




Systematic Review

Antiplatelet Therapy in Chronic Coronary Artery Disease Patients With a History of Angioplasty. When is Aspirin Not Enough? A Systematic Review

Stylianos Fiflis^{1,*}, Michail Papamichalis¹, Andrew Xanthopoulos¹¹Department of Cardiology, University Hospital of Larissa, Faculty of Medicine, University of Thessaly, 41110 Larissa, Greece*Correspondence: stylianosfiflis@yahoo.com (Stylianos Fiflis)

Academic Editor: Stefano De Servi

Submitted: 24 June 2025 Revised: 1 August 2025 Accepted: 13 August 2025 Published: 24 September 2025

Abstract

Background: Antiplatelet therapy represents a cornerstone of secondary prevention in patients with chronic coronary syndrome (CCS) who have undergone percutaneous coronary intervention (PCI). However, the optimal antiplatelet regimen and optimal duration remain under investigation, as treatment must be individualized to balance the thrombotic and bleeding risks. Thus, this systematic review aimed to present the most recent evidence on antiplatelet strategies in chronic coronary syndrome patients with prior PCI, highlighting findings relevant to subgroups with increased thrombotic risk. **Methods:** A systematic search of the PubMed database, the Cochrane Library, and ClinicalTrials.gov was conducted up to 29 May 2025. Studies were screened and selected based on predefined eligibility criteria. A total of 14 studies were included and were synthesized narratively. **Results:** Extended dual antiplatelet therapy (DAPT) with ticagrelor plus aspirin, compared to aspirin alone, improved primary outcomes in 5101 patients with stable coronary disease and diabetes mellitus (hazard ratio (HR) 0.81; 95% confidence interval (CI), 0.71–0.93; $p = 0.003$), and reduced major adverse cardiovascular events (HR 0.85; 95% CI, 0.75–0.96; $p = 0.009$) among 11,260 patients with history of prior myocardial infarction and additional risk factors such as multivessel coronary artery disease or chronic kidney disease. In 2431 patients, long-term clopidogrel monotherapy, compared to aspirin monotherapy, was associated with improved primary outcomes (HR 0.74; 95% CI 0.63–0.86; $p < 0.001$) along with a reduction in major bleeding (HR 0.65; 95% CI 0.47–0.90; $p = 0.008$). Long-term ticagrelor monotherapy, compared to aspirin, was associated with fewer ischemic events, as defined by the primary endpoint (HR 0.73; 95% CI 0.57–0.94; $p = 0.014$), but an increased risk of Bleeding Academic Research Consortium (BARC) type 2,3, or 5 bleeding (HR 1.52; 95% CI 1.11–2.08; $p = 0.009$). Subgroup analyses suggested benefits of extended DAPT versus aspirin in patients with peripheral artery disease ($n = 246$; HR 0.54; 95% CI 0.31–0.95; $p = 0.03$), in those with two or more implanted stents ($n = 505$; $p = 0.02$), and in patients treated for in-stent restenosis ($n = 224$; $p = 0.034$). **Conclusion:** Extended DAPT demonstrated benefits over 30 months, while clopidogrel monotherapy has shown sustained effectiveness for up to 5.8 years in CCS patients with a history of PCI. Individualized treatment based on thrombotic and bleeding risk remains essential. Large-scale randomized trials are warranted to define the populations most likely to benefit from long-term intensified antiplatelet therapy. **The PROSPERO Registration:** CRD420251069004, <https://www.crd.york.ac.uk/PROSPERO/view/CRD420251069004>.

Keywords: chronic coronary syndrome; history of percutaneous coronary intervention; aspirin; dual antiplatelet therapy; ticagrelor monotherapy; clopidogrel monotherapy

1. Introduction

Antiplatelet therapy is a cornerstone of secondary prevention in patients who have undergone percutaneous coronary intervention (PCI). The standard regimen in these patients involves 6 months of dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ inhibitor for chronic coronary syndrome (CCS) or 12 months for acute coronary syndrome (ACS), followed by aspirin monotherapy [1]. According to current European Society of Cardiology (ESC) guidelines, patients with CCS undergoing PCI who are at increased ischemic risk but low bleeding risk may benefit from prolonged potent antiplatelet therapy rather than standard aspirin monotherapy [2]. Alternative strategies include long-term monotherapy with clopidogrel or ticagrelor. Although clopidogrel demonstrated favorable

outcomes in the CAPRIE trial, its effectiveness is limited by variable platelet reactivity in a notable proportion of patients, a phenomenon less commonly observed with more potent thienopyridines such as prasugrel and ticagrelor [3,4]. However, use of ticagrelor has been associated with dyspnea in up to 1 in 15 patients, a side effect that may be mitigated by the use of the 60 mg dose [5]. Another option is prolonged DAPT, which offers enhanced ischemic protection through synergistic inhibition of multiple platelet activation pathways. However, this approach clearly carries increased risk of bleeding [6]. It is evident that the optimal antiplatelet therapy should be individualized to maintain protection against ischemic events without unnecessarily increasing bleeding risk, thus achieving maximal therapeutic benefit. Despite this, most clinical trials evaluate antiplatelet regimens across broad popula-



tions rather than in subgroups defined by comorbidities or high-risk clinical and anatomical features [7]. This systematic review explores the latest evidence on managing CCS, highlighting patient subgroups with a high thrombotic burden who may confer greater benefit from intensified antiplatelet regimens, such as prolonged DAPT or P2Y12 inhibitor monotherapy, compared to standard long-term aspirin monotherapy.

2. Methodology

2.1 Aim of the Review

The optimal antiplatelet strategy for patients with CCS and a history of PCI remains an area of ongoing research. According to recent ESC guidelines, aspirin is the agent of choice for secondary prevention following an initial period of DAPT. The duration of this initial DAPT may be shortened in patients at high bleeding risk or extended in those with high thrombotic burden and no significant bleeding risk factors [2]. This systematic review aims to present the current evidence on long-term antiplatelet strategies in patients with CCS and prior PCI. Specifically, it explores the use of prolonged therapy either as monotherapy with a non-aspirin antiplatelet agent or as combination antiplatelet therapy, compared with aspirin monotherapy. Although the included studies were not limited to patients at high thrombotic risk, as defined in subsection 2.6, particular emphasis was placed on findings relevant to such subgroups, where reported.

2.2 PICO Framework and Study Inclusion Criteria

The PICO framework was used to formulate the clinical question and guide the literature search strategy.

Population (P): Patients with CCS and a history of PCI.

Intervention (I): Long-term therapy with aspirin.

Comparison (C): Monotherapy with alternative antiplatelet agents such as clopidogrel, ticagrelor; prolonged DAPT with aspirin plus clopidogrel or plus a potent P2Y12 inhibitor.

Outcome (O): Effectiveness of more potent antiplatelet regimens in preventing ischemic events, including cardiovascular mortality, all-cause mortality, myocardial infarction, stent thrombosis, bleeding.

To be eligible for inclusion in this systematic review, studies were required to meet the following criteria: publication in English language, randomized controlled trial (RCT) design or subgroup analyses of RCT, provided that the subgroup met the inclusion criteria even if the primary trial did not. Eligible studies had to clearly document the antiplatelet regimens administered, including the duration of therapy and directly compare long-term aspirin therapy either with monotherapy using an alternative antiplatelet regimen or with DAPT in patients who had undergone PCI.

Observational studies were excluded from this review, as the aim was to include only high-quality data from ran-

domized trials to minimize the risk of bias. Patients receiving anticoagulation were also excluded.

2.3 Search Strategy

A comprehensive literature search was conducted independently by two reviewers using PubMed and the Cochrane Library. The search employed combinations of the following search terms: “PCI”, “percutaneous coronary intervention”, “angioplasty”, “prolonged DAPT”, “extended DAPT”, “intensified DAPT”, “monotherapy”, “clopidogrel”, “ticagrelor”, “prasugrel”, “P2Y12 inhibitor”, “P2Y inhibitor” and “long term”. No restrictions were applied regarding publication date or study design, but the search was limited to articles published in the English language. The final search was performed on 29 May 2025 and identified 1628 articles. After removing duplicates and screening for relevance based on predefined inclusion criteria, 14 studies were included in this review. Due to lack of institutional access, Embase was not searched. To address this limitation, additional efforts were undertaken, including manual screening of reference lists from relevant ESC and ACC guidelines on chronic coronary syndrome and coronary revascularization, a targeted search of ClinicalTrials.gov and screening the reference lists of included trials. These supplementary searches yielded 78 articles, of which 2 met the eligibility criteria [2,8,9]. The PRISMA 2020 flow diagram summarizing the study selection process is provided in Fig. 1.

In total, this systematic review included 11 original RCTs, 2 prespecified subgroup analyses and 1 post hoc subgroup analysis. These subgroup analyses were derived from RCTs that did not meet the predefined eligibility criteria in their primary analysis.

2.4 Data Extraction

From the 14 studies that were included, the following data were independently extracted by two reviewers: country of origin, study design, total number of enrolled patients, baseline characteristics and comorbidities such as age, sex, diabetes mellitus, smoking status and prior myocardial infarction (MI). Additional details included the indication for PCI, type of stent used, target vessel for revascularization, timing of randomization to treatment arms, and details of the intervention and comparator regimens, including duration of therapy. Study endpoints such as all-cause mortality, cardiovascular mortality, MI, stent thrombosis and bleeding events were recorded, along with follow-up duration and study limitations. The extracted data were organized into structured tables to enable systematic comparison of study characteristics and clinical outcomes. Disagreements between reviewers were resolved by consensus.

2.5 Quality Assessment

Two reviewers independently assessed the risk of bias for each study using the Cochrane Risk of Bias 2 (RoB 2.0)

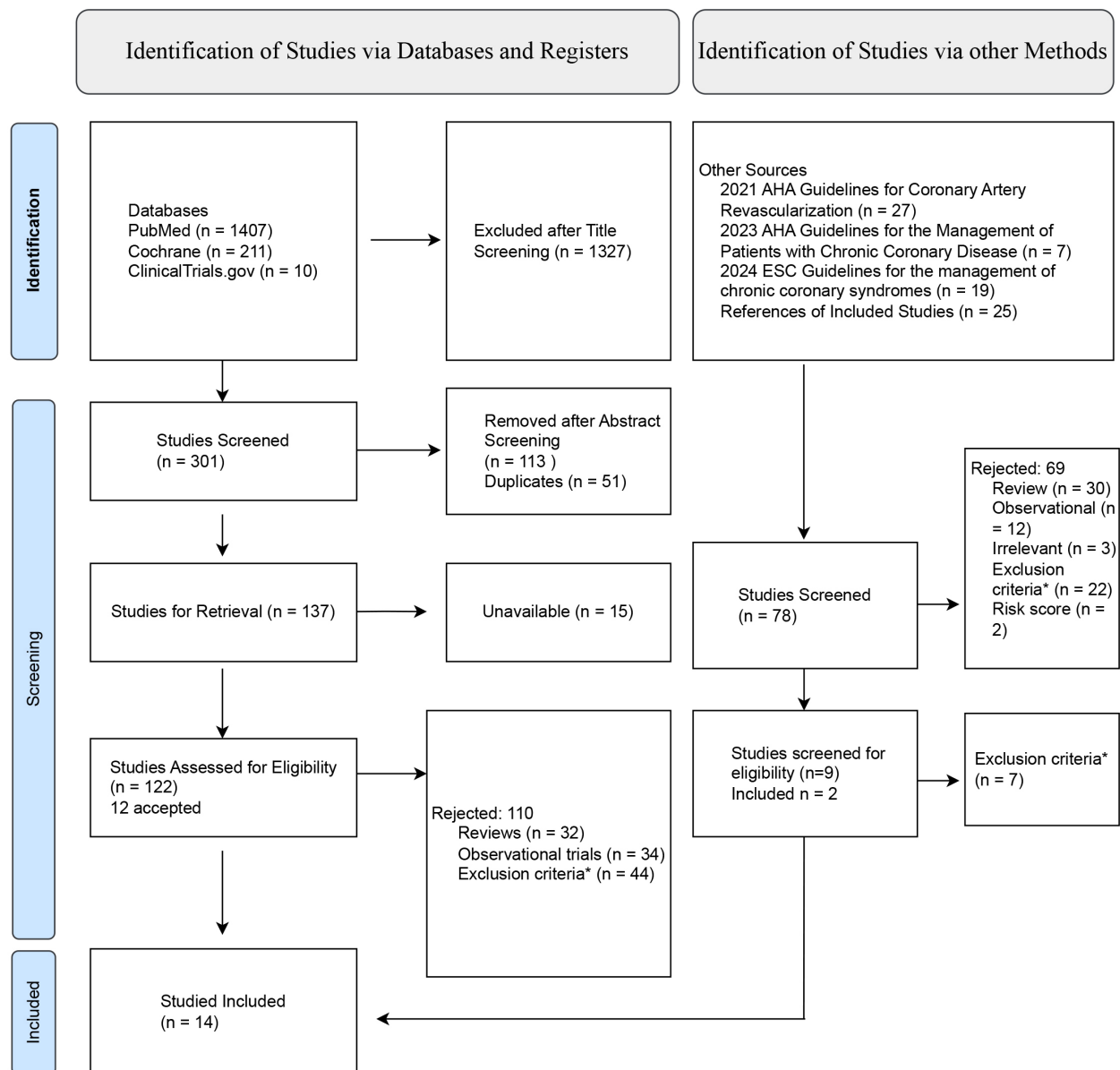


Fig. 1. PRISMA flowchart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; AHA, American Heart Association; ESC, European Society of Cardiology. *Does not include patients with history of angioplasty, anticoagulants in the treatment strategy, does not compare experimental treatment to aspirin.

tool. Discrepancies were resolved through discussion. Risk of bias was evaluated across five domains, as low, some concerns, or high. Of the 14 included studies, 10 were judged to be at low risk, 3 studies had some concerns, and 1 was judged to be at high risk. Full domain-level assessments for each study are provided in the **Supplementary Fig. 1**.

2.6 Data Synthesis

Given the substantial heterogeneity in study designs, patient populations, clinical endpoints, and follow-up durations, quantitative meta-analysis was not feasible. Instead, a narrative synthesis was conducted, focusing

on study design, population characteristics, primary outcomes, and subgroup analyses related to alternative long-term antiplatelet therapies after PCI, compared to aspirin monotherapy. The results were further organized according to the antiplatelet regimens administered.

2.7 Definitions

Standard DAPT was defined according to the 2023 ESC guidelines for acute coronary syndrome and the 2024 ESC guidelines for chronic coronary syndrome. Specifically, standard DAPT duration was considered to be 6 months following PCI for CCS and 12 months for ACS.

Table 1. Demographic and clinical characteristics of the patients.

Trial	Number of patients	Male sex	Age	Diabetes status	Prior MI	Smoking history
Studies on extended DAPT						
ARCTIC – Interruption [10]	635/624	80%/81%	64 (IQR 57–73)/64 (IQR 57–73)	31%/36%	31%/30%	A 23%/24%
ITALIC [11]	924/926	79%/81%	(61.5 ± 11.2)/(61.6 ± 10.9)	37%/36%	14%/15%	52%/51%
OPTIDUAL [12]	695/690	81%/79%	(64.1 ± 10.8)/(64.2 ± 11.5)	30%/32%	17%/17%	A or R 61%/57%
DAPT (BMS) [13]	842/845	74%/78%	(58.9 ± 10.5)/(59.2 ± 11.1)	21%/20%	19%/21%	A or R 43%/43%
DAPT (DES) [14]	5020/4941	75%/74%	(61.8 ± 10.2)/(61.6 ± 10.1)	31%/30%	22%/21%	A or R 24%/24%
DES LATE [15]	2531/2514	69%/69%	(62.5 ± 10)/(62.3 ± 10.1)	28%/28%	4%/3%	A 27%/28%
NIPPON [16]	1653/1654	79%/78%	(67.2 ± 9.9)/(67.4 ± 9.6)	38%/37%	11%/12%	A or R 60%/58%
REAL-LATE and ZEST-LATE [17]	1537/1344	70%/69%	(62 ± 9.8)/(61.9 ± 9.9)	25%/27%	3%/3%	A 29%/32%
PRODIGY [18]	987/983	77%/76%	(67.8 ± 11)/(67.9 ± 11)	24%/23%	27%/26%	A 22%/25%
PEGASUS-TIMI 54 [19]	ASA+T 90 mg 5612/ ASA+T 60 mg 5658/ ASA 5621	DES 79.9%, BMS 77.5%	65 (IQR 58–71)	DES 32%, BMS 29%	DES 16.7%, BMS 14.3%	A DES 17%, BMS 17%
THEMIS-PCI [20]	5101/5194	69%/69.3%	66 (IQR 61–72)	100%	0%	A 12%/11%
Studies on long-term P2Y12 inhibitor monotherapy						
HOST-EXAM Extended [21]	2431/2286	74%/75%	(63.3 ± 10.8)/(63.3 ± 10.7)	33%/33%	16%/15%	A 19.7%/21%
SMART-CHOICE 3 [22]	2752/2754	82%/18%	66 (IQR 58–73)/65 (IQR 58–73)	40%/41%	46.6%/46.1%	A 16%/18%
GLOBAL LEADERS [23]	5308/5813	77%/77%	(63.7 ± 10.2)/(64.1 ± 10)	24%/24%	21%/22%	A 26%/26%

Data are presented as (intervention/control group). A, active; R, recent; MI, myocardial infarction; ASA, aspirin; T, ticagrelor; IQR, interquartile range; DES, drug eluting stent; BMS, bare metal stent; DAPT, dual antiplatelet therapy; TIMI, thrombolysis in myocardial infarction.

Table 2. Study design and antiplatelet strategies.

Trial	Country	Trial type	Randomization	Follow up	Initial regimen	Long term regimen
Studies on extended DAPT						
ARCTIC – Interruption [10]	France	Open label, superiority RCT	12 m after initial DAPT	18 m	12 m DAPT	18 m DAPT/ASA
ITALIC [11]	France	Open label, noninferiority RCT	6 m after initial DAPT	24 m	6 m DAPT	24 m DAPT/ASA
OPTIDUAL [12]	France	Open label, superiority RCT	12 ± 3 m after initial DAPT	36 m	12 m DAPT	48 m DAPT/ASA
DAPT (BMS) [13]	International	Double blind, superiority RCT	12 m after initial DAPT	33 m after randomization	12 m DAPT	30 m DAPT 112 pts with prasugrel, 730 pts with clopidogrel/ASA
DAPT (DES) [14]	International	Double blind, superiority RCT	12 m after initial DAPT	33 m after randomization	12 m DAPT	30 m DAPT 1745 pts with prasugrel, 3275 with clopidogrel/ASA
DES LATE [15]	Korea	Open label, superiority RCT	12 m after initial DAPT	24.7–50.7 m after randomization	12 m DAPT	36 m DAPT/ASA
NIPPON [16]	Japan	Open label, noninferiority RCT	Shortly after PCI	361–540 days	6 m DAPT	18 m DAPT/ASA
REAL-LATE and ZEST-LATE [17]	Korea	Open label, superiority RCT	12.8 m after PCI	28–37 m after PCI	12 m DAPT	24 m DAPT/ASA
PRODIGY [18]	Italy	Open label, superiority RCT	30 ± 5 days after PCI	2 years after PCI	6 m DAPT	24 m DAPT/ASA
PEGASUS-TIMI 54 [19]	International	Prespecified analysis of Double blind superiority RCT	1–3 years after MI	33 m	Initial regimen NS	ASA and 1:1:1 ticagrelor 90 mg, ticagrelor 60 mg, placebo
THEMIS-PCI [20]	International	Prespecified analysis of Double blind superiority RCT	1–12 m after PCI	3.3 years	Initial regimen NS	After randomization aspirin with or without ticagrelor
Studies on long-term P2Y12 inhibitor monotherapy						
HOST-EXAM Extended [21]	Korea	Open label, superiority RCT	12 ± 6 m after initial DAPT	5.8 years	12 ± 6 m DAPT	clopidogrel/ASA
SMART-CHOICE 3 [22]	Korea	Open label, superiority RCT	17.5 m after PCI	2.3 years	DAPT with Clopidogrel 3431 pts Prasugrel 645 pts Ticagrelor 1430 pts	clopidogrel/ASA
GLOBAL LEADERS [23]	International	Post hoc analysis of Open label superiority RCT	Shortly after PCI	2 years	1 m DAPT followed by 11 m ticagrelor/12 m DAPT with clopidogrel or ticagrelor	After 12 m: ticagrelor/ASA

Data are presented as (intervention/control group). ASA, aspirin; NS, not stated; m, months; pts, patients; RCT, randomized controlled trial; DAPT, dual antiplatelet therapy; MI, myocardial infarction; PCI, percutaneous coronary intervention; DES, drug eluting stent; BMS, bare metal stent; TIMI, thrombolysis in myocardial infarction.

Long-term antiplatelet therapy was defined as any antiplatelet regimen administered after the completion of standard DAPT in patients with a history of PCI.

Extended DAPT referred to the continuation of DAPT beyond the standard duration.

Intensified antithrombotic therapy was defined as either switching from aspirin to a P2Y12 inhibitor or extending DAPT beyond standard duration with the intent to enhance protection against thrombotic events.

Control group was defined as the cohort receiving aspirin monotherapy.

Intervention group was defined as the cohort receiving the investigational therapy, such as long-term DAPT or P2Y12 inhibitor monotherapy compared with aspirin monotherapy.

Complex coronary artery disease was defined as PCI involving any of the following: at least three lesions treated or three stents implanted, bifurcation lesion treated with two stents, total stent length >60 mm, chronic total occlusion, or stenting of the last patent vessel.

High thrombotic risk was defined based on the 2024 ESC guidelines for the management of chronic coronary syndromes, which consider factors such as complex PCI and clinical characteristics such as diabetes mellitus, multivessel coronary artery disease (CAD), recurrent MI, polyvascular disease (CAD plus peripheral artery disease (PAD)), premature (<45 years) or accelerated (new lesion within 2-year time frame) CAD, concomitant systemic inflammatory and/or prothrombotic disease (e.g., HIV, chronic arthritis, antiphospholipoid syndrome).

3. Results and Discussion

3.1 Study Selection and Characteristics

This systematic review included 14 studies comprising a total of 77,875 CCS patients who underwent PCI. The characteristics of the enrolled patients and their comorbidities are summarized in Table 1 (Ref. [10–23]).

Long-term aspirin monotherapy was compared with alternative therapeutic strategies, including DAPT with a P2Y12 inhibitor in 11 studies and P2Y12 inhibitor monotherapy in 3 studies. Table 2 (Ref. [10–23]) summarizes the key design features of the included studies and the antiplatelet regimens administered during both the initial and long-term periods.

The angioplasty details, including the indication for the procedure, target vessel, and type of stent implanted are demonstrated in Table 3 (Ref. [10–23]).

All included trials excluded patients who experienced an ischemic or bleeding event during the standard DAPT period, with the exception of the PRODIGY trial, which included such patients. The exclusion of patients with early ischemic events introduces a risk of selection bias and limits the generalizability of trial findings to a lower-risk, event-free population. Consequently, the benefits of prolonged DAPT may be underestimated in clinical settings, where

early thrombotic events often prompt intensification or extension of antiplatelet therapy.

3.2 Efficacy and Safety of Intensified Antiplatelet Therapy

A total of nine studies including 29,345 patients evaluated whether extending DAPT to 18–48 months confers clinical benefit compared to standard duration DAPT followed by aspirin monotherapy in patients undergoing PCI [10–18]. Of these, 12,845 patients received extended DAPT with aspirin and clopidogrel, while 1942 patients across three studies received aspirin plus prasugrel. Only one of the nine studies, the DAPT trial, demonstrated a reduction in ischemic events with extended therapy in patients treated with drug eluting stent (DES). In that trial, treatment was continued for 30 months resulting in a significant reduction in the composite primary endpoint (HR 0.71; 95% CI 0.59–0.85; $p < 0.001$), without an increase in severe bleeding. Subgroup analyses by sex, age, body mass index, diabetes status, and smoking history did not reveal any significant interaction or enhanced benefit from extended therapy [14]. In contrast, the benefit was less evident in the BMS cohort of DAPT trial by Kereiakes *et al.* [13], where no significant reduction in the composite primary endpoint was observed (HR 0.92; 95% CI 0.57–1.47; $p = 0.72$). A post hoc interaction analysis found no statistically significant difference in treatment effect between DES and BMS groups for either stent thrombosis (interaction $p = 0.42$) or the primary endpoint (interaction $p = 0.32$), suggesting that the observed discrepancy may reflect limited statistical power in the smaller BMS subgroup rather than a true divergence in effect [13]. Nonetheless, reductions in stent thrombosis and spontaneous MI were seen in DES recipients but not in those with BMS, raising uncertainty about the underlying mechanism; particularly given that non–stent related MI reductions would be expected to occur irrespective of stent type [24]. Moreover, within the DES cohort, patients receiving everolimus-eluting stents (EES) did not appear to benefit from prolonged therapy for the primary endpoint, in contrast to those with paclitaxel-eluting stents (PES), who showed a more pronounced response [14]. This likely reflects the higher thrombotic risk associated with first-generation stents such as PES, which may have driven a greater absolute benefit.

Three other studies that compared prolonged DAPT with aspirin monotherapy did not show a benefit of extended DAPT over long-term aspirin monotherapy in terms of ischemic events, nor a significant increase in severe bleeding, also did not identify any subgroups, based on age, sex, diabetes status and ACS at presentation, who derived particular benefit [10,11,15]. The NIPPON study showed no overall benefit of prolonged DAPT with clopidogrel for 18 months compared to aspirin monotherapy, nor an increase in Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding. However, a significant benefit in the primary endpoint was observed exclusively in the

Table 3. Details of angioplasty procedure.

Trial	PCI indication	Target vessel	Stent type
Studies on extended DAPT			
ARCTIC – Interruption [10]	Elective	LCA 18/23 LAD 342/325 Cx 209/181 RCA 191/222	1st gen 43%/40% 2nd gen 62%/64%
ITALIC [11]	SA 41% SI 15% UA 20% NSTEMI 16% STEMI 7%	LAD 658/669 Cx 436/456 RCA 474/489	2nd gen Everolimus
OPTIDUAL [12]	SA 240/207 SI 138/151 ACS 239/262 Other 78/70	LAD 397/443 Cx 225/214 RCA 280/268	Sirolimus 214/186 Paclitaxel 164/169 Zotarolimus 89/114 Everolimus 540/522 Other 69/69
DAPT (BMS) [13]	SA 199/198 ACS 572/574 Other 71/73	LCA 0/1 LAD 308/306 Cx 206/207 RCA 437/452	BMS 100%
DAPT (DES) [14]	SA 1882/1870 ACS 2148/2103 Other 990/968	LCA 55/55 LAD 2715/2586 Cx 1473/1506 RCA 2153/2057	Everolimus 2345/2358 Paclitaxel 1350/1316 Zotarolimus 642/622 Sirolimus 577/541
DES LATE [15]	SA 1011/956 ACS 1512/1551 Other 8/7	LCA 112/90 LAD 1781/1768 Cx 715/651 RCA 976/972	Sirolimus 1566/1551 Paclitaxel 738/709 Zotarolimus 682/664 Everolimus 427/364 Other 190/210
NIPPON [16]	SA 734/805 ACS 552/527 Other 275/268	LCA 16/7 LAD 998/981 Cx 374/381 RCA 515/524	Nobori DES
REAL-LATE and ZEST-LATE [17]	SA 514/500 UA 543/559 NSTEMI 145/144 STEMI 155/141	LCA 55/44 LAD 912/921 Cx 372/334 RCA 533/546	Sirolimus 1057/1052 Paclitaxel 456/439 Zotarolimus 350/347 Other 9/9
PRODIGY [18]	SA 257/250 ACS 732/733 STEMI 321/327	LCA 55/56 LAD 518/518 Cx 321/318 RCA 346/363	3rd gen thin-strut BMS 246/246 Everolimus 248/245 Paclitaxel 245/245 Zotarolimus 248/247
PEGASUS-TIMI 54 [19]	STEMI 9552 NSTEMI 6609 Other 712	Multivessel CAD: ASA+T 90 mg 66.7%/ASA+T 60 mg 67%/ASA 67%	BMS 51%, DES 49% 1st gen DES 2289 2nd gen DES 4539 Unspecified DES 1466
THEMIS-PCI [20]	Stable CAD	NS	(DES 3371, BMS 1730)/(DES 3437, BMS 1757)
Studies on long-term P2Y12 inhibitor monotherapy			
HOST-EXAM Extended [21]	SA 620/593 SI 52/61 ACS 1759/1631	LCA 127/112 Bifurcation 261/232 Two vessel disease 763/716 Three vessel disease 439/428	1st gen 2%/1% 2nd gen 96%/97%

Table 3. Continued.

Trial	PCI indication	Target vessel	Stent type
SMART-CHOICE 3 [22]	CCS 672/662	LCA 227/198	DES
	UA 797/823	LAD 2081/1991	
	NSTEMI 678/652	Cx 1191/1155	
	STEMI 605/617	RCA 1285/1285	
GLOBAL LEADERS [23]	CCS 2742/3228	LCA 139/136	Biolimus A9 eluting stents
	UA 702/695	LAD 2670/3028	
	NSTEMI 1140/1139	Cx 1677/1824	
	STEMI 724/751	RCA 1990/2109	

Data are presented as (intervention/control group). SA, stable angina; ACS, acute coronary syndrome; UA, unstable angina; SI, silent ischemia; STEMI, ST-elevation myocardial infarction; NSTEMI, Non-ST-elevation myocardial infarction; LCA, left coronary artery; LAD, left anterior descending artery; Cx, circumflex; RCA, right coronary artery; gen, generation; DES, drug eluting stent; BMS, bare metal stent; d., disease; CAD, coronary artery disease; ASA, aspirin; T, ticagrelor; PCI, percutaneous coronary intervention; NS, not stated; DAPT, dual antiplatelet therapy; TIMI, thrombolysis in myocardial infarction.

subgroup of 505 patients who had two or more stents placed (1.2% with prolonged DAPT vs. 3.4% with standard therapy, $p = 0.02$) [16]. In the PRODIGY trial, 24-month DAPT with clopidogrel showed no overall clinical advantage and was associated with an increased risk of thrombolysis in myocardial infarction (TIMI) major bleeding compared to aspirin monotherapy. Nonetheless, long-term DAPT with clopidogrel compared to aspirin monotherapy demonstrated a significant reduction in death and MI among 224 patients treated for in-stent restenosis ($p = 0.034$), without a corresponding increase in bleeding [25]. Additionally, in a subgroup of 246 patients with PAD extended DAPT significantly reduced all-cause mortality, MI and cerebrovascular accident (HR 0.54; 95% CI 0.31–0.95; $p = 0.03$) and definite or probable stent thrombosis (HR 0.07; 95% CI 0.00–1.21, $p = 0.01$) versus aspirin monotherapy, without an associated increase in bleeding [26]. Furthermore, there was a significant reduction in definite or probable stent thrombosis in PRODIGY patients with 30% or more stenosis of the left main and/or proximal left anterior descending artery (LAD) artery, although this was accompanied by a significant increase in BARC type 3 or 5 bleeding [27].

Two studies that followed high ischemic-risk patients on 3-year DAPT with ticagrelor versus aspirin monotherapy showed significant benefit in terms of the primary composite endpoint and reduction in MI, without an increase in intracranial or fatal bleeding, though they did show a significant increase in major bleeding according to TIMI criteria. Specifically, the THEMIS-PCI trial enrolled 5101 patients with stable CAD and type 2 diabetes, demonstrating a reduction in the primary outcome with ticagrelor plus aspirin compared to aspirin alone (HR 0.81; 95% CI, 0.71–0.93; $p = 0.003$) [20]. The PEGASUS-TIMI 54 trial enrolled stable patients with a prior MI and at least one additional risk factor, such as multivessel CAD, chronic kidney disease (creatinine clearance < 60 mL/min), or a history of multiple MIs

[19,28]. In this systematic review, we included the prespecified analysis of the PEGASUS-TIMI 54 trial by Bergmark *et al.* [19], which focused on 11,260 patients with a history of PCI who received extended DAPT with ticagrelor (90 mg or 60 mg) plus aspirin. This subgroup showed a reduction in the primary endpoint compared to aspirin monotherapy (HR 0.85; 95% CI, 0.75–0.96; $p = 0.009$), with an increased risk of TIMI major bleeding (HR 2.65; 95% CI, 1.90–3.68; $p < 0.001$), but no excess in fatal or intracranial bleeding [19]. To better identify patients likely to derive net clinical benefit, Magnani *et al.* [29] conducted a post hoc analysis of PEGASUS-TIMI 54. High bleeding risk was defined by the presence of baseline anemia or a history of spontaneous bleeding requiring hospitalization. Patients without either of these characteristics, classified as having low bleeding risk, extended DAPT with ticagrelor 60 mg, resulted in significantly fewer bleeding events and was associated with a 20% relative reduction in the composite of cardiovascular death, MI, or stroke compared to aspirin monotherapy [29]. Similarly, Bonaca *et al.* [30] showed in another post hoc analysis that the number of ischemic risk factors was directly associated with the clinical benefit of extended DAPT with ticagrelor among patients without high bleeding risk, as defined by Magnani *et al.* [29]. The relative risk reduction for the primary composite endpoint was 13% in those with 0–1 risk factor, 19% with two, and 23% with three or more. These ischemic risk factors included those defined in the original PEGASUS-TIMI 54 criteria, as well as diabetes and PAD. However, the findings of these two post hoc analyses are exploratory and hypothesis-generating and should be interpreted with caution. Additionally, they evaluated the overall cohort of PEGASUS-TIMI 54 cohort, which included patients without a history of PCI.

A total of three studies evaluated the efficacy and safety of long-term P2Y12 inhibitor monotherapy compared with aspirin monotherapy in patients with CCS and

Table 4. Primary endpoint and main conclusion.

Trial	Primary endpoint	Primary endpoint [hazard ratio (95% CI)]	Conclusion
Studies on extended DAPT			
ARCTIC – Interruption [10]	All-cause death, MI, ST, stroke, or urgent revascularisation	24 (4%)/27 (4%) [1.17 (0.68–2.03) $p = 0.58$]	No superiority of extended DAPT beyond 12 to 18 months compared to aspirin monotherapy
ITALIC [11]	All-cause death, MI, urgent TVR, stroke, and major bleeding	34 (3.7%)/32 (3.5%) [0.939 (0.580–1.522) $p = 0.799$]	Non-inferiority of 6 m of DAPT compared to 24 m of therapy
OPTIDUAL [12]	All-cause death, MI, stroke, or major bleeding	40 (5.8%)/52 (7.5%) [0.75 (0.5–1.28) $p = 0.17$]	Extension of DAPT to 18–48 months did not demonstrate superiority over aspirin monotherapy
DAPT (BMS) [13]	All-cause death, MI, stroke	33 (4.04%)/38 (4.69%) [0.92 (0.57–1.47) $p = 0.72$]	Extension of DAPT to 30 m with clopidogrel or prasugrel did not demonstrate superiority in ischemic endpoints
DAPT (DES) [14]	All-cause death, MI, stroke	211 (4.3%)/285 (5.9%) [0.71 (0.59–0.85) $p < 0.001$]	Extension of DAPT to 30 m demonstrated superiority for the primary endpoint
DES LATE [15]	All-cause death, MI, stroke	61 (2.6%)/57 (2.4%) [0.94 (0.66–1.35) $p = 0.75$]	Extension of DAPT to 24 m did not confer benefit over aspirin monotherapy for the primary endpoint
NIPPON [16]	All-cause death, MI, stroke, major bleeding	24 (1.5)/34 (2.1%) [–0.6 (–1.5–0.3) $p = 0.24$]	Non-inferiority of 6m of DAPT compared to extended 18 months DAPT
REAL-LATE and ZEST-LATE [17]	MI, CV death	20 (1.8%)/12 (1.2%) [1.65 (0.8–3.36) $p = 0.15$]	Extension of DAPT to 24 m did not provide benefit in reducing MI or all-cause mortality
PRODIGY [18]	All-cause death, nonfatal MI, stroke	100 (10.1%)/98 (10%) [0.98 (0.74–1.29) $p = 0.91$]	Extension of DAPT to 24 m did not confer benefit for the primary endpoint
PEGASUS-TIMI 54 [19]	CV death, MI, stroke	ticagrelor 90 mg vs placebo: (7.13%)/(7.98%) [0.86 (0.75–0.99) $p = 0.042$] ticagrelor 60 mg vs placebo: (6.8%)/(7.98%) [0.84 (0.73–0.97) $p = 0.016$]	Both ticagrelor doses reduced the primary endpoint, with a number needed to treat (NNT) of 118 for the 90 mg dose and 85 for the 60 mg dose
THEMIS-PCI [20]	CV death, MI, stroke	367 (7.2%)/457 (8.8%) [0.81 (0.71–0.93) $p = 0.003$]	The addition of ticagrelor resulted in a significant benefit for the primary endpoint
Studies on long-term P2Y12 inhibitor monotherapy			
HOST-EXAM Extended [21]	All-cause death, nonfatal MI, stroke, readmission attributable to ACS, and BARC type 3 or greater bleeding	311 (12.8%)/387 (16.9%) [0.74 (0.63–0.86) $p < 0.001$]	Superiority of clopidogrel over long-term aspirin monotherapy was demonstrated for the primary composite endpoint
SMART-CHOICE 3 [22]	All-cause death, MI, stroke	92 (4.4%)/128 (6.6%) [0.71 (0.54–0.93) $p = 0.013$]	In high risk of recurrent ischaemic events patients, clopidogrel monotherapy results in lower risk of primary end point without an increase in bleeding
GLOBAL LEADERS [23]	All-cause death, MI, stroke	101 (1.9%)/151 (2.6%) [0.73 (0.57–0.94) $p = 0.014$]	Ticagrelor monotherapy between 12 and 24 m following initial therapy, compared to aspirin, significantly reduced the primary endpoint and the risk of MI

Data are presented in the format (intervention/control group). ST, stent thrombosis; TVR, target vessel revascularization; m, months; CV, cardiovascular; MI, myocardial infarction; DES, drug eluting stent; BMS, bare metal stent; CI, confidence interval; DAPT, dual antiplatelet therapy; TIMI, thrombolysis in myocardial infarction; BARC, Bleeding Academic Research Consortium.

history of PCI [21–23]. Extended follow-up data from the HOST-EXAM study showed that in 2431 patients clopidogrel monotherapy over a median of 5.8 years was associated with improved outcomes in the primary composite endpoint (HR 0.74; 95% CI, 0.63–0.86; $p < 0.001$) and significantly reduced major bleeding (HR 0.65; 95% CI 0.47–0.90; $p = 0.008$) compared to aspirin monotherapy. These benefits were consistent across all predefined subgroups, without any significant interaction [21]. Similarly, the SMART-CHOICE 3 trial demonstrated that clopidogrel monotherapy was superior to aspirin in patients with high thrombotic burden including those with a prior MI or diabetes or complex PCI [22]. Notably, a significant interaction was observed between clinical presentation and treatment effect (p for interaction = 0.04), as patients without prior MI derived greater benefit from clopidogrel, reflected by a reduced incidence of major adverse cardiovascular and cerebrovascular events over 3 years (HR 0.56, 95% CI 0.39–0.81). Both trials are still undergoing extended follow-up, and final results are awaited. Due to the known variability in clopidogrel effectiveness associated with CYP2C19 loss-of-function alleles, the authors of the SMART-CHOICE 3 trial conducted an exploratory analysis to assess whether metabolic genotype influenced clinical outcomes among patients receiving clopidogrel monotherapy. Among the 731 patients who underwent genotyping, no significant differences in outcomes were observed between normal/rapid and intermediate/poor metabolizers of clopidogrel. Interestingly, a separate substudy from the PLATO trial found that clopidogrel modestly reduced leukocyte counts, independent of genotype, inflammatory biomarkers, or baseline clinical characteristics [31]. This finding raises the possibility of an off-target anti-inflammatory effect of clopidogrel, which may contribute to its clinical benefit in reducing cardiovascular events [32].

In the GLOBAL LEADERS study, extended ticagrelor monotherapy for 12 months after initial DAPT resulted in a reduction in the primary composite outcome (HR 0.73; 95% CI 0.57–0.94; $p = 0.014$), and in MI (HR 0.57; 95% CI 0.38–0.85; $p = 0.006$) compared to aspirin. No significant interaction was noted among the analyzed subgroups and although ticagrelor significantly increased BARC type 2, 3, or 5 bleedings (HR 1.52; 95% CI 1.11–2.08; $p = 0.009$), it did not increase the more serious type 3 or 5 [23]. However, because the analysis was post-hoc and non-prespecified, the findings should be interpreted with caution, given the high risk of bias.

A detailed summary of the primary endpoints, as well as myocardial infarction and stent thrombosis outcomes for each study, is provided in Tables 4,5 (Ref. [10–23]), while bleeding outcomes are presented in Table 6 (Ref. [10–23]).

3.3 Heterogeneity of Included Studies

The included studies exhibited significant heterogeneity across clinical, procedural, and methodological do-

main. The systematic review included eleven RCTs, alongside two prespecified analyses and one post hoc analysis of RCTs [10–23]. Trial designs differed in blinding, with some conducted as double-blind and others open-label (Table 2), potentially influencing risk of bias. Baseline demographics were generally comparable across studies, with similar age distributions, diabetes prevalence, and smoking history, although prior MI rates ranged notably, from 0% in THEMIS-PCI selected diabetic cohort up to 46% in SMART-CHOICE 3. Included trials covered diverse geographic regions and demonstrated wide variation in follow-up durations, ranging from 18 months to nearly 6 years. Considerable heterogeneity was also evident regarding the duration, type, and sequencing of both initial DAPT and long-term antiplatelet regimens compared to aspirin monotherapy (Table 2). Procedural characteristics varied broadly with PCI indications ranging from elective interventions (e.g., ARCTIC-Interruption) to ACS presentations and stent types ranging from bare-metal stents to several types of drug-eluting stents (Table 3). Primary endpoints were generally consistent and comprised composite ischemic outcomes with all-cause mortality, MI, and stroke; however, several studies incorporated additional components such as urgent revascularization or major bleeding, adding variability that complicates cross-trial comparisons (Table 4). Importantly, ischemic outcomes like MI and definite or probable stent thrombosis were uniformly reported and presented separately to facilitate meaningful comparisons (Table 5). Moreover, bleeding outcomes differed in classification methods, as detailed in Table 6, which limits direct comparability of safety data. More detailed information on study design, clinical and procedural characteristics, outcomes, and bleeding classification systems utilized in each study can be found in Tables 1,2,3,4,5,6.

Patient populations also showed substantial variation in risk profiles. Several trials focused specifically on populations with high thrombotic risk. PEGASUS-TIMI 54, THEMIS-PCI, and SMART-CHOICE 3 each selected patients meeting high-risk criteria based on clinical and procedural characteristics detailed in subsection 3.2 [19,20,22]. Conversely, other large RCTs, including ARCTIC-Interruption, ITALIC, DAPT, DES LATE, PRODIGY, NIPPON and HOST-EXAM, enrolled all-comer CCS patients post-PCI without selective restriction to high-risk subgroups and these trials performed subgroup analyses based on clinical features such as age, diabetes, or PCI complexity [10,11,13–16,18,21]. Moreover, two RCTs did not conduct subgroup analyses and reported only aggregate outcomes for their overall populations [12,17]. This variability in patient selection and subgroup focus contributes to important clinical heterogeneity influencing both ischemic and bleeding outcomes.

Together, these clinical, procedural, and methodological differences underscore the complexity of balancing ischemic benefits against bleeding risks, highlighting the ne-

Table 5. Risk of myocardial infarction and stent thrombosis.

Trial	MI [hazard ratio (95% CI)]	<i>p</i>	ST (definite or probable). [hazard ratio (95% CI)]	<i>p</i>
Studies on extended DAPT				
ARCTIC – Interruption [10]	9 (1%)/9 (1%) [1.04 (0.41–2.62)]	<i>p</i> = 0.94	0/3 (1%)	-
ITALIC [11]	9 (1%)/12 (1.3%) [1.335 (0.562–3.167)]	<i>p</i> = 0.513	3 (0.3%)/6 (0.6%) [1.995 (0.499–7.976)]	<i>p</i> = 0.329
OPTIDUAL [12]	11 (1.6%)/16 (2.3%) [0.67 (0.31–1.44)]	<i>p</i> = 0.31	3 (0.4%)/1 (0.1%) [2.97 (0.31–28.53)]	<i>p</i> = 0.35
DAPT (BMS) [13]	22 (2.7%)/25 (3.1%) [0.91 (0.51–1.62)]	<i>p</i> = 0.74	definite 4 (0.5%)/9 (1.1%) [0.49 (0.15–1.64)]	<i>p</i> = 0.24
DAPT (DES) [14]	99 (2.1%)/198 (4.1%) [0.47 (0.37–0.61)]	<i>p</i> < 0.001	19 (0.4%)/65 (1.4%) [0.29 (0.17–0.48)]	<i>p</i> < 0.001
DES LATE [15]	19 (0.8%)/27 (1.2%) [1.43 (0.80–2.58)]	<i>p</i> = 0.23	definite 7 (0.3%)/11 (0.5%) [1.59 (0.61–4.09)]	<i>p</i> = 0.34
NIPPON [16]	Non fatal 1 (0.1%)/4 (0.2%) [-0.2 (-0.6–0.1)]	<i>p</i> = 0.37	1 (0.1%)/2 (0.1%) [-0.1 (-0.4–0.2)]	<i>p</i> = 1.00
REAL-LATE and ZEST-LATE [17]	10 (0.8%)/7 (0.7%) [1.41 (0.54–3.71)]	<i>p</i> = 0.49	definite 5 (0.4%)/4 (0.4%) [1.23 (0.33–4.58)]	<i>p</i> = 0.76
PRODIGY [18]	39 (4.0%)/41 (4.2%) [1.06 (0.69–1.63)]	<i>p</i> = 0.80	definite 8 (0.8%)/7 (0.7%) [0.88 (0.32–2.42)]	<i>p</i> = 0.80
PEGASUS-TIMI 54 [19]	ticagrelor 90 mg: (4.33%)/(5.18%) [0.79 (0.66–0.95)]	90 mg: <i>p</i> = 0.012	definite ticagrelor 90 mg: (0.5%)/(0.71%) [0.6 (0.35–1.01)]	90 mg: <i>p</i> = 0.055
	ticagrelor 60 mg: (4.47%)/(5.18%) [0.84 (0.7–1.0)]	60 mg: <i>p</i> = 0.046	ticagrelor 60 mg: (0.64%)/(0.71%) [0.94 (0.59–1.49)]	60 mg: <i>p</i> = 0.793
THEMIS-PCI [20]	155 (3%)/208 (4%) [0.76 (0.61–0.93)]	<i>p</i> = 0.008	NS	-
Studies on long-term P2Y12 inhibitor monotherapy				
HOST-EXAM Extended [21]	Non fatal, 40 (1.6%)/53 (2.3%) [0.71 (0.47–1.07)]	<i>p</i> = 0.102	12 (0.5%)/17 (0.7%) [0.67 (0.32–1.39)]	<i>p</i> = 0.28
SMART-CHOICE 3 [22]	23 (1%)/42 (2.2%) [0.54 (0.33–0.9)]	<i>p</i> < 0.05	definite or probable 1 (0%)/5 (0.2%) [0.20 (0.02–1.68)]	<i>p</i> > 0.05
GLOBAL LEADERS [23]	37 (0.7%)/71 (1.2%) [0.57 (0.38–0.85)]	<i>p</i> = 0.006	definite or probable 10 (0.2%)/16 (0.3%) [0.68 (0.31–1.51)]	<i>p</i> = 0.347

Data are presented as (intervention/control group). In SMART-CHOICE 3 trial the *p* values for myocardial infarction and stent thrombosis are not stated in text, but they are mentioned as significant or non-significant. MI, myocardial infarction; ST, stent thrombosis; DES, drug eluting stent; BMS, bare metal stent; CI, confidence interval; NS, not stated; DAPT, dual antiplatelet therapy; TIMI, thrombolysis in myocardial infarction.

cessity of individualized patient risk stratification and tailored therapeutic strategies in interpreting and applying the evidence.

3.4 Insights From Observational Data and Risk Stratification

Although observational studies were excluded from this systematic review, numerous such studies have explored whether specific clinical or angiographic character-

istics may identify patients with a history of PCI who would benefit from prolonged DAPT. For example, three observational studies demonstrated that DAPT with clopidogrel beyond 12 months provided benefit in patients undergoing PCI of the left main coronary artery [33–35]. Similarly, four studies reported benefit in ischemic endpoints with prolonged DAPT in patients undergoing left main bifurcation or complex PCI [36–39]. In contrast, one trial found no benefit in patients undergoing treatment for chronic to-

Table 6. Bleeding classification and incidence.

Trial	Bleeding classification	Bleeding incidence	Hazard ratio (95% CI), <i>p</i>
Studies on extended DAPT			
ARCTIC-Interruption [10]	STEEPLE major	1%/($<0.5\%$)	0.15 (0.02–1.20), <i>p</i> = 0.07
ITALIC [11]	TIMI major	4 (0.4%)/0	Not applicable
OPTIDUAL [12]	TIMI major	4 (0.6%)/4 (0.6%)	<i>p</i> = 1.00
DAPT (BMS) [13]	BARC	Type 2, 3 or 5: 36 (4.56%)/14 (1.8%)	Type 2, 3 or 5: <i>p</i> = 0.002
		Type 5: 0/1	Type 5: <i>p</i> = 0.31
DAPT (DES) [14]	BARC	Type 2, 3 or 5: 263 (5.6%)/137 (2.9%)	Type 2, 3 or 5: <i>p</i> < 0.001
		Type 5: 7/4	Type 5: <i>p</i> = 0.38
DES LATE [15]	TIMI major	34 (1.4%)/24 (1.1%)	0.71 (0.42–1.2), <i>p</i> = 0.2
NIPPON [16]	BARC	Type 3 or 5: 12 (0.7%)/11 (0.7%)	Type 3 or 5: 0.1 (–0.6–0.7), <i>p</i> = 0.83
		Type 5: 2/0	
REAL-LATE and ZEST-LATE [17]	TIMI major	3 (0.2%)/1 (0.1%)	2.96 (0.31–28.46), <i>p</i> = 0.35
PRODIGY [18]	TIMI major	16 (1.6%)/6 (0.6%)	0.38 (0.15–0.97), <i>p</i> = 0.041
PEGASUS-TIMI 54 [19]	TIMI major	ticagrelor 90 mg (2.7%)/(1.05%)	ticagrelor 90 mg : 2.86 (2.01–4.08), <i>p</i> < 0.001
		ticagrelor 60 mg (2.46%)/(1.05%)	ticagrelor 60 mg : 2.45 (1.71–3.5), <i>p</i> < 0.001
THEMIS-PCI [20]	TIMI major	122/84	1.51 (1.14–1.99), <i>p</i> < 0.05
Studies on long-term P2Y12 inhibitor monotherapy			
HOST-EXAM Extended [21]	BARC type 2, 3 or 5	62 (2.6%)/90 (3.9%)	0.65 (0.47–0.90), <i>p</i> = 0.008
SMART-CHOICE 3 [22]	BARC	Type 2, 3 or 5: 53 (3%)/55 (3%)	Type 2, 3 or 5: 0.97 (0.67–1.42)
		Type 3 or 5: 26 (1.6%)/26 (1.3%)	Type 3 or 5: 1.00 (0.58–1.73)
GLOBAL LEADERS [23]	BARC	Type 2, 3 or 5: 94 (1.8%)/68 (1.2%)	Type 2, 3 or 5: 1.52 (1.11–2.08), <i>p</i> = 0.009
		Type 3 or 5: 28 (0.5%)/17 (0.3%)	Type 3 or 5: 1.80 (0.99–3.30), <i>p</i> = 0.055

Data are presented in the format (intervention/control group). In SMART-CHOICE 3 trial the *p* values for bleeding outcomes are intentionally not stated by the authors to avoid misinterpretation of statistical significance, as bleeding outcomes were secondary endpoints; DES, drug eluting stent; BMS, bare metal stent; CI, confidence interval; DAPT, dual antiplatelet therapy; STEEPLE, safety and efficacy of enoxaparin in PCI patients, an international randomized evaluation; TIMI, thrombolysis in myocardial infarction; BARC, Bleeding Academic Research Consortium.

tal occlusion of coronary arteries [40]. Other studies evaluated the potential benefit based on patient comorbidities. Prolonged DAPT was associated with better outcomes in diabetic patients, but not in those with anemia or chronic kidney disease on dialysis [41–44]. Moreover, no benefit was observed in patients presenting with ACS, whereas one study noted significant benefit in patients with elevated lipoprotein(a) undergoing PCI [45–47].

These observational studies, despite their limitations, reflect a growing effort to refine the optimal, individualized antiplatelet strategy. There is ongoing interest to identify specific patient subpopulations defined by biomarkers or clinical and angiographic characteristics, who may benefit from intensified antiplatelet treatment. This direction is consistent with the findings of this systematic review and a recent meta-analysis by Elliott *et al.* [7], which reported that patients with prior MI, those younger than 75 years, and individuals presenting with ACS may benefit from pro-

longed DAPT. Still, they highlight the importance of careful patient selection when considering long-term intensive therapy.

Personalization of antiplatelet treatment is crucial, as unjustified prolongation of DAPT increases bleeding risk, while premature discontinuation of DAPT may lead to adverse cardiovascular events [48]. To support individualization, various risk scores have been developed using patient data to predict who may benefit from DAPT extension [5]. Some of the most commonly used are the PRECISE-DAPT DAPT, and PARIS risk scores, which help guide the decision to continue therapy based on clinical parameters [9,49]. Even though these tools were initially validated in Western populations, their predictive accuracy has been questioned in specific populations including those of Sweden and China [50,51]. In contrast, recent evidence highlights the central role of bleeding risk scores, particularly PRECISE-DAPT and ARC-HBR, in guiding

antiplatelet therapy selection and duration after PCI. The PRECISE-DAPT score, which incorporates clinical and laboratory parameters, identifies patients at high bleeding risk (score ≥ 25) who may benefit from abbreviated DAPT durations without increasing ischemic events. Similarly, the ARC-HBR criteria provide standardized definitions for high bleeding risk, including factors such as advanced age, anemia, prior major bleeding, and chronic kidney disease. Applying these tools enables a more individualized approach to balancing ischemic and bleeding risks and supports tailoring antiplatelet strategies to the patient's risk profile. In clinical practice, this often translates to shortening DAPT duration to 1–3 months in high bleeding risk patients. Such abbreviated DAPT regimens may be followed by single antiplatelet therapy, often with a P2Y12 inhibitor rather than aspirin, or even by initiation of aspirin-free strategies consisting of potent P2Y12 inhibitors immediately post-PCI, as supported by recent trials. These evolving strategies emphasize precision medicine, ensuring therapy intensity and duration align with individual patient risk profiles. As patients meeting high bleeding risk criteria constitute a substantial subset in contemporary practice, the use of validated risk scores combined with these tailored therapeutic options is now considered essential for optimal, patient-centered decision-making [52].

While optimal antiplatelet therapy remains central to reducing ischemic risk post-PCI, it is critical to recognize that comprehensive management of all modifiable thrombotic risk factors is essential for improving cardiovascular outcomes in all patients and particularly so in those at high bleeding risk, who may not tolerate intensified antiplatelet regimens. Among these factors, individualized lipid management plays a pivotal role. High-intensity statins are first-line in order to effectively lower low-density lipoprotein cholesterol (LDL-C) levels and reduce atherosclerotic cardiovascular risk, often combined early with ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors as needed to achieve LDL-C targets. Lipid-lowering therapies should be personalized based on patient comorbidities, prior treatment tolerance, and risk profile. In patients with statin intolerance or inadequate responses or genetic lipid disorders, newer agents such as bempedoic acid or emerging RNA-based therapies targeting lipoprotein(a), apolipoprotein C3, and ANGPTL3 offer additional promising options. By addressing residual lipid-mediated risk factors, clinicians can optimize secondary prevention beyond antiplatelet therapy alone. Incorporating individualized lipid control into the broader risk factor modification plan embodies a patient-centered approach essential for long-term management in CCS populations [53].

At present, the decision to pursue alternative long-term therapy remains an area of active research [54]. While the role of aspirin in secondary prevention is well established, robust results from large, randomized, international, double-blind clinical trials are necessary in order to deter-

mine the optimal long-term antiplatelet therapy to individual patient profiles.

3.5 Limitations

This systematic review has several limitations, primarily related to the heterogeneity and methodological differences among the included trials. There was considerable variability in patient comorbidities, PCI indications, comparator antiplatelet regimens, treatment duration and definitions of both primary efficacy and bleeding outcomes. Except for the PRODIGY trial, most studies enrolled only patients who remained free of ischemic and bleeding events during the standard DAPT period. As a result, higher-risk patients were excluded, thus limiting generalizability. Additionally, the availability of data for subgroup analyses from the trials was limited, restricting the ability to draw robust conclusions regarding specific patient subgroups.

4. Conclusion

Long-term intensified antiplatelet therapy may provide benefit in patients with CCS and a history of PCI. Specific subgroups with high thrombotic burden, such as those with a history of acute myocardial infarction, diabetes mellitus, peripheral artery disease or complex coronary artery disease may derive even greater benefit, provided they are not at increased risk for bleeding. These findings highlight the importance of carefully balancing ischemic protection against bleeding risk, to achieve optimal, individualized therapy.

Availability of Data and Materials

All data relevant to the study are included in the article or uploaded as supplementary information.

Author Contributions

All authors contributed to the concept and design of the systematic review. SF and MP conducted the literature search and data extraction. SF and AX performed the data analysis and risk of bias assessment. SF drafted the initial manuscript. MP and AX provided critical revisions and contributed to the interpretation of results. All authors contributed to editorial revisions of the manuscript. All authors read and approved the final version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

This systematic review is a revised and updated version of a thesis submitted as part of the MSc program “*Thrombosis and Antithrombotic Therapy*” at the Medical School of the University of Thessaly, Greece. While the

core methodology and research question remain the same, changes have been made to the structure and content to meet the standards of a peer-reviewed publication.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/RCM44227>.

References

- [1] Landi A, De Servi S, De Luca L. Aspirin-free strategies after percutaneous coronary intervention: Old habits, consolidated evidence and future perspectives. *European Journal of Internal Medicine*. 2025; 133: 35–38. <https://doi.org/10.1016/j.ejim.2025.01.012>.
- [2] Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, *et al.* 2024 ESC Guidelines for the management of chronic coronary syndromes [published erratum in *European Heart Journal*. 2025; 46: 1565. doi: 10.1093/eurheartj/ehaf079]. *European Heart Journal*. 2024; 45: 3415–3537. <https://doi.org/10.1093/eurheartj/ehae177>.
- [3] CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* (London, England). 1996; 348: 1329–1339. [https://doi.org/10.1016/s0140-6736\(96\)09457-3](https://doi.org/10.1016/s0140-6736(96)09457-3).
- [4] Capodanno D, Mehran R, Valgimigli M, Baber U, Windecker S, Vranckx P, *et al.* Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nature Reviews. Cardiology*. 2018; 15: 480–496. <https://doi.org/10.1038/s41569-018-0049-1>.
- [5] Cao D, Chandiramani R, Chiarito M, Claessen BE, Mehran R. Evolution of antithrombotic therapy in patients undergoing percutaneous coronary intervention: a 40-year journey. *European Heart Journal*. 2021; 42: 339–351. <https://doi.org/10.1093/eurheartj/ehaa824>.
- [6] Costa F, Valgimigli M. The optimal duration of dual antiplatelet therapy after coronary stent implantation: to go too far is as bad as to fall short. *Cardiovascular Diagnosis and Therapy*. 2018; 8: 630–646. <https://doi.org/10.21037/cdt.2018.10.01>.
- [7] Elliott J, Kelly SE, Bai Z, Skidmore B, Boucher M, So D, *et al.* Extended dual antiplatelet therapy following percutaneous coronary intervention in clinically important patient subgroups: a systematic review and meta-analysis. *CMAJ Open*. 2023; 11: E118–E130. <https://doi.org/10.9778/cmajo.20210119>.
- [8] Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, *et al.* 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published erratum in *Circulation*. 2022; 145: e771. doi: 10.1161/CIR.0000000000001061]. *Circulation*. 2022; 145: e4–e17. <https://doi.org/10.1161/CIR.0000000000001039>.
- [9] Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, *et al.* 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines [published erratum in *Circulation*. 2023; 148: e148. doi: 10.1161/CIR.0000000000001183]. *Circulation*. 2023; 148: e9–e119. <https://doi.org/10.1161/CIR.0000000000001168>.
- [10] Collet JP, Silvain J, Barthélémy O, Rangé G, Cayla G, Van Belle E, *et al.* Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. *Lancet* (London, England). 2014; 384: 1577–1585. [https://doi.org/10.1016/S0140-6736\(14\)60612-7](https://doi.org/10.1016/S0140-6736(14)60612-7).
- [11] Didier R, Morice MC, Barragan P, Noryani AAL, Noor HA, Majwal T, *et al.* 6- Versus 24-Month Dual Antiplatelet Therapy After Implantation of Drug-Eluting Stents in Patients Nonresistant to Aspirin: Final Results of the ITALIC Trial (Is There a Life for DES After Discontinuation of Clopidogrel). *JACC. Cardiovascular Interventions*. 2017; 10: 1202–1210. <https://doi.org/10.1016/j.jcin.2017.03.049>.
- [12] Helft G, Steg PG, Le Feuvre C, Georges JL, Carrie D, Dreyfus X, *et al.* Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial. *European Heart Journal*. 2016; 37: 365–374. <https://doi.org/10.1093/eurheartj/ehv481>.
- [13] Kereiakes DJ, Yeh RW, Massaro JM, Driscoll-Shempp P, Cutlip DE, Steg PG, *et al.* Antiplatelet therapy duration following bare metal or drug-eluting coronary stents: the dual antiplatelet therapy randomized clinical trial [published erratum in *JAMA*. 2015; 313: 2185. doi: 10.1001/jama.2015.4806. erratum in: *JAMA*. 2016; 316: 105. doi: 10.1001/jama.2016.8640. erratum in: *JAMA*. 2016; 316: 105. doi: 10.1001/jama.2016.8646]. *JAMA*. 2015; 313: 1113–1121. <https://doi.org/10.1001/jama.2015.1671>.
- [14] Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, *et al.* Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *The New England Journal of Medicine*. 2014; 371: 2155–2166. <https://doi.org/10.1056/NEJMoa1409312>.
- [15] Lee JY, Park DW, Kim YH, Ahn JM, Kim WJ, Kang SJ, *et al.* Comparison of biolimus A9-eluting (Nobori) and everolimus-eluting (Promus Element) stents in patients with de novo native long coronary artery lesions: a randomized Long Drug-Eluting Stent V trial. *Circulation. Cardiovascular Interventions*. 2014; 7: 322–329. <https://doi.org/10.1161/CIRCINTERVENTIONS.113.000841>.
- [16] Nakamura M, Iijima R, Ako J, Shinke T, Okada H, Ito Y, *et al.* Dual Antiplatelet Therapy for 6 Versus 18 Months After Biodegradable Polymer Drug-Eluting Stent Implantation. *JACC. Cardiovascular Interventions*. 2017; 10: 1189–1198. <https://doi.org/10.1016/j.jcin.2017.04.019>.
- [17] Park SJ, Park DW, Kim YH, Kang SJ, Lee SW, Lee CW, *et al.* Duration of dual antiplatelet therapy after implantation of drug-eluting stents. *The New England Journal of Medicine*. 2010; 362: 1374–1382. <https://doi.org/10.1056/NEJMoa1001266>.
- [18] Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, *et al.* Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation*. 2012; 125: 2015–2026. <https://doi.org/10.1161/CIRCULATIONAHA.111.071589>.
- [19] Bergmark BA, Bhatt DL, Steg PG, Budaj A, Storey RF, Gurmur Y, *et al.* Long-Term Ticagrelor in Patients With Prior Coronary Stenting in the PEGASUS-TIMI 54 Trial. *Journal of the American Heart Association*. 2021; 10: e020446. <https://doi.org/10.1161/JAHA.120.020446>.
- [20] Bhatt DL, Steg PG, Mehta SR, Leiter LA, Simon T, Fox K, *et al.* Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary

- intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. *Lancet* (London, England). 2019; 394: 1169–1180. [https://doi.org/10.1016/S0140-6736\(19\)31887-2](https://doi.org/10.1016/S0140-6736(19)31887-2).
- [21] Kang J, Park KW, Lee H, Hwang D, Yang HM, Rha SW, *et al.* Aspirin Versus Clopidogrel for Long-Term Maintenance Monotherapy After Percutaneous Coronary Intervention: The HOST-EXAM Extended Study. *Circulation*. 2023; 147: 108–117. <https://doi.org/10.1161/CIRCULATIONAHA.122.062770>.
- [22] Choi KH, Park YH, Lee JY, Jeong JO, Kim CJ, Yun KH, *et al.* Efficacy and safety of clopidogrel versus aspirin monotherapy in patients at high risk of subsequent cardiovascular event after percutaneous coronary intervention (SMART-CHOICE 3): a randomised, open-label, multicentre trial. *Lancet* (London, England). 2025; 405: 1252–1263. [https://doi.org/10.1016/S0140-6736\(25\)00449-0](https://doi.org/10.1016/S0140-6736(25)00449-0).
- [23] Ono M, Hara H, Kawashima H, Gao C, Wang R, Wykrzykowska JJ, *et al.* Ticagrelor monotherapy versus aspirin monotherapy at 12 months after percutaneous coronary intervention: a landmark analysis of the GLOBAL LEADERS trial. *EuroIntervention: Journal of EuroPCR in Collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2022; 18: e377–e388. <https://doi.org/10.4244/EIJ-D-21-00870>.
- [24] Kumbhani DJ, Bhatt DL. DAPT Study. *American College of Cardiology*. 2014. Available at: <https://www.acc.org/latest-in-cardiology/clinical-trials/2014/11/18/16/27/dapt-study> (Accessed: 20 May 2025).
- [25] Campo G, Tebaldi M, Vranckx P, Biscaglia S, Tumscitz C, Ferrari R, *et al.* Short- versus long-term duration of dual antiplatelet therapy in patients treated for in-stent restenosis: a PRODIGY trial substudy (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia). *Journal of the American College of Cardiology*. 2014; 63: 506–512. <https://doi.org/10.1016/j.jacc.2013.09.043>.
- [26] Franzone A, Piccolo R, Gargiulo G, Ariotti S, Marino M, Santucci A, *et al.* Prolonged vs Short Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients With or Without Peripheral Arterial Disease: A Subgroup Analysis of the PRODIGY Randomized Clinical Trial. *JAMA Cardiology*. 2016; 1: 795–803. <https://doi.org/10.1001/jamacardio.2016.2811>.
- [27] Costa F, Adamo M, Ariotti S, Ferrante G, Navarese EP, Leonardi S, *et al.* Left main or proximal left anterior descending coronary artery disease location identifies high-risk patients deriving potentially greater benefit from prolonged dual antiplatelet therapy duration. *EuroIntervention: Journal of EuroPCR in Collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2016; 11: e1222–30. https://doi.org/10.4244/EIJY15M08_04.
- [28] Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, *et al.* Long-term use of ticagrelor in patients with prior myocardial infarction. *The New England Journal of Medicine*. 2015; 372: 1791–1800. <https://doi.org/10.1056/NEJMoa1500857>.
- [29] Magnani G, Ardissino D, Im K, Budaj A, Storey RF, Steg PG, *et al.* Predictors, Type, and Impact of Bleeding on the Net Clinical Benefit of Long-Term Ticagrelor in Stable Patients With Prior Myocardial Infarction. *Journal of the American Heart Association*. 2021; 10: e017008. <https://doi.org/10.1161/JAHA.120.017008>.
- [30] Bonaca MP, Im K, Magnani G, Bansilal S, Dellborg M, Storey RF, *et al.* Patient selection for long-term secondary prevention with ticagrelor: insights from PEGASUS-TIMI 54. *European Heart Journal*. 2022; 43: 5037–5044. <https://doi.org/10.1093/eurheartj/ehac402>.
- [31] Nelson TA, Parker WAE, Ghukasyan Lakic T, Westerbergh J, James SK, Siegbahn A, *et al.* Differential effect of clopidogrel and ticagrelor on leukocyte count in relation to patient characteristics, biomarkers and genotype: a PLATO substudy. *Platelets*. 2022; 33: 425–431. <https://doi.org/10.1080/09537104.2021.1934667>.
- [32] De Servi S, Landi A, Savonitto S. Clopidogrel induced reduction in neutrophil count: An overlooked beneficial effect? *European Journal of Internal Medicine*. 2024; 124: 32–34. <https://doi.org/10.1016/j.ejim.2024.03.026>.
- [33] Cho S, Kim JS, Kang TS, Hong SJ, Shin DH, Ahn CM, *et al.* Long-Term Efficacy of Extended Dual Antiplatelet Therapy After Left Main Coronary Artery Bifurcation Stenting. *The American Journal of Cardiology*. 2020; 125: 320–327. <https://doi.org/10.1016/j.amjcard.2019.10.046>.
- [34] Cho S, Kang DY, Kim JS, Park DW, Kim IS, Kang TS, *et al.* Dual antiplatelet therapy after percutaneous coronary intervention for left main coronary artery disease. *Revista Espanola De Cardiologia (English Ed.)*. 2023; 76: 245–252. <https://doi.org/10.1016/j.rec.2022.07.007>.
- [35] Choi J, Kim IS, Cho S, Kim JS, Hong SJ, Shin DH, *et al.* Optimal Duration for Dual Antiplatelet Therapy After Left Main Coronary Artery Stenting. *Circulation Journal: Official Journal of the Japanese Circulation Society*. 2020; 85: 59–68. <https://doi.org/10.1253/circj.CJ-20-0362>.
- [36] De Filippo O, Kang J, Bruno F, Han JK, Saglietto A, Yang HM, *et al.* Benefit of Extended Dual Antiplatelet Therapy Duration in Acute Coronary Syndrome Patients Treated with Drug Eluting Stents for Coronary Bifurcation Lesions (from the BIFURCAT Registry). *The American Journal of Cardiology*. 2021; 156: 16–23. <https://doi.org/10.1016/j.amjcard.2021.07.005>.
- [37] Jang WJ, Ahn SG, Song YB, Choi SH, Chun WJ, Oh JH, *et al.* Benefit of Prolonged Dual Antiplatelet Therapy After Implantation of Drug-Eluting Stent for Coronary Bifurcation Lesions: Results From the Coronary Bifurcation Stenting Registry II. *Circulation. Cardiovascular Interventions*. 2018; 11: e005849. <https://doi.org/10.1161/CIRCINTERVENTIONS.117.005849>.
- [38] Khelimsii D, Bessonov I, Sapozhnikov S, Badoyan A, Baranov A, Mamurjon M, *et al.* Impact of Prolonged Dual Antiplatelet Therapy After Bifurcation Percutaneous Coronary Intervention in Patients with High Ischemic Risk. *American Journal of Cardiovascular Drugs: Drugs, Devices, and other Interventions*. 2024; 24: 577–588. <https://doi.org/10.1007/s40256-024-00657-1>.
- [39] Wang HY, Dou KF, Yin D, Xu B, Zhang D, Gao RL. Risk/Benefit Tradeoff of Prolonging Dual Antiplatelet Therapy More Than 12 Months in TWILIGHT-Like High-Risk Patients After Complex Percutaneous Coronary Intervention. *The American Journal of Cardiology*. 2020; 133: 61–70. <https://doi.org/10.1016/j.amjcard.2020.07.033>.
- [40] Lee SH, Yang JH, Choi SH, Park TK, Jang WJ, Song YB, *et al.* Duration of dual antiplatelet therapy in patients treated with percutaneous coronary intervention for coronary chronic total occlusion. *PloS One*. 2017; 12: e0176737. <https://doi.org/10.1371/journal.pone.0176737>.
- [41] Wang HY, Cai ZX, Yin D, Yang YJ, Song WH, Dou KF. Benefits and Risks of Prolonged Duration Dual Antiplatelet Therapy (Clopidogrel and Aspirin) After Percutaneous Coronary Intervention in High-Risk Patients With Diabetes Mellitus. *The American Journal of Cardiology*. 2021; 142: 14–24. <https://doi.org/10.1016/j.amjcard.2020.11.043>.
- [42] Lee SJ, Choi DW, Kim C, Suh Y, Hong SJ, Ahn CM, *et al.* Prolonged dual antiplatelet therapy after drug-eluting stent implantation in patients with diabetes mellitus: A nationwide retrospective cohort study. *Frontiers in Cardiovascular Medicine*. 2022; 9: 954704. <https://doi.org/10.3389/fcvm.2022.954704>.

- [43] Kim HT, Lee JH, Nam JH, Lee CH, Son JW, Kim U, *et al.* Long-Term Safety and Efficacy of Prolonged Dual Antiplatelet Therapy according to Baseline Anemia after Percutaneous Coronary Intervention. *Yonsei Medical Journal.* 2022; 63: 211–219. <https://doi.org/10.3349/ymj.2022.63.3.211>.
- [44] Asami M, Aoki J, Sato T, Tanimoto S, Watanabe M, Horiuchi Y, *et al.* Impact of stent type and prolonged dual antiplatelet therapy on long-term clinical outcomes in hemodialysis patients with coronary artery disease. *Cardiovascular Intervention and Therapeutics.* 2018; 33: 84–94. <https://doi.org/10.1007/s12928-016-0447-4>.
- [45] Christensen DM, Schjerning AM, Sindet-Pedersen C, Lamberts M, Olesen JB, Barcella CA, *et al.* Outcomes of prolonged dual anti-platelet therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention: A nationwide registry-based study. *American Heart Journal.* 2022; 245: 81–89. <https://doi.org/10.1016/j.ahj.2021.11.018>.
- [46] D'Ascenzo F, Bertaina M, Fioravanti F, Bongiovanni F, Raposeiras-Roubin S, Abu-Assi E, *et al.* Long versus short dual antiplatelet therapy in acute coronary syndrome patients treated with prasugrel or ticagrelor and coronary revascularization: Insights from the RENAMI registry. *European Journal of Preventive Cardiology.* 2020; 27: 696–705. <https://doi.org/10.1177/2047487319836327>.
- [47] Cui K, Wang HY, Yin D, Zhu C, Song W, Wang H, *et al.* Benefit and Risk of Prolonged Dual Antiplatelet Therapy After Percutaneous Coronary Intervention With Drug-Eluting Stents in Patients With Elevated Lipoprotein(a) Concentrations. *Frontiers in Cardiovascular Medicine.* 2021; 8: 807925. <https://doi.org/10.3389/fcvm.2021.807925>.
- [48] Palmerini T, Bacchi Reggiani L, Della Riva D, Romanello M, Feres F, Abizaid A, *et al.* Bleeding-Related Deaths in Relation to the Duration of Dual-Antiplatelet Therapy After Coronary Stenting. *Journal of the American College of Cardiology.* 2017; 69: 2011–2022. <https://doi.org/10.1016/j.jacc.2017.02.029>.
- [49] Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, *et al.* Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet (London, England).* 2017; 389: 1025–1034. [https://doi.org/10.1016/S0140-6736\(17\)30397-5](https://doi.org/10.1016/S0140-6736(17)30397-5).
- [50] Song L, Guan C, Yan H, Qiao S, Wu Y, Yuan J, *et al.* Validation of contemporary risk scores in predicting coronary thrombotic events and major bleeding in patients with acute coronary syndrome after drug-eluting stent implantations. *Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions.* 2018; 91: 573–581. <https://doi.org/10.1002/ccd.27468>.
- [51] Ueda P, Jernberg T, James S, Alfredsson J, Erlinge D, Omerovic E, *et al.* External Validation of the DAPT Score in a Nationwide Population. *Journal of the American College of Cardiology.* 2018; 72: 1069–1078. <https://doi.org/10.1016/j.jacc.2018.06.023>.
- [52] Dimitriadis K, Pyrpyris N, Iliakis P, Kanatas P, Theofilis P, Sakalidis A, *et al.* Optimal management of high bleeding risk patients undergoing percutaneous coronary interventions: Where do we stand? *Journal of Cardiology.* 2025; 85: 79–87. <https://doi.org/10.1016/j.jjcc.2024.08.002>.
- [53] Dimitriadis K, Theofilis P, Iliakis P, Pyrpyris N, Dri E, Sakalidis A, *et al.* Management of dyslipidemia in coronary artery disease: the present and the future. *Coronary Artery Disease.* 2024; 35: 516–524. <https://doi.org/10.1097/MCA.0000000000001375>.
- [54] Capranzano P, Moliterno D, Capodanno D. Aspirin-free antiplatelet strategies after percutaneous coronary interventions. *European Heart Journal.* 2024; 45: 572–585. <https://doi.org/10.1093/eurheartj/ehad876>.