Abbreviated duration of dual antiplatelet therapy in patients with percutaneous coronary intervention and high bleeding risk: a systematic review and meta-analysis

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Authors contribution

JY Zhang, ZX Chen, C Li, CY Luo, and FB Luo independently performed the searches and screening of the titles and abstracts. The statistical analysis was performed by JY Zhang, ZX Chen, and DL Wang. ZX Chen wrote the manuscript. Y He conceived, instructed, reviewed, and revised the manuscript. All authors read and approved the final version of the manuscript.

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Abstract

Background: The appropriate duration of dual antiplatelet therapy (DAPT) in patients at high risk of bleeding after implantation of a drug-eluting coronary stent remains unclear. Thus, we performed a systematic review and meta-analysis to compare the effectiveness and safety of abbreviated and standard DAPT in patients with high bleeding risk (HBR) who underwent percutaneous coronary intervention (PCI) (PCI-HBR patients).

Methods: The Cochrane Library, PubMed, EMBASE, and Ovid MEDLINE databases were searched for relevant studies from their inceptions to November 11, 2021. All studies reporting incidences of major adverse cardiac events (MACE) and net adverse clinical events (NACE) in PCI-HBR patients were retained. Data extraction was performed by three independent reviewers.

Results: Nine studies (10 cohorts) were included in the meta-analysis. The results indicated that PCI-HBR patients with short-term DAPT had a lower NACE risk and a similar MACE risk than those with long-term DAPT, with a pooled risk ratio of 0.88 (95% CI 0.77–1.00], P = 0.04) and (95% CI: 0.87–1.16, P = 0.97), respectively. Moreover, the meta-analysis revealed that the reduction in NACE was mainly attributed to a reduction in bleeding (48% reduction in the risk of major bleeding, P < 0.001).

Conclusions: These findings suggest that abbreviated DAPT is feasible and favorable in PCI-HBR patients because it does not increase MACE while it reduces bleeding events. More studies specifically designed for HBR patients are needed, and a

personalized DAPT regimen is warranted to comprehensively balance the risk of bleeding and ischemia.

Keywords: Percutaneous coronary intervention; High bleeding risk; Dual antiplatelet therapy.

Abbreviations

ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; BMS, bare metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; HBR, high bleeding risk; MACE, major adverse cardiac event; MI, myocardial infarction; NACE, net adverse clinical event; PCI, percutaneous coronary intervention

1. Introduction

Percutaneous coronary intervention (PCI) is an important reperfusion strategy for patients with obstructive coronary artery disease. Identifying and managing high bleeding risk (HBR) in those undergoing PCI (PCI-HBR patients) is important because bleeding events after successful PCI are independently associated with increased mortality and morbidity, and this association is possibly causal [1,2]. In HBR patients, current guidelines recommend shorter dual antiplatelet therapy (DAPT) for 6 months in acute coronary syndrome (ACS) and for 1 month in stable coronary artery disease [3]. Since HBR patients are often excluded or underrepresented in randomized trials, the appropriate DAPT duration in this population for preventing ischemic complications, while limiting bleeding risk, after coronary stenting remains unclear. Recent studies have revealed that, compared with long-term DAPT, a shorter DAPT strategy should be considered in HBR patients to prevent future bleeding events without increasing ischemic events [4].

2. Methods

2.1. Search strategy

This meta-analysis was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) guidelines [5]. We systematically searched the PubMed, Embase, Ovid-Medline, and Cochrane Library databases for relevant studies from their respective inceptions until November 11, 2021. The following medical subject heading terms and keywords were used to identify relevant articles: percutaneous coronary intervention or PCI or coronary stenting, high bleeding risk or high risk of bleeding or HBR, and antiplatelet therapy. The references of studies were also checked for suitable articles. No language restrictions were imposed.

2.2. Study selection

Several assessments were performed, followed by the removal of duplicate articles after the initial screening. Relevant publication titles and abstracts were screened for suitability before full article retrieval. Additionally, meeting abstracts, editorials, and reviews were excluded from the analysis[6]. The inclusion criteria were as follows: 1) study subjects were PCI-HBR patients or had this subgroup; 2) studies published in peer-reviewed journals with available full texts; 3) articles comparing short-term DAPT with long-term DAPT as one of their research objectives; 4) studies reporting net adverse clinical events (NACE) or major adverse cardiac events (MACE), including either death/cardiovascular death, bleeding, myocardial infarction (MI), ischemic stroke, or stent thrombosis; and 5) studies with sufficient data for pooling (number of subjects, frequencies of subjects in a contingency table of short-term /

long-term DAPT groups for categorical data). We excluded trials that compared different DAPT durations in patients with only high ischemia risk. Three investigators (ZXC, JYZ, and FBL) independently reviewed all retrieved studies, and the differences were resolved via consensus.

2.3. Data extraction and quality assessment

Data pertaining to the following: study design, location of study, type of patients, HBR definition, type of $P2Y_{12}$ inhibitors, sample size, DAPT duration, clinical baseline characteristics, type of stents, types of NACE and MACE, and frequency of patients in the short-term and long-term DAPT groups, were independently extracted by three investigators (ZXC, JYZ, and CYL). Study quality was evaluated with the Newcastle-Ottawa Quality scale. High-quality studies were defined as studies with a modified Newcastle-Ottawa score of ≥5 (maximum, 9).

2.4. Statistical analysis

Risk ratios of NACE, MACE, or death among the short- and long-term DAPT groups were estimated for each study, given that different studies used different DAPT duration thresholds to define short-term and long-term DAPT. In both cases, the heterogeneity of the effect measure was assessed using the Q statistic and I^2 value. A random-effect model (Dersimonian and Laird method) was applied if heterogeneity was detected (P-value < 0.10 or I^2 ≥25%); otherwise, a fixed-effect model (inverse-variance method) was used. Statistical significance was set at $p < 0.05$. RevMan 5.3 software (Cochrane, London, UK) was used for the statistical analysis.

3. Results

3.1 Study selection

We identified 315 publications in PubMed, 358 publications in the Cochrane Library, and 347 publications in EMBASE and Ovid MEDLINE. Of these 1020 studies, 243 were duplicates. Nine of the remaining studies (10 cohorts) [6-14] met the inclusion criteria. The detailed search strategy is presented in Figure 1.

3.2 Study characteristics and quality assessment

Of the nine included studies [4,6-9,13-16], one study was a randomized trial and the others were post hoc analysis, prespecified subgroup analysis, pooled analysis, or cohort studies. Five of the included studies reported the rates of NACE between the DAPT groups that are short-term and long-term [1-9,11,13], while eight reported MACE rates [6,8-14]. Six of the included studies assessed HBR patients according to the Academic Research Consortium definition [6,8,14]. The mean risk of bias criterion score in Newcastle and Ottawa was 8.1, and all included studies had quality scores (> 5). The participants in the research varied in age from 66.1 to 76.1 years. The percentages of the male sex, hypertension, diabetes, chronic kidney disease, and patients with previous PCI ranged from 43.8% to 69.8%, 61.9 to 90.5%, 26.9 to 44.2%, 2.4 to 72.2%, and 6.3 to 44.0%, respectively. Six cohorts in the included studies used aspirin as a single antiplatelet agent, and four cohorts adopted $P2Y_{12}$ inhibitors. The general characteristics and the definitions of outcome event in the included studies are summarized in Table 1–3.

3.3 Risk of NACE in PCI-HBR patients with short-term vs. long-term DAPT

Five of the studies with NACE as the outcome provided the number of patients with short-term and long-term DAPT. The effects of the short-term DAPT regimen were homogeneous among these studies (Chi-square = 4.42, df = 4, P-value = 0.35, I^2 = 9%) with a pooled risk ratio of 0.88 (95% CI 0.77–1.00, P = 0.04, Figure 2A). This suggests that PCI-HBR patients with short-term DAPT had a 22% reduction in NACE risk compared to those with long-term DAPT. The reduction in NACE was mainly attributed to the reduction in bleeding. Compared to those with long-term DAPT, PCI-HBR patients with short-term DAPT had a pooled 48% reduction in the risk of major bleeding, defined as a bleeding event of Bleeding Academic Research Consortium (BARC) type 2, 3, and 5, (P < 0.001, Figure 2B).

3.4 Risk of MACE in PCI-HBR patients with short-term vs. long-term DAPT

Eight of the studies (nine cohorts) with MACE as the outcome provided the number of patients with short-term and long-term DAPT. The effects of the short-term DAPT regimen were heterogeneous among these studies (Chi-square = 13.04, df = 8, P-value = 0.11, I^2 = 39%), with a pooled risk ratio of 1.00 (95% CI 0.87–1.16, P = 0.97) (Figure 3A). This suggests that PCI-HBR patients with short-term DAPT did not show increased MACE compared to those with long-term DAPT. In particular, PCI-HBR patients with short-term DAPT did not show an increase in all-cause death (Figure 3B), cardiac death (Figure 3C), MI (Figure 3D), ischemic stroke (Figure 3E), or stent thrombosis (Figure 3F) compared to those with long-term DAPT.

4. Discussion

This systematic review and meta-analysis examined the effectiveness and safety of short-term DAPT compared with long-term DAPT in PCI-HBR patients. To the best of our knowledge, this is the first meta-analysis to assess this topic in this population. Our findings indicated that PCI-HBR patients with short-term DAPT had a 22% reduction in NACE risk compared to those with long-term DAPT. The reduction in NACE was mainly attributed to a reduction in bleeding. However, PCI-HBR patients with short-term DAPT did not show increased MACE compared to those with long-term DAPT. These results demonstrate that the abbreviated duration of DAPT is feasible and favorable in PCI-HBR patients because it does not increase MACE while it reduces bleeding events. However, stent types, patient category, proportion of potent $P2Y_{12}$ inhibitors, antiplatelet monotherapy, and DAPT duration varied among the included studies. Moreover, some post hoc analyses were included in this meta-analysis from studies not specifically designed for HBR patients. Thus, to a certain extent, our results do not reflect the actual treatment status of HBR patients. In view of the heterogeneity of the studies, physicians should be aware of individual patient characteristics in clinical practice. Ongoing randomized trials among PCI-HBR patients, ONYX ONE (a randomized controlled trial of HBR patients after stent placement with 1 month of DAPT, NCT03344653) [18] and COBRA REDUCE (a randomized trial of COBRA PzF stenting to REDUCE the duration of triple therapy, NCT02594501) [19], should provide more evidence to support the recommendation of an abbreviated DAPT regimen in HBR patients following PCI.

4.1 Accompanying ischemia risk in PCI-HBR patients

Current European and American guidelines provide cautious recommendations on the use of DAPT regimens of 3 months or less after drug-eluting stent (DES) implantation, acknowledging the limited available evidence derived mostly from trials on low-risk populations [3,19]. Our meta-analysis revealed that abbreviated therapy as short as 1-month DAPT was noninferior to therapy for 12 months with regard to the occurrence of NACE and MACE; abbreviated therapy also resulted in a lower incidence of major or clinically relevant non-major bleeding [4]. The accompanying ischemia risk of PCI-HBR patients is also an important aspect that needs consideration in the prescription of the DAPT regimen.

A pooled analysis by Costa et al. [21] investigated the effects of ischemic (by PCI complexity) and bleeding (by PRECISE-DAPT [PREdicting bleeding complications in patients undergoing stent implantation and SubsequEnt Dual AntiPlatelet Therapy] score) risks on clinical outcomes and on the impact of DAPT duration after coronary stenting, and demonstrated that patients who underwent complex PCI had a higher risk of ischemic events, but benefited from long-term DAPT only if HBR features were absent. These data suggest that when both risks exist, bleeding, more than ischemic risk, should inform decision-making regarding the duration of DAPT. The TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial examined the effect of ticagrelor alone compared with ticagrelor plus aspirin with regard to clinically relevant bleeding among patients who were at high risk for bleeding or an ischemic event and had undergone PCI [17]. The prespecified subgroup analysis TWILIGHT-HBR [13] demonstrated that early aspirin

withdrawal followed by ticagrelor monotherapy was a bleeding avoidance strategy without increasing ischemic events among HBR patients undergoing PCI, who completed 3-month DAPT without experiencing major adverse events.

Controversially, in the primary results of the EVOLVE Short DAPT (Evaluation of 3-Month Dual Antiplatelet Therapy in High Bleeding Risk Patients Treated With a Bioabsorbable Polymer-Coated Everolimus-Eluting Stent) study [7], patients with acute MI or complex lesions were excluded considering the risk of a shorter DAPT duration in patients at highest ischemic risk. Additionally, the primary results of the ongoing STOPDAPT-2 (Short and Optimal Duration of DAPT after Everolimus-Eluting Cobalt-Chromium Stent) ACS trial (NCT03462498), presented at ESC Congress 2021, demonstrated that clopidogrel monotherapy after 1 month of DAPT, compared with standard DAPT, reduced bleeding events at the expense of an increased risk of cardiovascular events. The ongoing OPT-BIRISK (Extended antiplatelet therapy with clopidogrel alone versus clopidogrel plus aspirin after completion of 9- to 12-month DAPT for ACS patients with both high bleeding and ischemic risk) trial (NCT 03431142), which aims to explore the optimal antiplatelet strategy for ACS patients with both high bleeding and high ischemic risks, should shed light on de-escalation antiplatelet therapy for patients at special risk [22]. In conclusion, in PCI patients with a high risk of ischemia and HBR, attention regarding the shortened DAPT duration is especially crucial to comprehensively balance the bleeding and ischemic risk. More studies including HBR patients with high ischemia risk are needed to assess the optimal DAPT regimen in this cohort.

4.2 Impact of coronary stents on DAPT duration in PCI-HBR patients

Bare metal stents (BMSs) may be an alternative for PCI-HBR patients because they are a shorter requirement for DAPT [20]. However, the high rate of stent restenosis hinders the clinical application of BMS. First-generation DES were initially studied with durations of DAPT as short as 3 to 6 months; however, following observations of late stent thrombosis over a decade ago, regulatory bodies and societies extended the recommended DAPT duration to a minimum of 12 months. Specific modifications in current second-generation DES designs, including thin-strut platforms and ultrathin bioabsorbable polymers, facilitate rapid endothelialization, alleviate the ongoing risk of stent thrombosis, and enable shorter durations of DAPT [20]. More recent data with newer-generation DESs have led to a revision of these recommendations, with the most recent guideline updates from both the US and the European Union recommending shorter DAPT durations, especially for patients with HBR [19].

Innovations in DES technology have facilitated the investigation of shorter durations of DAPT in patients with HBR. The LEADERS-FREE study [24], which evaluated a polymer-free DES, demonstrated superior safety and efficacy of the polymer-free DES compared to a BMS in patients with HBR treated with 1-month DAPT, and the ONYX ONE trial [25] demonstrated similar outcomes of a durable polymer DES with 1-month DAPT compared to a polymer-free DES. Similarly, the SENIOR (SYNERGY everolimus-eluting stent) trial [26] and the ZEUS (Zotarolimus-eluting Endeavor Sprint stent) trial [27] demonstrated lower rates of major cardiac events in current-generation DES implantation with 1-month DAPT compared with

conventional BMS. D'Ascenzo et al. [28] performed a network meta-analysis to reveal the impact of coronary stent design and DAPT length on ischemic and bleeding events. Their results demonstrated that durable and biodegradable polymer stents along with bioresorbable scaffolds yielded a similar rate of MACE irrespective of DAPT duration. Therefore, new-generation DESs are a safe approach and may be preferentially considered in PCI-HBR patients.

4.3 Selection of a single antiplatelet agent

Aspirin is a widely used agent for antiplatelet monotherapy during the chronic maintenance period in patients who undergo coronary stenting. However, recent trials found that clopidogrel monotherapy compared with aspirin monotherapy provides clinical benefit with fewer thrombotic and bleeding events, when given in the chronic maintenance period for patients who received PCI with DES [27-31]. Controversially, the OPT-PEACE (Optimal Antiplatelet Therapy for Prevention of Gastrointestinal Injury Evaluation by ANKON magnetically controlled capsule endoscopy) trial demonstrated that, in patients who underwent PCI predominantly for ACS and who had a low risk of bleeding, DAPT for 6 months followed by antiplatelet monotherapy with aspirin or clopidogrel between 6 and 12 months resulted in less gastrointestinal mucosal injury and clinical bleeding compared with DAPT for 12 months. Interestingly, investigators found no difference in bleeding or gastrointestinal mucosal injury between aspirin and clopidogrel monotherapy, a finding that challenges the conventional notion that aspirin has greater gastrointestinal toxicity than clopidogrel [33]. The nearly ubiquitous appearance of gastrointestinal erosions suggests that

erosion as a marker of gastrointestinal injury is not really useful as a clinical endpoint or as a discriminator of safety. Doctors should be more concerned about symptomatic ulceration or overt bleeding than about incidental endoscopic erosions when prescribing the DAPT regimen.

Moreover, within the first year after PCI, trials comparing the efficacy and safety of $P2Y_{12}$ inhibitor monotherapy versus DAPT reported that 1 to 3 months of DAPT followed by $P2Y_{12}$ inhibitor monotherapy was associated with a reduced risk of adverse clinical events [32]. In patients with HBR, after the abbreviated DAPT (1 to 3 months), clinicians prefer a $P2Y_{12}$ inhibitor as the antiplatelet monotherapy for the secondary prevention of cardiovascular events and to reduce the risk of bleeding. However, there are no recommendations regarding the specific type of $P2Y_{12}$ inhibitors for monotherapy. In the PLATO trial, ticagrelor proved to be superior to clopidogrel in patients with ACS, while increasing the rate of non-procedure-related bleeding [36]. Additionally, in a pooled analysis of the SMART-DATE and SMART-CHOICE trials, $P2Y_{12}$ inhibitor monotherapy after 3 months of DAPT reduced the risk of bleeding compared with conventional DAPT and aspirin monotherapy after 6 months of DAPT without increasing major adverse events among ACS patients undergoing PCI [16]. To date, no dedicated study has assessed the value of ticagrelor versus clopidogrel in PCI-HBR patients. A systematic review by Guo et al. showed that third-generation $P2Y_{12}$ inhibitors were associated with an increased risk of gastrointestinal bleeding and non-coronary-artery-bypass-graft major bleeding when compared with clopidogrel [33]. Hence, the administration of ticagrelor in

patients with HBR requires a patient-by-patient decision. Evidence from the MASTER DAPT trial [4] and TWILIGHT-HBR study [13] showed that clopidogrel may be a first-choice monotherapy agent in HBR patients, while ticagrelor may be more suitable in HBR patients accompanied by a high ischemic risk.

5. Conclusion

Bleeding is strongly associated with an increased risk of subsequent mortality in patients undergoing PCI. The net clinical benefit of DAPT reflects the trade-off effects of an increased risk of bleeding and a reduced risk of MACE. Monotherapy with a $P2Y_{12}$ inhibitor after a minimum period of DAPT is an emerging approach to reduce the risk of bleeding after PCI in HBR patients. The choice of DAPT duration and single antiplatelet agent is still a difficult issue, and individualized treatment is mandatory to manage the risk of residual ischemia and bleeding events. However, the optimal DAPT regimen for HBR patients undergoing PCI requires personalized treatment approaches as well as further investigation and longer follow-up.

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Figure legends:

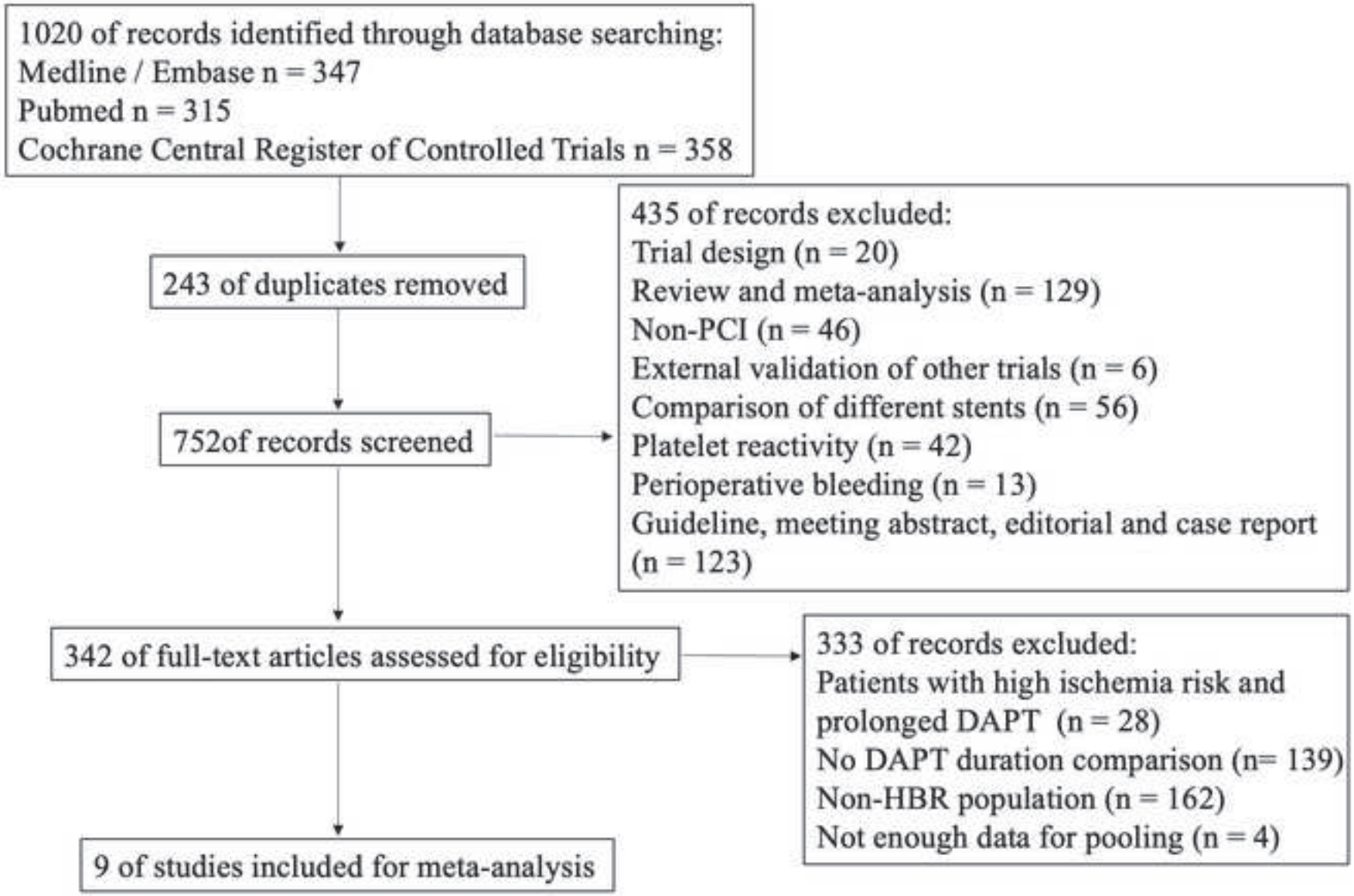
Figure 1. PRISMA flow diagram of the study selection.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement; PCI, percutaneous coronary intervention; DAPT, dual antiplatelet therapy; HBR, high bleeding risk.

Figure 2. Pooled relative risks of NACE(A) and major bleeding(B) in patients with short-term vs. long-term DAPT. Major bleeding was defined as a bleeding event of Bleeding Academic Research Consortium (BARC) type 2, 3, and 5 or BARC 3 and 5 according to included studies. NACE, net adverse clinical events; DAPT, dual antiplatelet therapy.

Figure 3. Pooled relative risks of MACE(A), all-cause death(B), cardiac death (C), MI(D), ischemic stroke(E) and ST(F) in patients with short-term vs. long-term DAPT. MACE, major adverse cardiac events; MI, myocardial infarction; ST, stent thrombosis; DAPT, dual antiplatelet therapy.

Figure



Figure

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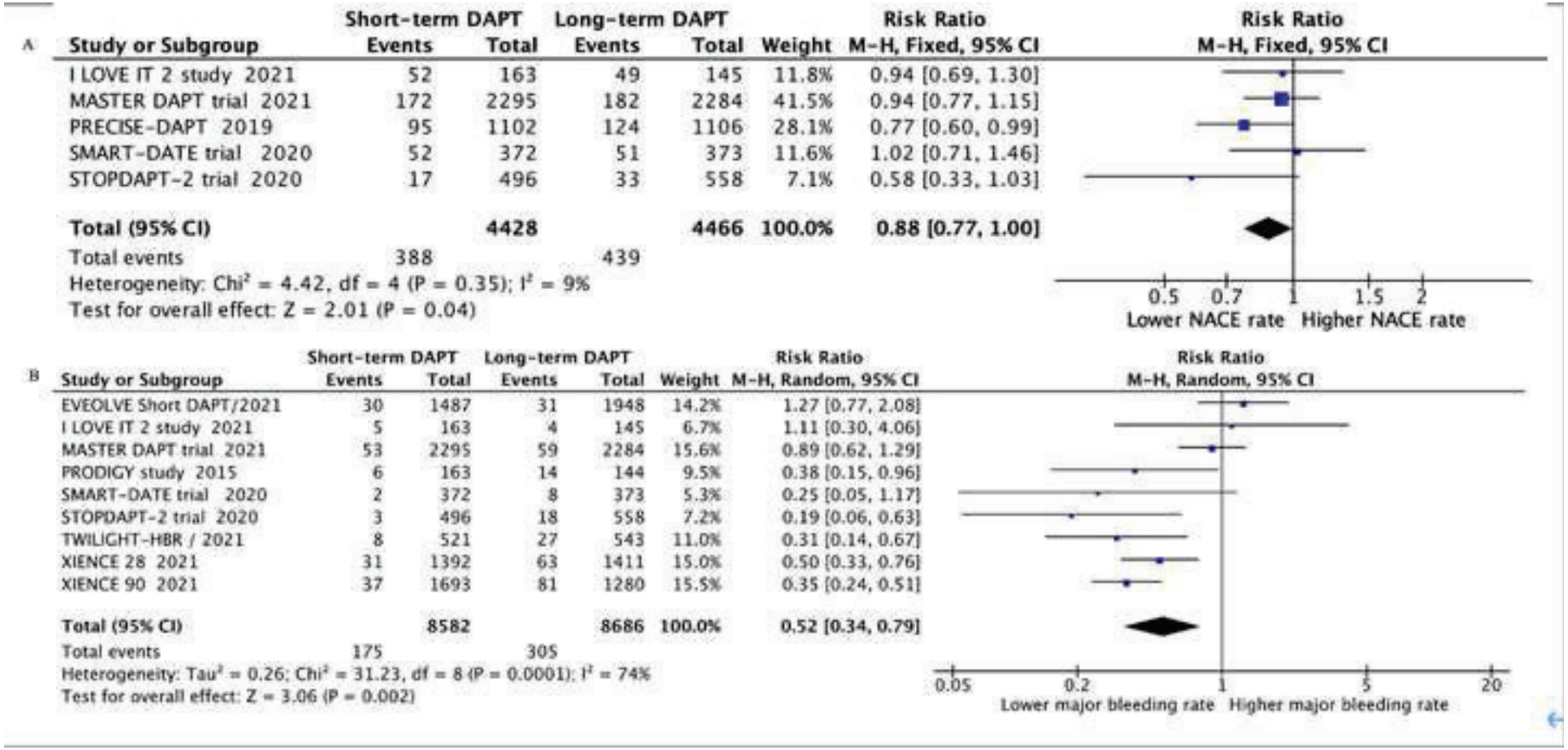

Figure

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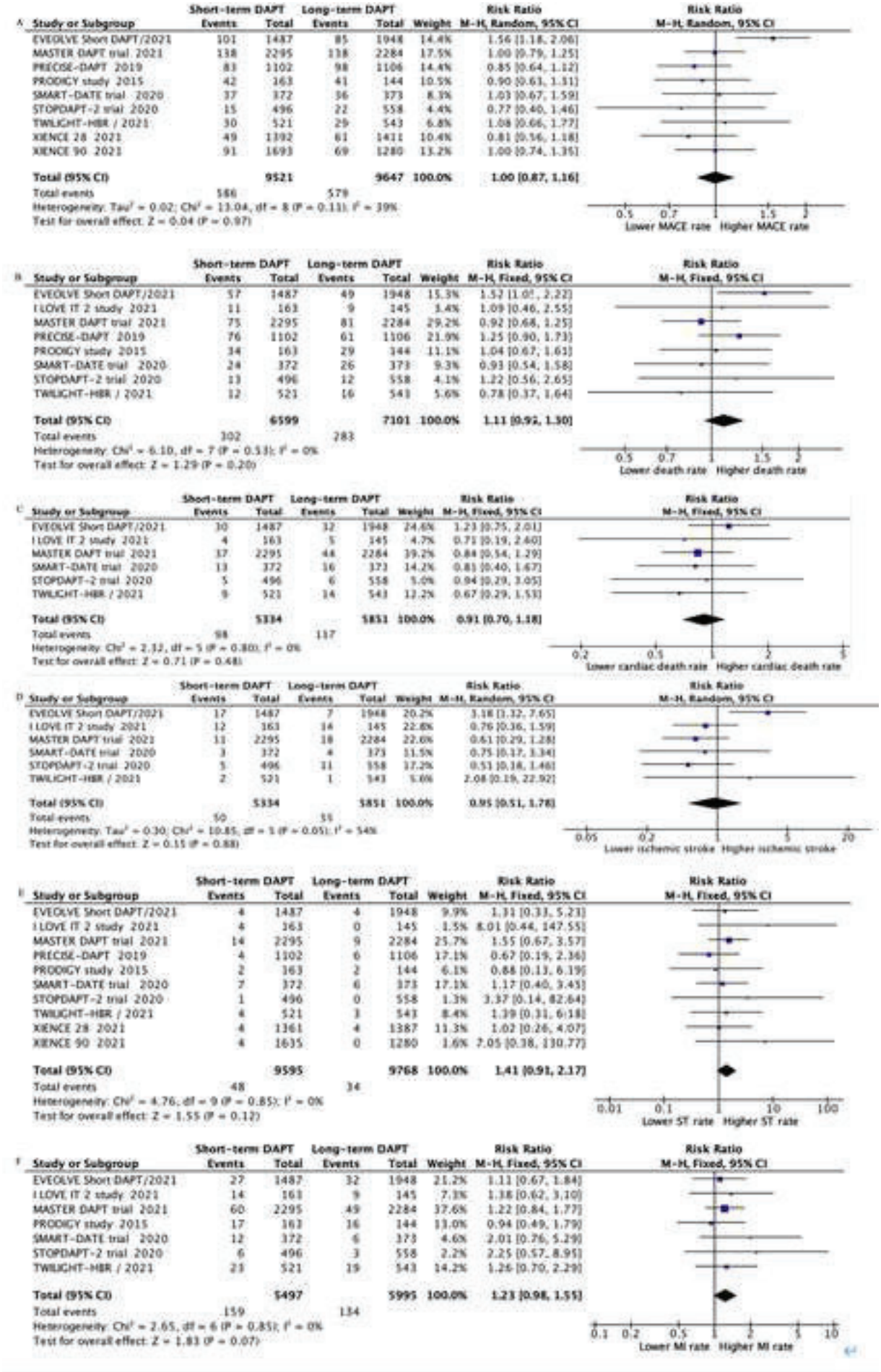

Table 1 Baseline characteristics of the included studies.

Research / Year	**Study type**	**Quality score**	**Setting**	**Type of patients**	**HBR definition**	**Stent type**	**Type of $P2Y_{12}$ inhibitors**	**Mono-antiplatelet**	**DAPT duration (months)**	**Outcome measurement**
MASTER DAPT trial / 2021	Randomized trial	9	Worldwide (at 140 sites in 30 countries)	Acute or chronic coronary syndrome	ARC- HBR definition	Biodegradable-polymer sirolimus-eluting coronary stent (Ultimaster, Terumo)	79.3% clopidogrel, 9.8% ticagrelor	$P2Y_{12}$ inhibitors	1 vs. 3	335 days
I LOVE IT 2 study / 2021	Post hoc analysis	9	China	CAD patients	ARC- HBR definition	Biodegradable polymer-coated sirolimus-eluting stent (BP-SES, Tivoli, Essen Tech, Beijing, China)	Clopidogrel	Aspirin	6 vs. 12	4 years
TWILIGHT-HBR /	Prespecified	9	Worldwide (at 187 sites	All PCI comers	ARC- HBR definition	Drug-eluting stent	Ticagrelor	Ticagrelor	3 vs. 15	1 year

2021	subgroup analysis		from 11 countries)							
EVOLVE Short DAPT / 2021	Cohort study	7	Worldwide (at 110 centers)	Subjects at HBR undergoing PCI	ARC- HBR definition	SYNERGY everolimus-eluting stent	$P2Y_{12}$ inhibitors (included clopidogrel, prasugrel, and ticagrelor)	$P2Y_{12}$ inhibitors	3 vs. 12	15 months
XIENCE 28 / 2021	Cohort study	7	52 sites in Europe and Asia	Subjects at HBR undergoing PCI	ARC- HBR definition	Fluoropolymer-based cobalt-chromium everolimus-eluting stent (XIENCE)	92.3% clopidogrel	Aspirin	1 vs. 6	6 months
XIENCE 90 / 2021	Cohort study	7	101 sites in the United States	Subjects at HBR undergoing PCI	ARC- HBR definition	Fluoropolymer-based cobalt-chromium everolimus-eluting stent (XIENCE)	88.8% clopidogrel	Aspirin	3 vs. 12	12 months
STOPDAPT - 2 trial / 2020	Post hoc analysis	9	Japan	All PCI comers	ARC- HBR definition	Cobalt-chromium everolimus- eluting stent (CoCr-EES)	67.7% clopidogrel, 32% prasugrel	Clopidogrel	1 vs. 12	1 year

SMART-DATE trial / 2020	Post hoc analysis	9	Korea	ACS	PRECISE-DAPT Score ≥25	Zotarolimus-eluting stent, everolimus-eluting stent, and biolimus A9-eluting stent	85% clopidogrel, 15% potent $P2Y_{12}$ inhibitors	Aspirin	6 vs. 12	18 months
PRECISE-DAPT / 2019	Pooled study	7	Worldwide (at 139 sites from 12 countries)	All PCI comers	PRECISE-DAPT Score ≥25	BMS, first-generation drug-eluting stents, second-generation drug eluting stents	85% clopidogrel	Aspirin	3 or 6 vs. 12 or 24	2 years
PRODIGY study / 2015	Post hoc analysis	8	3 Italian sites	All PCI comers	CRUSADE Score >40	Everolimus-eluting stent (EES), paclitaxel-eluting stent (PES), zotarolimus-eluting endeavor sprintw stent (ZES-S), or thin-strut bare metal stent	Clopidogrel	Aspirin	6 vs. 24	1 year

ARC-HBR, the academic research consortium for high bleeding risk; ACS, acute coronary syndrome; CAD, coronary artery disease; CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; PRECISE-DAPT, PREdicting bleeding Complications in patients undergoing stent Implantation and SubsequEnt Dual AntiPlatelet Therapy.

Table 2 Baseline characteristics of the included studies.

Research / Year	**Age, yr.**	**Male, n (%)**	**BMI, kg/m^2**	**Hypertension, n (%)**	**Diabetes, n (%)**	**Dyslipidemia, n (%)**	**Chronic kidney disease, n (%)**	**Previous PCI, n (%)**
MASTER DAPT trial / 2021 (n = 4579)	76.1	3171 (69.3)	27.35	3553 (77.6)	1538 (33.6)	3097 (67.6)	876 (19.1)	1188 (25.9)
I LOVE IT 2 study / 2021 (n = 308)	66.1	135 (43.8)	25.03	238 (77.3)	83 (26.9)	76 (24.7)	91 (29.5)	24 (7.8)
TWILIGHT-HBR / 2021 (n=1064)	71.9	710 (67.7)	28.6	865(81.3)	503(47.3)	713(67.0)	664(61.0)	483(45.4%)

EVOLVE Short DAPT / 2021(n=2009)	75.6	1312 (65.3)	28.7	1782(88.7)	762(37.9)	1594(79.3)	208 (10.4)	678(33.7)
XIENCE 28 / 2021 (n = 2803)	74.3	1774 (63.3)	/	2462/2794 (88.1)	1106/2786 (39.7)	2193/2775 (79.3)	1215/2657 (45.7)	904/2747 (32.9)
XIENCE 90 / 2021 (n = 2973)	74.0	1853 (62.3)	/	2683/2965 (90.5)	1209/2965 (40.8)	2541/2950 (86.1)	1209/2884 (41.9)	997/2923 (34.1)
STOPDAPT- 2 trial / 2020 (n = 1054)	75.8	736 (69.8)	23.5	855 (81.1)	466 (44.2)	765 (72.6)	761 (72.2)	464 (44.0)
SMART-DATE trial / 2020 (n = 745)	73.7	412 (55.3)	23.1	461 (61.9)	252 (33.8)	171 (23.0)	18 (2.4)	47 (6.3)
PRECISE-DAPT / 2019 (n = 3708)	/	2145 (57.9)	/	2944 (79.4)	1134 (30.6)	2087 (56.3)	/	660 (17.8)

PRODIGY study / 2015 (n = 307)	/	/	/	/	/	/	/	/

BMI, body mass index; PCI, percutaneous coronary intervention.

Table 3 Baseline characteristics and outcome events definition of the included studies.

Research / Year	**Previous MI, n (%)**	**Current smoking, n (%)**	**Previous bleeding, n (%)**	**Atrial fibrillation, n (%)**	**LVEF, %**	**Hemoglobin, g/L**	**NACE**	**MACE or MACCE**
MASTER DAPT trial / 2021 (n = 4579)	864 (18.9)	414/4566 (9.1)	320 (7.0)	1490 (32.5)	53.2	132.2	A composite of death from any cause, MI, stroke, or major bleeding	A composite of death from any cause, MI, or stroke
I LOVE IT 2 study / 2021 (n = 308)	53 (17.2)	95 (30.8)	/	/	59.5	127.8	A composite of all-cause death, MI, ischemia-driven revascularization,	/

							stroke, stent thrombosis, or any bleeding events	
TWILIGHT-HBR / 2021 （n=1064）	306(28.8)	110(10.4)	54(5.1)	/	/	/	/	Death, MI or stroke
EVOLVE Short DAPT / 2021(n=2009)	377(18.8)	138(6.9)	/	627 (31.2)	/	/	/	All death, MI and stroke
XIENCE 28 / 2021 (n = 2803)	620/2677 (23.2)	/	/	/	/	/	/	All-cause mortality or MI
XIENCE 90 / 2021 (n = 2973)	617/2843 (21.7)	/	/	/	/	/	/	All-cause mortality or MI

STOPDAPT-2 trial / 2020 (n = 1054)	164 (15.6)	145 (13.8)	42 (4.0)	33 (3.1)	58.7	/	A composite of cardiovascular death, MI, definite ST, stroke, or TIMI major or minor bleeding	A composite of cardiovascular death, MI, definite ST, or stroke
SMART-DATE trial / 2020 (n = 745)	22 (3.0)	156 (20.9)	45 (6.0)	/	53.6	127.5	A composite of all-cause death, MI, cerebrovascular accident, and BARC 2 to 5 bleeding	A composite of all-cause death, MI, and cerebrovascular accident
PRECISE-DAPT / 2019 (n = 3708)	787 (21.2)	466 (12.6)	198 (5.3)	/	/	/	A composite of MI, definite ST, stroke, TVR, and major and minor TIMI bleeding	A composite of MI, definite ST, stroke, or TVR

PRODIGY study / 2015 (n = 307)	/	/	/	/	/	/	/	A composite of all-cause death, MI, and cerebrovascular accident

LVEF, left ventricular ejection fraction; MI, myocardial infarction; MACE, major adverse cardiac events; MACCE, major adverse cardiac and cerebrovascular events; NACE, net adverse clinical events; ST, stent thrombosis; TVR, target vessel revascularization; TIMI, thrombolysis in myocardial infarction.