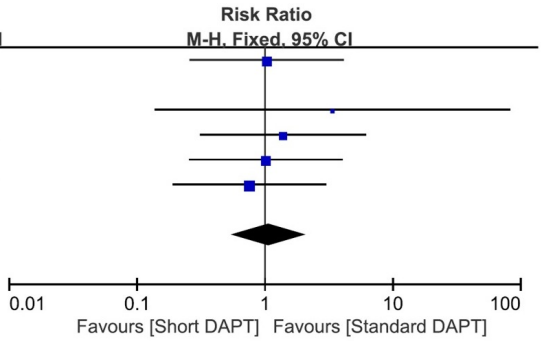
Heterogeneity: Tau² = 0.21; Chi² = 14.61, df = 4 (P = 0.006); I² = 73%
Test for overall effect: Z = 2.20 (P = 0.03)



B

Study or Subgroup	Short DAPT Events	Short DAPT Total	Standard DAPT Events	Standard DAPT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
EVOLVE Short DAPT 2021	4	1457	4	1502	24.8%	1.03 [0.26, 4.11]
MASTER DAPT 2021	14	2204	8	2230	0.0%	1.77 [0.74, 4.21]
STOPDAPT-2 2019	1	496	0	558	3.0%	3.37 [0.14, 82.64]
TWILIGHT -HBR 2021	4	516	3	535	18.5%	1.38 [0.31, 6.15]
XIENCE 28 2021	4	1392	4	1411	25.0%	1.01 [0.25, 4.05]
XIENCE 90 2021	4	1693	4	1280	28.7%	0.76 [0.19, 3.02]
Total (95% CI)		**5554**		**5286**	**100.0%**	**1.08 [0.55, 2.13]**
Total events	17		15			

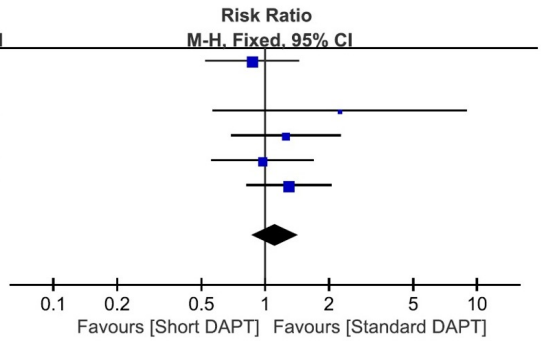
Heterogeneity: Chi² = 0.86, df = 4 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)



C

Study or Subgroup	Short DAPT Events	Short DAPT Total	Standard DAPT Events	Standard DAPT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
EVOLVE Short DAPT 2021	27	1457	32	1502	28.7%	0.87 [0.52, 1.44]
MASTER DAPT 2021	59	2204	46	2230	0.0%	1.30 [0.89, 1.90]
STOPDAPT-2 2019	6	496	3	558	2.6%	2.25 [0.57, 8.95]
TWILIGHT -HBR 2021	23	516	19	535	17.0%	1.26 [0.69, 2.28]
XIENCE 28 2021	24	1392	25	1411	22.6%	0.97 [0.56, 1.70]
XIENCE 90 2021	48	1693	28	1280	29.1%	1.30 [0.82, 2.05]
Total (95% CI)		**5554**		**5286**	**100.0%**	**1.12 [0.87, 1.44]**
Total events	128		107			

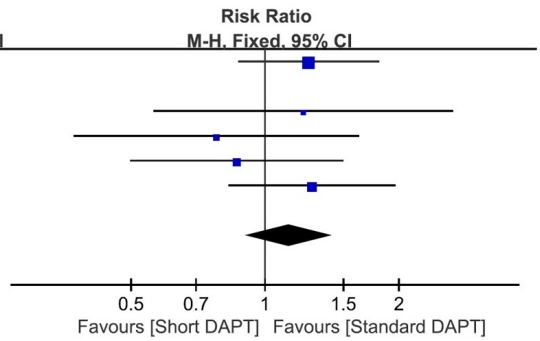
Heterogeneity: Chi² = 2.71, df = 4 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)



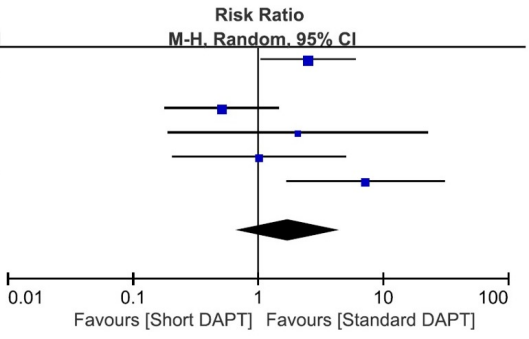
D

Study or Subgroup	Short DAPT Events	Short DAPT Total	Standard DAPT Events	Standard DAPT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
EVOLVE Short DAPT 2021	62	1457	51	1502	35.7%	1.25 [0.87, 1.80]
MASTER DAPT 2021	72	2204	79	2230	0.0%	0.92 [0.67, 1.26]
STOPDAPT-2 2019	13	496	12	558	8.0%	1.22 [0.56, 2.65]
TWILIGHT -HBR 2021	12	516	16	535	11.2%	0.78 [0.37, 1.63]
XIENCE 28 2021	23	1392	27	1411	19.1%	0.86 [0.50, 1.50]
XIENCE 90 2021	54	1693	32	1280	25.9%	1.28 [0.83, 1.96]
Total (95% CI)		**5554**		**5286**	**100.0%**	**1.13 [0.90, 1.41]**
Total events	164		138			

Heterogeneity: Chi² = 2.55, df = 4 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.06 (P = 0.29)



E

Study or Subgroup	Short DAPT Events	Short DAPT Total	Standard DAPT Events	Standard DAPT Total	Weight	Risk Ratio M-H, Random, 95% CI
EVOLVE Short DAPT 2021	17	1457	7	1502	27.1%	2.50 [1.04, 6.02]
MASTER DAPT 2021	10	2204	17	2230	0.0%	0.60 [0.27, 1.30]
STOPDAPT-2 2019	5	496	11	558	24.7%	0.51 [0.18, 1.46]
TWILIGHT -HBR 2021	2	516	1	535	11.0%	2.07 [0.19, 22.80]
XIENCE 28 2021	3	1392	3	1411	17.8%	1.01 [0.20, 5.01]
XIENCE 90 2021	19	1693	2	1280	19.4%	7.18 [1.68, 30.78]
Total (95% CI)		**5554**		**5286**	**100.0%**	**1.73 [0.66, 4.52]**
Total events	46		24			

Heterogeneity: Tau² = 0.68; Chi² = 10.14, df = 4 (P = 0.04); I² = 61%
Test for overall effect: Z = 1.12 (P = 0.26)