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Aspirin plus clopidogrel versus cilostazol -based triple antiplatelet therapy in patients with ischemic heart disease undergoing PCI: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Introduction Cilostazol has been widely used to prevent peripheral vascular events after PCI. However, guidelines in cilostazol-based triple antiplatelet therapy for patients with ischemic heart disease undergoing PCI remain unclear. The purpose of this study was to assess the efficacy and safety of DAPT (aspirin and clopidogrel) compared to cilostazol -based TAPT (aspirin, clopidogrel and cilostazol).

Methods We conducted a comprehensive search of the Medline, Embase, Scopus, Cochrane, and Web of Science databases until November 2024 to identify RCTs comparing DAPT with cilostazol -based TAPT in patients with ischemic heart disease undergoing PCI. Pooled risk ratios (RRs) with 95% CIs were calculated.

Results Eight RCTs (5,299 patients) were included in this systematic review and meta-analysis. A significantly reduced risk of all-cause mortality in hospital was observed with DAPT compared to cilostazol -based TAPT (RR: 0.27, 95% CI: 0.07 to 0.94, $p=0.04$). Also, A significantly reduced risk of headache and palpitation was observed with DAPT compared to cilostazol -based TAPT, with pooled RR (RR: 0.15, 95% CI: 0.06 to 0.33, $p<0.001$) and (RR: 0.24, 95% CI: 0.08 to 0.73, $p=0.01$), respectively. However, no difference was observed between DAPT and cilostazol -based TAPT on vessel revascularization, stroke, stent thrombosis, myocardial infarction and major adverse cardiac events.

Conclusion Aspirin and clopidogrel were associated with a lower risk of adverse events compared to cilostazol-based TAPT. However, the addition of cilostazol did not improve clinical outcomes. Further trials are needed to clarify the role of cilostazol -based TAPT for patients with ischemic heart disease undergoing PCI.

Keywords DAPT, TAPT, Heart, Cilostazol, PCI

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Introduction

Ischemic heart disease (IHD) continues to be the leading cause of morbidity and mortality globally despite developments in diagnosis and treatment [1]. Percutaneous coronary intervention (PCI) remains the cornerstone treatment for revascularization in IHD patients [1, 2], aimed at reducing ischemic complications and improving outcomes. Post-PCI antiplatelet therapy is essential in reducing the risk of thrombotic events [2, 3]. Dual antiplatelet therapy (DAPT), combining aspirin and clopidogrel, has traditionally been the standard of care [3]. Early studies demonstrated a lower rate of stent thrombosis and major adverse cardiovascular events (MACE) with DAPT compared to aspirin alone [4]. Recent guidelines recommend a DAPT regimen for at least 6–12 months post-PCI, followed by indefinite aspirin use [5].

Aspirin, a COX-1 irreversible inhibitor, has been a cornerstone antiplatelet agent for preventing arterial thrombus formation [6]. The P2Y12 receptor antagonist clopidogrel was added following the CURE trial, which showed reduced ischemic events when combined with aspirin in acute coronary syndrome (ACS) patients [7]. However, despite DAPT's effectiveness, recurrent ischemic episodes remain a concern, especially in high-risk groups such as patients with diabetes or multivessel disease [8]. Furthermore, the variability in individual responses to clopidogrel and its hypo responsiveness contribute to residual platelet activity, which has been associated to adverse cardiovascular events following PCI [9]. To address these limitations, triple antiplatelet therapy (TAPT) was introduced, incorporating a third agent such as a glycoprotein IIb/IIIa inhibitor or newer P2Y12 inhibitors like ticagrelor or prasugrel alongside aspirin and clopidogrel [8]. While TAPT offers enhanced ischemic protection, it also increases bleeding risk, necessitating individualized treatment [9]. Cilostazol, a phosphodiesterase III inhibitor, is a promising addition to TAPT due to its antiplatelet and vasodilatory effects [10]. It has been shown to enhance platelet inhibition after PCI [11] in the OPTIMUS-2 study, consistent with ACCEL-AMI study which demonstrated better platelet inhibition with cilostazol-based TAPT, supporting its potential as a viable antithrombotic strategy in patient subsets after PCI [10].

Other recent studies have investigated cilostazol-based TAPT in PCI patients. Xu et al. [12] found no substantial reduction in periprocedural myocardial infarction (PMI) in ACS patients [12], whereas Tang et al. [13] reported better outcomes in clopidogrel non-responders without increased bleeding risk [13]. Park et al. [14] observed inconsistent results, suggesting no decrease in MACE but a potential increase in side effects [14]. However, Lee et al. (2017) and Han et al. (2009) reported reduced ischemic events and restenosis in high-risk patients [15, 16]. Cilostazol also demonstrated benefits in vascular healing following drug-eluting stent placement, particularly among smokers [17, 18]. A retrospective analysis showed that cilostazol-based TAPT in patients undergoing PCI reduced in-hospital cardiac death and MACE at 8 months compared to DAPT [19]. Prospective studies also observed reduced adverse cardiovascular events and stent thrombosis with cilostazol TAPT without an increased bleeding risk; such clinical advantages may be related to cilostazol's effects on thrombosis, restenosis, and endothelial function [16, 19, 20]. However, concerns about bleeding risk, as highlighted by trials such as PLATO and TRITON-TIMI 38, highlight the significance of balancing thrombotic protection with safety [21, 22].

This systematic review and meta-analysis evaluate the safety and efficacy of DAPT (aspirin and clopidogrel) versus cilostazol-based TAPT in PCI patients. By synthesizing data from recent randomized controlled trials (RCTs), this analysis aims to guide clinical decision-making by balancing thrombotic prevention with bleeding complications.

Methods

This systematic review and meta-analysis adhered to Cochrane recommended guidelines for SR-MA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [23]. We registered our protocol in PROSPERO (ID: CRD42024610147).

Data sources and search strategy

We comprehensively searched the five major medical electronic databases: Cochrane, Scopus, PubMed (MEDLINE), Web of Science (WoS) and Embase. The literature review covered a time frame until November 10th, 2024, and no restrictions were applied to the research criteria. Details of the search strategy are available in Table S1.

Eligibility criteria

We followed the PICOS framework to select relevant studies using the following inclusion criteria: (1) Population included patients with ischemic heart disease undergoing Percutaneous Coronary Intervention. (2) Intervention of interest was cilostazol-based TAPT. (3) Comparator was Aspirin plus clopidogrel (DAPT). (4) Outcomes analysed included target vessel revascularization, target lesion revascularization, stroke, stent thrombosis, myocardial infarction, cardiac death, major adverse cardiac events, All-cause death, non-cardiac adverse events and bleeding. Only randomized clinical trials were included, therefore excluding review articles, pilot studies, observational studies, case reports, commentaries, editorials, letters to editors, animal trials, in vitro studies, conference abstracts, and studies with overlapping data.

Study selection

Following the systemic literature review, studies fulfilling the search strategy were obtained and uploaded to EndNote Reference Library. After removing duplicates, two authors (T.A. and A.M.) independently screened the titles and abstracts of the results via Rayyan website. Studies passing the preliminary screening underwent further evaluation through full-text screening to ensure relevance. Discrepancies regarding trials' eligibility were discussed among the authors, and a senior author (R.O.) was consulted if needed.

Data extraction

An Excel sheet with information regarding trial design, baseline characteristics and efficacy/safety outcomes was created. Three authors independently extracted data of interest from eligible studies, and any possible disagreements were resolved by a senior author (R.O., H.J. and R.A.). Extracted data included study year, country, study design, number of patients in each group, follow-up period, aim and conclusion. Patients' baseline characteristics included gender, age, smoking history, hypertension, diabetes, dyslipidemia and previous PCI. Data on safety and efficacy were collected, focusing on the following primary safety outcomes: target vessel revascularization, target lesion revascularization, stroke, stent thrombosis, myocardial infarction, cardiac death, major adverse cardiac events, All-cause death, non-cardiac adverse events and bleeding.

Risk of bias and certainty of evidence

Two investigators (A.M. and B.Q.) carried out the quality assessment process independently, a third investigator was involved in case of any disagreements. We used Cochrane Risk of Bias 2 (ROB2) [24] for all studies included, and based on different domains assessed, each study was assigned as being of 1: high risk of bias, 2: some concerns of bias or 3: low risk of bias. Aspects evaluated include the randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome and patients, selection of reported bias, and overall bias. The final visualization figures were performed by robvis which is a shiny web app for visualizing risk-of-bias assessments [25].

Statistical analysis

We utilized Review Manager software 5.4 (Cochrane Collaboration, Denmark) and the DerSimonian-Laird random-effects model to perform all statistical analyses indicated. For dichotomous variables, we pooled risk ratios (RRs) along with their corresponding 95% confidence intervals (CIs) and applied the inverse variance (I-V) method. A P-value below 0.05 was considered significant. Heterogeneity across studies was measured using Higgins I^2 static; studies showing a value higher than 50% demonstrate significantly high heterogeneity.

Results

Search results

We retrieved 4,048 papers from five electronic databases. Using EndNote software, duplicate articles were eliminated, leaving us with a total of 2,785 papers. After reviewing titles and abstracts, 2,771 papers were excluded. We then assessed the full texts of the remaining 14 studies for final eligibility. Ultimately, eight papers were included in our meta-analysis [12–18, 26]. The study selection process is illustrated in Figure S1.

Baseline characteristics of included studies

This review included 8 RCTs published from 2009 to 2023. The analyzed RCTs reported data for 5299 patients. DAPT was administered in 2,679 patients while 2,620 individuals received TAPT. The mean age of patients was 61.4 years. Male patients constituted > 70% of the study sample. 3 trials were conducted in China, 4 in Korea, and 1 in Brazil. Duration of follow-up ranged from 9 months to 2 years across included RCTs. 21.4% of patients were smokers, 19.47% had dyslipidemia, 5% patients had undergone PCI previously, and 35.2% patients had diabetes. The details of study characteristics and patients' baselines are reported in Tables 1 and 2.

Clinical outcomes

All-cause death

The pooled analysis demonstrated a comparable risk of all-cause death with DAPT and TAPT (RR: 1.41, 95% CI: 0.89 to 2.22, $p = 0.14$). Heterogeneity was low ($I^2 = 19\%$). A subgroup analysis was performed based on duration of follow-up. The relative risk remained nonsignificant for all-cause death at a follow-up of 2 years, 18 months, and 1 year (RR: 1.15; 95% CI: 0.74 to 1.79, $p = 0.55$). However, a significantly increased risk was observed for all-cause death at 1 month with DAPT (RR: 1.15; 95% CI: 0.74 to 1.79, $p = 0.02$). The difference between subgroups was non-significant ($P_{interaction} = 0.19$). Figure S2.

Cardiac death

The pooled analysis demonstrated a comparable risk of cardiac death with DAPT and TAPT (RR: 1.40, 95% CI: 0.72 to 2.69, $p = 0.32$). Heterogeneity was low ($I^2 = 23\%$). The relative risk remained nonsignificant for cardiac death at all follow-up intervals (2 years, RR: 1.50, 95% CI: 0.25 to 8.93, $p = 0.66$; 18 months RR: 2.97, 95% CI: 0.12 to 72.58, $p = 0.51$; 1 year, RR: 0.87, 95% CI: 0.32 to 2.37, $p = 0.79$-, and 1-month RR: 3.64, 95% CI: 1.02 to 12.99, $p = 0.05$). The difference between subgroups was non-significant ($P_{interaction} = 0.37$). Figure S3.

Table 1 Characteristics of the included studies

Name	Year	Country	Type of DAPT	Type of TAPT	Male	Female	Mean Age	Number of participants in each group	Follow up period	Aim	Conclusion
Han et al.	2009	China	Aspirin and clopidogrel	Aspirin, clopidogrel and cilostazol	DAPT (443)// TAPT (446)	DAPT (165)// TAPT (158)	DAPT (60.2)// TAPT (59.6)	DAPT (608)// TAPT (604)	1-year	The primary end point was a composite of cardiac death, nonfatal myocardial infarction, stroke, or target vessel revascularization (TVR) at 1 year after randomization. The secondary end points were TVR and hemorrhagic events.	For patients with acute coronary syndromes, triple-antiplatelet therapy consisting of cilostazol, aspirin, and clopidogrel reduced long-term cardiac and cerebral events after PCI, especially for patients with high-risk profiles.
Kim et al.	2014	Korea	Aspirin and clopidogrel	Aspirin, clopidogrel and cilostazol	DAPT (321)// TAPT (309)	DAPT (136)// TAPT (148)	DAPT (62.8)// TAPT (62.9)	DAPT (457)/ TAPT (457	2-year	The present study was performed to determine (1) whether a 6-month addition of cilostazol to DAT has a potential legacy effect beyond the period of its use; (2) whether cilostazol can eliminate adverse smoking outcome; and (3) whether the prognostic meaning of PPR (according to PRU) is dependent on smoking status, through analysis of the 2-year clinical results from the CILON-T (Influence of CILostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting Stent implantation) trial.	Adverse clinical effects of smoking may be eliminated by the addition of cilostazol to DAT after DES implantation. This may be due to the stimulation of cilostazol's antiplatelet effects by smoking.
Lee et al.	2011	Korea	Aspirin and clopidogrel	Aspirin, clopidogrel and cilostazol	DAPT (175)/ TAPT (178	DAPT (75)/ TAPT (71)	DAPT (62.1)/ TAPT (60.9)	DAPT (249)/ TAPT (250)	12-month	Patients receiving triple antiplatelet therapy after long zotarolimus-eluting stent implantation had decreased extent of late luminal loss, percent intimal hyperplasia volume, and angiographic restenosis, resulting in a reduced risk of 12-month target lesion revascularization compared with patients receiving dual antiplatelet therapy.	Patients receiving triple antiplatelet therapy after long zotarolimus-eluting stent implantation had decreased extent of late luminal loss, percent intimal hyperplasia volume, and angiographic restenosis, resulting in a reduced risk of 12-month target lesion revascularization compared with patients receiving dual antiplatelet therapy.
Lee et al.	2017	Korea	Aspirin and clopidogrel	Aspirin, clopidogrel and cilostazol	DAPT (151)/ TAPT (137)	DAPT (51)/ TAPT (65)	DAPT (62.5)/ TAPT (61.9)	DAPT (202)/ TAPT (202)	1 year.	This study sought to evaluate the impact of triple antiplatelet therapy on clinical outcomes in patients treated with second-generation drug-eluting stents (DES) for coronary artery disease.	Triple antiplatelet therapy with cilostazol after implantation of second-generation DES improved clinical outcomes, mainly by reducing TVR.

Table 1 (continued)

Name	Year	Country	Type of DAPT	Type of TAPT	Male	Female	Mean Age	Number of participants in each group	Follow up period	Aim	Conclusion
Park et al.	2023	Korea	Aspirin and clopidogrel	Aspirin, clopidogrel and cilostazol	DAPT (262)/ TAPT 1 M (256)/ TAPT 6 M (255)	DAPT (58)/ TAPT 1 M (61)/TAT 6 M (56)	DAPT (62.6)/ TAPT 1 M (61.4)/ TAPT 6 M (60.9)	DAPT (320)/ TAPT 1 M (317)/TAT 6 M (311)	1-year	This study aimed to compare the efficacy and safety of short-term TAT (cilostazol for 1 month) and long-term TAT (cilostazol for 6 months) with those of DAT in patients with STEMI undergoing primary PCI with DESs.	The addition of cilostazol to DAT did not reduce the incidence of 1-year MACEs compared with DAT alone. Instead, it may be associated with an increased risk of drug intolerance and side effects, including in-hospital bleeding and headaches.
Tang et al.	2018	China.	Aspirin and clopidogrel	Aspirin, clopidogrel and cilostazol	DAPT (219)/ TAPT (211)	DAPT (140)/TAPT (144)	DAPT (58.12)/ TAPT (58.39)	DAPT (359)/ TAPT (355)	18-month	The goal of this study is to conduct a head-to-head comparison of the safety and effectiveness of intensified antiplatelet therapies (either double dose clopidogrel [DOUBLE] or adjunctive cilostazol [TRIPLE]) and conventional strategy (STANDARD) in patients after percutaneous coronary intervention.	In patients with low responsiveness to clopidogrel, as measured by thromboelastography, the intensified antiplatelet strategies with adjunctive use of cilostazol significantly improved the clinical outcomes without increasing the risk of major bleeding. Decreased trend of negative outcomes could be observed in patients with double dosage of clopidogrel, but the difference was not significant.
Xu et al.	2016	China	Aspirin and clopidogrel	Aspirin, clopidogrel and cilostazol	DAPT (44)/ TAPT (46)	DAPT (13)/ TAPT (10)	DAPT (63.21)/ TAPT (61.71)	DAPT (57)/ TAPT (56)	1-month	This study evaluated the safety and efficacy of adjunctive loading dose of cilostazol in preventing PMI in patients with acute coronary syndrome (ACS).	The present single-center, randomized study indicates that TAPT with adjunctive cilostazol was not associated with lower incidence of PCI-related PMI in patients with ACS. Further study with large study population is needed to get definite conclusions.
Mauro et al.	2017	Brazil	Aspirin and clopidogrel	Aspirin, clopidogrel and cilostazol	DAPT (37)/ TATP (38)	DAPT (28)/ TAPT (30)	DAPT (60)/ TAPT (61.6)	DAPT (65)/ TAPT (68)	9-month	This study aimed to assess the intravascular ultrasound (IVUS) of neointimal tissue hyperplasia (NIH) after triple-antiplatelet therapy (TAPT), especially in diabetic patients treated with DES.	In diabetic patients treated with DES implantation, the addition of cilostazol to standard DAPT did not result in significant improvement in 9-month angiographic and IVUS assessments. Conversely, this phosphodiesterase III inhibitor demonstrated acceptable safety clinical profile, with low rates of bleeding and vascular complications.

Table 2 Characteristics of the included patients

Name	Year	hypertension	Smoking	Dyslipidemia	Previous PCI	Diabetes
Han et al.	2009	DAPT (341)//TAPT (350)	NA	NA	NA	DAPT (122)//TAPT (141)
Kim et al.	2014	DAPT (341)//TAPT (350)	DAPT (120)//TAPT (109)	DAPT (181)//TAPT (199)	DAPT (12)//TAPT (32)	DAPT (143)//TAPT (169)
Lee et al.	2011	DAPT (341)//TAPT (350)	DAPT (75)/TAPT (76)	NA	DAPT (16)/TAPT (18)	DAPT (84)/TAPT (92)
Lee et al.	2017	DAPT (341)//TAPT (350)	DAPT (50)/TAPT (54)	NA	DAPT (15)/TAPT (20)	DAPT (68)/TAPT (57)
Park et al.	2023	DAPT (341)//TAPT (350)	DAPT (137)/TAPT 1 M (151)/TAPT 6 M (145)	DAPT (36)/TAPT 1 M (28)/TAPT 6 M (30)	NA	DAPT (85)/TAPT 1 M (93)/ TAPT 6 M (74)
Tang et al.	2018	DAPT (341)//TAPT (350)	DAPT (137)/TAPT (137)	DAPT (246)/TAPT (229)	DAPT (77)/TAPT (67)	DAPT (115)/TAPT (121)
Xu et al.	2016	DAPT (341)//TAPT (350)	DAPT (29)/TAPT (29)	NA	NA	DAPT (24)/TAPT (22)
Mauro et al.	2017	DAPT (341)//TAPT (350)	DAPT (15)/TAPT (16)	DAPT (54)/TAPT (59)	DAPT (3)/TAPT (6)	Non-insulin dependent DAPT (121)/TAPT (58)///insulin dependent DAPT (12)/TAPT (7)

MACE

The pooled analysis demonstrated a comparable risk of MACE with DAPT and TAPT (RR: 1.27, 95% CI: 0.90 to 1.78, $p = 0.18$). Heterogeneity was moderate ($I^2 = 56\%$). A similar effect was observed at a follow-up of 1 year (RR: 1.13, 95% CI: 0.73 to 1.74, $p = 0.58$), and 18 months (RR: 1.29, 95% CI: 0.76 to 2.18, $p = 0.34$). However, at short-term follow-up of 1 month, a significantly increased risk for MACE was observed with DAPT (RR: 2.98, 95% CI: 1.09 to 8.15, $p = 0.03$). The difference between subgroups was non-significant ($P_{interaction} = 0.22$). Figure S4.

Myocardial infarction

The pooled analysis demonstrated a comparable risk of myocardial infarction with DAPT and TAPT (RR: 1.20, 95% CI: 0.77 to 1.85, $p = 0.42$). Heterogeneity was low ($I^2 = 0\%$). The relative risk remained nonsignificant for myocardial infarction at all follow-up intervals (2 years, RR: 1.33, 95% CI: 0.47 to 3.81, $p = 0.59$; 18 months RR: 1.24, 95% CI: 0.59 to 2.60, $p = 0.58$; 1 year, RR: 1.08, 95% CI: 0.55 to 2.12, $p = 0.83$, and 1-month RR: 1.49, 95% CI: 0.25 to 8.89, $p = 0.66$). The difference between subgroups was non-significant ($P_{interaction} = 0.98$). Figure S5.

Stroke

The pooled analysis demonstrated a comparable risk of stroke with DAPT and TAPT (RR: 1.51, 95% CI: 0.85 to 2.68, $p = 0.16$). Heterogeneity was low ($I^2 = 0\%$). A subgroup analysis was performed based on duration of follow-up which showed a non-significant difference across a follow-up of 1 month (RR: 6.95, 95% CI: 0.36 to 134.34, $p = 0.20$), 1 year (RR: 2.24, 95% CI: 0.82 to 6.15, $p = 0.12$), 18 months (RR: 1.41, 95% CI: 0.54 to 3.67, $p = 0.48$), and 2 years (RR: 0.86, 95% CI: 0.29 to 2.53, $p = 0.78$, $P_{interaction} = 0.44$). Figure S6.

Stent thrombosis

The pooled analysis demonstrated a comparable risk of stent thrombosis with DAPT and TAPT (RR: 0.64, 95% CI: 0.26 to 1.55, $p = 0.32$). Heterogeneity was low ($I^2 = 0\%$). The subgroup based on the duration of follow-up showed a non-significant difference across a follow-up of 1 month (RR: 1.49, 95% CI: 0.25 to 8.89, $p = 0.66$), 1 year (RR: 0.48, 95% CI: 0.13 to 1.73, $p = 0.26$), and 18 months (RR: 0.49, 95% CI: 0.09 to 2.68, $p = 0.41$, $P_{interaction} = 0.57$). Figure S7.

Target vessel revascularization

The pooled analysis demonstrated a trend of increased risk of target vessel revascularization with DAPT compared to TAPT without reaching statistical significance (RR: 1.61, 95% CI: 1.00 to 2.58, $p = 0.05$). Heterogeneity was low ($I^2 = 41\%$). The relative risk remained non-significant for myocardial infarction at 1-year RR: 1.45, 95% CI: 0.89 to 2.35, $p = 0.13$). At 18 months, a significantly increased risk was observed in the DAPT group (RR: 3.21, 95% CI: 1.06 to 9.76, $p = 0.04$). The difference between subgroups was non-significant ($P_{interaction} = 0.20$). Figure S8.

Target lesion revascularization

The pooled analysis demonstrated a comparable risk of target lesion revascularization with DAPT and TAPT (RR: 1.35, 95% CI: 0.73 to 2.51, $p = 0.33$). Heterogeneity was moderate ($I^2 = 52\%$). A subgroup analysis was performed based on duration of follow-up which showed a non-significant difference across a follow-up of 1 month, 1 year, and 2 years ($P_{interaction} = 0.95$). Figure S9.

In-hospital events

No statistically significant difference was observed between DAPT and TAPT for reducing overall in-hospital events (RR: 0.40, 95% CI: 0.13 to 1.20, $p = 0.33$). No heterogeneity was observed ($I^2 = 0\%$). The risk remained comparable for myocardial infarction (RR: 0.77, 95% CI: 0.10 to 5.82, $p = 0.80$), and cardiac death (RR: 0.16, 95% CI: 0.02 to 1.34, $p = 0.09$). However, for in-hospital all-cause death DAPT was associated with a significantly

reduced risk (RR: 0.27, 95% CI: 0.07 to 0.94, $p = 0.04$). Figure S10.

Bleeding

The pooled analysis demonstrated a comparable risk of bleeding with DAPT and TAPT (RR: 0.71, 95% CI: 0.44 to 1.13, $p = 0.15$). Heterogeneity was low ($I^2 = 36\%$). Figure S11.

Adverse events

A significantly reduced risk of headache and palpitation was observed with DAPT compared to cilostazol -based TAPT, with pooled RR (RR: 0.15, 95% CI: 0.06 to 0.33, $p < 0.001$) and (RR: 0.24, 95% CI: 0.08 to 0.73, $p = 0.01$), respectively. Figure S12–S13.

Quality assessment

The ROB-2 quality assessment tool was employed to evaluate the quality of the included RCTs. All studies included were determined to have a low risk of bias. The details of the quality assessment are presented in Figure S14.

Discussion

Studies comparing DAPT and TAPT for ischemic heart disease indicate that DAPT, typically combining aspirin with a P2Y12 inhibitor, such as clopidogrel, is an effective post-PCI strategy that reduces the risk of stent thrombosis and ischemic events [27]. In our study, the TAPT regimen specifically included cilostazol as one of its components, distinguishing it from the other TAPT strategies. Our analysis aligns with prior findings showing a comparable stent thrombosis risk between DAPT and TAPT with cilostazol (RR, 0.64; 95% CI: 0.26 to 1.55, $p = 0.32$), indicating no significant advantage of TAPT with cilostazol in preventing stent thrombosis. TAPT is generally reserved for high-risk patients because of an increased risk of bleeding. Extending antiplatelet therapy mitigates ischemic risks but increases bleeding complications, emphasizing the importance of individualized treatment [28].

Studies comparing single versus dual antiplatelet therapy after coronary artery bypass grafting (CABG) found similar major adverse cardiac and cerebrovascular events (MACCE) between the SAPT and DAPT groups, with no notable increase in bleeding, suggesting a limited survival benefit for DAPT in certain post-CABG patients [29]. Our findings focus specifically on TAPT incorporating cilostazol, showing its comparable effectiveness to DAPT, with no significant differences in MACE observed between the two therapies (RR: 1.27, 95% CI: 0.90 to 1.78, $p = 0.18$). This finding reinforces DAPT's suitability of DAPT for a broad patient population. Additionally, in patients with a high bleeding risk undergoing PCI, DAPT with ticagrelor showed lower rates of recurrent myocardial infarction but increased bleeding risk, supporting a more personalized, risk-adjusted therapy approach [30]. However, in patients after rug-eluting stent implantation the addition of cilostazol to aspirin and clopidogrel was associated with significant reduction in MACE [31].

Evaluating the effectiveness of TAPT with cilostazol compared with DAPT in reducing cardiovascular events post-PCI, evidence generally favors DAPT for balancing ischemic prevention with a lower bleeding risk. Our study demonstrated comparable myocardial infarction risks between DAPT and TAPT with cilostazol (RR: 1.20, 95% CI: 0.77 to 1.85, $p = 0.42$), suggesting no significant ischemic benefit of adding cilostazol to TAPT compared with DAPT. TAPT regimens, which include aspirin, a P2Y12 inhibitor, and cilostazol, may provide additional ischemic protection in specific cases such as concurrent atrial fibrillation. However, this results in a higher bleeding rate. A previous meta-analysis study showed that cilostazol did not reduce the bleeding significantly post-PCI [32]. Also, Tan et al. [33] observed no significant differences in MACCE between TAPT and DAPT in post-PCI patients with atrial fibrillation, although TAPT resulted in significantly higher bleeding rates. Similarly, our findings showed an increased risk of adverse events with TAPT with cilostazol compared to DAPT (RR: 0.29, 95% CI: 0.16 to 0.53, $p < 0.01$), supporting the preference for DAPT in most patients owing to its safer profile [34].

Quality improvement initiatives that reduce TAPT use demonstrate fewer bleeding complications with DAPT, while maintaining similar ischemic protection. These findings suggest that DAPT is safe and equally effective in many post-PCI patients [35]. In our bleeding outcome analysis, there was no significant difference between DAPT and TAPT with cilostazol (RR, 0.71; 95% CI: 0.44 to 1.13, $p = 0.15$), reinforcing the favorable bleeding profile of DAPT. Even after drug-eluting stent implantation, a meta-analysis study by Chen et al., 2013, revealed that the addition of cilostazol to aspirin and clopidogrel did not associated with significant reduction in the risk of bleeding and stent thrombosis [31]. Current data support DAPT as the preferred post-PCI option owing to its balanced efficacy and safety, reserving TAPT regimens, including cilostazol, for specific high-risk cases requiring enhanced ischemic protection despite increased bleeding risks.

The choice between DAPT and TAPT with cilostazol is crucial for managing patients with ischemic heart disease, balancing ischemic event reduction, and bleeding risk. DAPT, which combines aspirin and a P2Y12 inhibitor (e.g., clopidogrel or ticagrelor), is the standard post-PCI treatment. It effectively reduces stent thrombosis and recurrent ischemic events with a relatively low bleeding risk and is suitable for most patients [36]. TAPT with

cilostazol is warranted in cases of high thrombotic risk, such as concurrent atrial fibrillation or complex coronary artery disease, in which enhanced antithrombotic protection justifies the higher bleeding risk. Studies indicate that although TAPT with cilostazol may offer additional ischemic protection, it significantly increases the risk of bleeding. Our results show higher adverse event rates with TAPT with cilostazol than with DAPT, supporting its use in high-risk cases only. For instance, in patients with atrial fibrillation undergoing PCI, TAPT increases major bleeding without substantially reducing adverse cardiovascular events, emphasizing individualized treatment [33].

Clinical guidelines recommend tailoring therapy based on individual risk factors such as age, bleeding history, and comorbidities using predictive scores such as CHA2DS2-VASc for stroke risk and HAS-BLED for bleeding risk to aid risk stratification [34].

Research on short-term mortality and MACE risks with DAPT versus TAPT with cilostazol post-PCI generally favors DAPT as a safer option with fewer bleeding complications, especially in the early post-PCI period. DAPT effectively reduces thrombotic events and MACE without significantly increasing the bleeding risk, making it preferable for most patients. Our subgroup analysis revealed a significantly increased all-cause death risk with DAPT at 1 month (RR, 1.15; 95% CI: 0.74 to 1.79; $p = 0.02$), although this risk did not persist over a longer follow-up period.

Studies indicate that although TAPT with cilostazol may provide better thrombotic protection in high-risk cases, it significantly increases the risk of bleeding, potentially negating the reduction in ischemic events. This results in MACE rates like those observed with DAPT [33]. The WOEST 2 registry also reported more bleeding events with TAPT regimens without significantly reducing short-term mortality or MACE compared to DAPT, supporting guidelines favoring DAPT for reducing bleeding risk while preventing early ischemic events [34]. Previous meta-analyses study by Tan et al., 2021 [37], showed that Cilostazol has greater efficacy, and a better safety profile compared to traditional antiplatelet therapies like aspirin and clopidogrel for secondary stroke prevention; however, it does not seem to influence functional outcomes.

Patient demographics and baseline characteristics, such as age, comorbidities, and genetic factors, significantly affect antiplatelet therapy outcomes in patients undergoing PCI. In adults aged > 80 years, stopping antiplatelet therapy correlates with increased MACE without raising minor bleeding risks, highlighting the need for continued therapy in high-risk older populations [38]. In our study, over 70% of male patients had a mean age of 61.4 years and high comorbidity rates. These findings are particularly relevant to this demographic and support the need for careful risk stratification. The SMART Registry indicates that intensified antiplatelet therapy is often used in older patients with more comorbidities to prevent MACE, reflecting the necessity of tailored approaches for complex clinical profiles [39].

Comparative studies on DAPT and TAPT in treating ischemic heart disease suggest that DAPT generally has a safer profile with reduced major bleeding risk, especially in patients without a high thrombotic risk. DAPT, which combines aspirin and a P2Y12 inhibitor, is widely used post-PCI to effectively reduce ischemic events while minimizing bleeding complications. Our analysis of adverse events demonstrated that TAPT regimens specifically including cilostazol were associated with increased adverse events without significant improvement in ischemic outcomes, reinforcing the safer profile of DAPT. WOEST 2 reported fewer bleeding events with DAPT than with TAPT, without increased thrombotic complications, supporting its use in standard-risk patients [34]. TAPT regimens, including cilostazol or anticoagulants, are often reserved for high-risk cases because of the increased risk of bleeding. In patients with atrial fibrillation, TAPT including cilostazol provided additional ischemic protection but significantly increased the risk of major bleeding, potentially offsetting its benefits [33]. Our findings align with these observations, as TAPT's higher bleeding risk without substantial ischemic benefits supports its reservation in specific high-risk cases.

Several limitations should be acknowledged in this meta-analysis. First, the included studies were conducted predominantly in China, Korea, and Brazil, which may limit the generalizability of the findings to other populations. Second, while the overall risk of bias was low, variations in follow-up duration and sample sizes might introduce heterogeneity in certain outcomes. Third, the differences in the TAPT regimens across studies may have influenced the results. Additionally, DAPT with aspirin plus clopidogrel was consistently used across all studies, which could impact the comparative analysis and overall interpretation of the findings.

Conclusion

This meta-analysis demonstrates that DAPT and TAPT, specifically including cilostazol, offer comparable clinical outcomes for patients with ischemic heart disease undergoing PCI. While no significant differences were observed in key endpoints such as all-cause mortality, cardiac death, and myocardial infarction. Given the increased bleeding risks associated with extended antiplatelet therapy, individualized treatment approaches remain crucial. Future large-scale, multicenter RCTs are needed to further assess the efficacy and safety of

cilostazol- based TAPT compared to DAPT across diverse patient populations.

Supplementary Information

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Supplementary Material 1

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Author contributions
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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

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Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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