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Research article

Aspirin-free P2Y12 inhibitor monotherapy immediately after percutaneous coronary intervention: A systematic review

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ABSTRACT

Background: A modified antiplatelet therapy approach after percutaneous coronary intervention (PCI), specifically reducing dual antiplatelet therapy (DAPT) duration and transitioning to P2Y12 inhibitor monotherapy, may offer advantages in terms of bleeding risk reduction. However, the impact of initiating aspirin-free P2Y12 inhibitor monotherapy immediately after PCI is not yet fully understood.

Methods: We systematically searched the PubMed and Embase databases until January 2024 for studies that examined the use of P2Y12 inhibitor monotherapy as a treatment approach without initial DAPT following PCI.

Results: Four single-arm pilot prospective studies and 1 randomized controlled trial were included. In acute coronary syndrome patients with P2Y12 monotherapy following aspirin withdrawal immediately after PCI, the occurrence rates of the primary ischemic and bleeding endpoint were 2.91 % (8 out of 275 patients) and 1.09 % (3 out of 275 patients) respectively, whereas both the incidence rates of the primary ischemic and bleeding endpoints were 0.25 % (1 out of 407 patients) in individuals with stable coronary artery disease. In the STOPDAPT-3 trial comparing the effect of aspirin-free prasugrel monotherapy with standard DAPT after PCI, no differences were found in the primary ischemic or bleeding endpoints and most secondary outcomes (death, stroke, and myocardial infarction). However, there was an increased risk of coronary revascularization and stent thrombosis in the no-aspirin group.

Conclusions: Single-arm studies suggest the safety and feasibility of aspirin-free P2Y12 inhibitor monotherapy without initial DAPT after PCI in selected patients with acute coronary syndrome or stable coronary artery disease. However, the safety and efficacy of this aspirin-free approach compared with standard DAPT strategies following PCI still require further investigation.

1. Introduction

Dual antiplatelet therapy (DAPT) is the recommended standard treatment strategy for patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stents (DES) implantation [1]. This strategy involves the administration of two antiplatelet

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medications (aspirin and a P2Y12 inhibitor used in combination), which prevents blood clot formation and reduces the risk of cardiovascular complications but comes at the expense of increased bleeding events. Therefore, there is a need for further research to detect a modified antiplatelet therapy approach after PCI, aiming to achieve a more favorable safety profile.

Recent randomized controlled trials (RCTs) such as GLOBAL LEADERS, TWILIGHT, TICO, T-PASS, SMART-CHOICE, and STOPDAPT-2 [2–8] have highlighted the potential benefits of a short duration of DAPT, ranging from 1 to 3 months, followed by a switch to a single antiplatelet therapy with a potent P2Y12 inhibitor in patients undergoing PCI. Several meta-analyses [9–12] by pooling these RCTs have shown that compared with continued DAPT after PCI, P2Y12 inhibitor monotherapy in the absence of aspirin after short DAPT is associated with less bleeding risks without an increase in ischaemic events. Despite these findings, the impact of initiating aspirin-free P2Y12 inhibitor monotherapy immediately after PCI remains largely unknown. Therefore, our current systematic review was conducted to evaluate the potential benefits and risks associated with P2Y12 inhibitor monotherapy as a treatment approach without initial DAPT in patients undergoing PCI.

2. Methods

Our present study was conducted based on the preferred reporting items for systematic reviews and meta-analysis (PRISMA) 2020 statement. Fig. 1 shows the flowchart of the literature retrieval. As this study solely relied on published studies, ethical approval was not deemed necessary as no direct involvement with human subjects was conducted. For those interested in accessing the detailed data

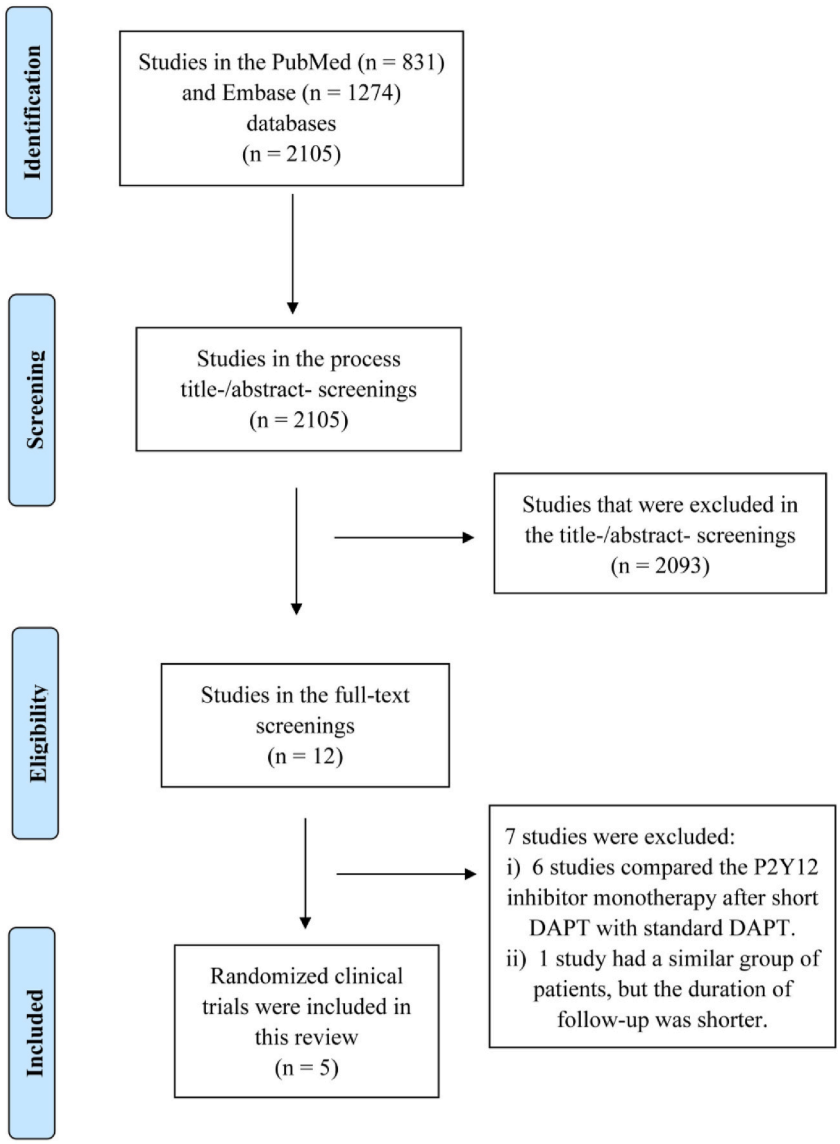

Fig. 1. The selection process of the literature retrieval of this study.

supporting the findings of this meta-analysis, it is available from the corresponding authors upon reasonable request.

2.1. Data sources and searches

Two reviewers systematically carried out the initial search in the PubMed and Embase electronic databases until January 2024. We searched for relevant articles that examined the use of P2Y12 inhibitor monotherapy as a treatment approach without initial DAPT following PCI. To identify eligible studies, we used a comprehensive set of search terms as follows: (i)"P2Y12 inhibitors", "clopidogrel", "prasugrel", "ticagrelor"; (ii)"monotherapy", "aspirin-free", "single antiplatelet therapy"; and (iii)"coronary artery stenting", "percutaneous coronary intervention", "coronary revascularization", "drug-eluting stents". To combine these three categories of search terms, the Boolean operator "and" was applied (Supplemental Table 1). Furthermore, we reviewed previously published reviews to identify additional eligible studies.

2.2. Inclusion and exclusion criteria

Studies would be included if they met the following prespecified eligibility criteria: (i) study design: RCTs or observational studies; (ii) population: adult acute coronary syndrome (ACS) or stable coronary artery disease (CAD) patients who underwent PCI with DES implantation; (iii) intervention: P2Y12 inhibitor monotherapy without initial DAPT or after very short DAPT following PCI (no-aspirin group); (iv) control group: standard DAPT with aspirin and a P2Y12 inhibitor (DAPT group). In addition, we included also single-arm studies with no study controls if they had satisfied aspirin-free antiplatelet strategies as the intervention. We excluded studies comparing the P2Y12 inhibitor monotherapy after a brief period of DAPT (1–3 months) with standard DAPT in patients undergoing PCI. In addition, if different studies focused on the same studied population, we selected studies with a longer follow-up time in this review.

2.3. Studied outcomes

The primary ischemic endpoint was defined as a composite of death, myocardial infarction, stent thrombosis, or stroke, whereas the primary major bleeding endpoint was defined as Bleeding Academic Research Consortium (BARC) type 3 or 5. The secondary outcomes mainly included all-cause death, cardiovascular death, stroke, myocardial infarction, definite or probable stent thrombosis, repeat coronary revascularization (non–target-lesion or target-lesion), major or minor bleeding endpoint (BARC type 2, 3 or 5), and any bleeding events (BARC type 1 to 5). The studied outcomes and their definitions were selected according to the originally included studies.

2.4. Study selection and data extraction

We first screened their titles and abstracts for potentially relevant studies independently. They carefully read the title and abstract of each retrieved record and assessed whether it aligned with the research objective. Subsequently, we moved on to the full-text screenings of these studies by assessing whether the study met the inclusion criteria, which were predefined based on the research question. If there were any disagreements or discrepancies in our decisions, we engaged in discussion to resolve them. In situations where reaching a consensus seemed challenging, the reviewers sought valuable insights from senior researchers.

Among the included studies, we meticulously extracted the relevant data and findings. We collected data on study characteristics such as author names, year of publication, study design, age, gender, sample size, data source, inclusion period, and geographical location. Additionally, we extracted outcome measures, statistical analyses, and any other pertinent information that could contribute to our research objectives.

2.5. Descriptive analysis

The Cochrane Risk of Bias Tool 2.0 was employed in this study to evaluate the potential bias risk of the RCTs included [13]. In order to evaluate the quality of observational studies, the researchers employed the Newcastle-Ottawa Scale tool [14]. For the single-arm study, we gathered information on both the sample size and the number of events that occurred in the group of patients who did not take aspirin. Using this data, we performed calculations to determine and combine the frequencies of outcomes that occurred in this group. Due to the limited data between aspirin-free P2Y12 inhibitor monotherapy versus standard DAPT strategies following PCI, our analysis in this section was primarily descriptive in nature, focusing on summarizing and presenting the available information without performing any statistical comparisons. The effect measure for the studied outcomes was the hazard ratios (HRs) and their corresponding 95 % confidence intervals (CIs)

3. Results

3.1. Study selection

The selection process of the literature retrieval of this study is shown in Fig. 1. A comprehensive search was conducted in the PubMed and Embase databases, resulting in a total of 2105 records being retrieved. Out of these, 831 records were found in PubMed

and 1274 records in Embase. We also checked the reference lists of prior reviews, but no additional studies were identified. To screen these records, we first assessed their titles and abstracts. After applying our pre-defined inclusion and exclusion criteria, we excluded a total of 2093 studies that did not meet our requirements. Next, we proceeded to conduct full-text screenings of the remaining 12 studies. During this full-text screening phase, we further excluded 7 studies because 6 studies compared the P2Y12 inhibitor monotherapy after short DAPT with standard DAPT following PCI, and one study [15] had a similar group of individuals being studied, but the duration of follow-up was relatively shorter. Eventually, a final set of 5 trials [16–20] were included in the present study.

Baseline characteristics of the included studies in this review are presented in Table 1. These studies consisted of 1 RCT (STOPDAPT-3 [16]) and 4 single-arm pilot prospective studies (OPTICA [15], MACT [18], ASET-JAPAN [19], and ASET-BRAZIL [20]), and their populations were from Japan, Netherlands, Brazil, and Korea. The mean age of patients ranged from 59.5 to 71.6 years. The STOPDAPT-3 trial compared the outcomes between the no-aspirin and DAPT strategies during 1-month follow-up, whereas other single-arm studies examined the incidence rates of outcomes in patients who initiated aspirin-free P2Y12 inhibitor monotherapy immediately after PCI. Outcome measures and results of the included studies in this review are shown in Table 2.

3.2. Aspirin-free P2Y12 inhibitor monotherapy after PCI in patients with stable CAD

The ASET-JAPAN and ASET-BRAZIL trials assessed aspirin-free P2Y12 inhibitor monotherapy immediately after PCI in patients with stable CAD. These two prospective, multicenter, single-arm pilot trials had similar study designs, and enrolled low ischemic and bleeding risk patients with stable chronic coronary syndrome requiring PCI. They assessed the effect of prasugrel monotherapy without aspirin immediately after PCI with DES but applied different maintenance doses of prasugrel until 3-month follow-up (10 mg once daily in ASET-BRAZIL, and 3.75 mg once daily in ASET-JAPAN). These two trials involved a total of 407 patients and acquired similar primary findings, consistently demonstrating the safety and feasibility of prasugrel monotherapy immediately after PCI.

After combining the data from ASET-JAPAN and ASET-BRAZIL, the incidence rate of the primary ischemic endpoint was found to be 0.25 % (1 out of 407 patients). Similarly, the incidence rate of the primary bleeding endpoint was also 0.25 %. Furthermore, the rates of secondary outcomes were relatively low, including all-cause death (0.25 %[1/407]), cardiovascular death (0.25 %[1/407]), stroke (0.49 %[2/407]), myocardial infarction (0.49 %[2/407]), repeat coronary revascularization (0.49 %[2/407]), and any bleeding events (1.47 %[6/407]). No occurrences of stent thrombosis were observed among the 407 patients included in the study.

Table 1
Baseline characteristics of the included studies in this review.

Author, year	Population	Study type; location	Age (years)	Male ratio (%)	Sample size (N)	P2Y12 inhibitor monotherapy group	DAPT group	Follow-up
Natsuaki et al., 2023	Patients with ACS (75 %) regardless of HBR or non-ACS (25 %) with HBR, with planned PCI using cobalt-chromium everolimus-eluting stents	RCT, **STOPDAPT-3** (NCT04609111); Japan	71.6 ± 11.7	76.6	5966	N = 2984; Prasugrel (3.75 mg once daily)	N = 2982; Aspirin (81–100 mg/day) and prasugrel (3.75 mg/day)	1 month after randomization
van der Sangen et al., 2023	NSTE-ACS patients underwent PCI using new generation drug-eluting stents	Single-arm pilot study; **OPTICA** (NCT04766437); Netherlands	64.5 ± 11.6	70.7	75	N = 75 ticagrelor (90 mg twice daily) or prasugrel (10 mg once daily)	None	12 months following PCI
Lee et al., 2023	NSTE-ACS or STEMI patients with drug-eluting stents	Single-arm pilot study, **MACT** (NCT04949516); Korea	61.4 ± 10.7	10.0	200	N = 200; colchicine (0.6 mg once daily) + ticagrelor (90 mg twice daily) or prasugrel (10 mg once daily)	None	3 months following PCI
Muramatsu et al., 2023	CCS patients (SYNTAX score <23) underwent PCI with biodegradable-polymer platinum-chromium everolimus-eluting stents	Single-arm pilot study; **ASET-JAPAN** (NCT05117866); Japan	69.0 ± 9.8	18.4	206	N = 206; Prasugrel (3.75 mg once daily)	None	3 months following PCI
Kogame et al., 2023	CCS patients (SYNTAX score <23) underwent PCI with everolimus-eluting stent implantation	Single-arm pilot study, **ASET-BRAZIL** (NCT03469856); Brazil	59.5 ± 7.7	35.3	201	N = 201; Prasugrel (10 mg once daily)	None	3 months following PCI

ACS = acute coronary syndrome; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; STEMI=ST-segment elevation myocardial infarction; CCS = chronic coronary syndrome; DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; HBR = high bleeding risk; STOPDAPT-3 = Short and Optimal Duration of Dual Antiplatelet Therapy-3; OPTICA=Optical Coherence Tomography-Guided PCI with Single Antiplatelet Therapy; MACT = Mono Antiplatelet and Colchicine Therapy; ASET = Acetyl Salicylic Elimination Trial; SYNTAX=Synergy Between PCI With Taxus and Cardiac Surgery.

Table 2
Outcome measures and results of the included studies in this review.

Author, year	Outcome measures and results
Natsuaki et al., 2023	**No-aspirin group vs. DAPT group:** Primary ischemic endpoint-a composite of cardiovascular death, MI, definite stent thrombosis, or ischemic stroke: 4.12 % vs. 3.69 %; HR = 1.12, 95 % CI: 0.87–1.45; $P_{noninferiority} = 0.01$ Net adverse clinical outcomes-a composite of the primary bleeding and ischemic endpoints: 7.14 % vs. 7.38 %; HR = 0.97, 95 % CI: 0.80–1.17 All-cause death: 2.28 % vs. 2.11 %; HR = 1.08, 95 % CI: 0.77–1.52 Cardiovascular death: 2.21 % vs. 2.05 %; HR = 1.08, 95 % CI: 0.76–1.53 Stroke: 0.91 % vs. 0.88 %; HR = 1.04, 95 % CI: 0.61–1.78 MI: 1.28 % vs. 0.94 %; HR = 1.36, 95 % CI: 0.83–2.21 Definite or probable stent thrombosis: 0.71 % vs. 0.44 %; HR = 1.62, 95 % CI: 0.81–3.23 Acute definite or probable stent thrombosis: 0.13 % vs. 0.27 %; HR = 0.50, 95 % CI: 0.15–1.65 Subacute definite or probable stent thrombosis: 0.58 % vs. 0.17 %; HR = 3.04, 95 % CI: 1.26–9.23 Repeat coronary revascularization: 1.05 % vs. 0.57 %; HR = 1.83, 95%CI: 1.01–3.30 Non–target-lesion revascularization: 0.37 % vs. 0.17 %; HR = 2.20, 95 % CI: 0.77–6.34 Primary bleeding endpoint-BARC type 3 or 5: 4.47 % vs. 4.71 %; HR = 0.95, 95 % CI: 0.75–1.20; $P_{superiority} = 0.66$
van der Sangen et al., 2023	Primary ischemic endpoint-a composite of all-cause death, MI, definite or probable stent thrombosis or stroke: 5/75 (6.7 %) All-cause death: 1/75 (1.3 %) Cardiovascular death: 0/75 (0 %) Stroke: 0/75 (0 %) Definite or probable stent thrombosis: 0/75 (0 %) MI: 4/75 (5.3 %) Periprocedural MI: 3/75 (4.0 %) Repeat coronary revascularization: 6/75 (8.0 %) Non–target-lesion revascularization: 5/75 (6.7 %) Primary major or minor bleeding endpoint-BARC type 2, 3 or 5: 9/75 (12 %) Major bleeding-BARC type 3 or 5: 2/75 (2.7 %)
Lee et al., 2023	A composite of all-cause death, all MI, or all revascularization: 3/200 (1.5 %) A composite of cardiovascular death, target-vessel MI, or target lesion revascularization: 2/200 (1.0 %) All-cause death: 1/200 (0.5 %) Cardiovascular death: 1/200 (0.5 %) Definite, probable, or possible stent thrombosis: 2/200 (1.0 %) Target-vessel MI: 1/200 (0.5 %) Target-lesion revascularization: 1/200 (0.5 %) Major bleeding endpoint-BARC type 3 or 5: 1/200 (0.5 %) Any bleeding: BARC types 1–5: 36/200 (18.0 %) Major or minor bleeding endpoint defined as BARC type 2, 3 or 5: 21/200 (10.5 %)
Muramatsu et al., 2023	Primary ischemic endpoint-a composite of cardiovascular death, target-vessel spontaneous MI, or definite stent thrombosis: 0/206 (0 %) All-cause death: 0/206 (0 %) Cardiovascular death: 0/206 (0 %) Stroke: 1/206 (0.5 %) Definite or probable stent thrombosis: 0/206 (0 %) Non-target-vessel related MI: 1/206 (0.5 %) Target-vessel spontaneous MI (48h after index PCI): 0/206 (0 %) Repeat coronary revascularization: 1/206 (0.5 %) Non–target-lesion revascularization: 1/206 (0.5 %) Primary bleeding endpoint-BARC type 3 or 5: 0/206 (0 %) Any bleeding: BARC types 1–5: 5/206 (2.4 %)
Kogame et al., 2023	Primary ischemic endpoint-a composite of cardiovascular death, target vessel spontaneous MI, or definite stent thrombosis: 1/201 (0.5 %) All-cause death: 1/201 (0.5 %) Cardiovascular death: 1/201 (0.5 %) Stroke: 1/201 (0.5 %) Definite or probable stent thrombosis: 0/201 (0 %) Non-target-vessel related MI: 0/201 (0 %) Target-vessel spontaneous MI (48h after index PCI): 0/201 (0 %) Non-target-vessel periprocedural MI: 0/201 (0 %) Target-vessel periprocedural MI: 1/201 (1.0 %) Non–target-lesion revascularization: 1/201 (0.5 %) Primary major bleeding endpoint-BARC type 3 or 5: 1/201 (0.5 %) Any bleeding: BARC types 1–5: 1/201 (0.5 %)

HR = hazard ratio; MI = myocardial infarction; BARC=Bleeding Academic Research Consortium; HR = hazard ratio; CI = confidence interval.

3.3. Aspirin-free P2Y12 inhibitor monotherapy after PCI in patients with ACS

The OPTICA and MACT single-arm pilot studies enrolled a total of 275 ACS patients (non–ST-segment elevation ACS or ST-segment elevation myocardial infarction). Both of these two trials assessed the effect of ticagrelor (90 mg twice daily) or prasugrel (10 mg once

daily) monotherapy without aspirin immediately after PCI with DES. In addition, the MACT trial also added colchicine (0.6 mg once daily).

After analyzing the combined data from OPTICA and MACT, we discovered that the occurrence rates of the primary ischemic endpoint and primary major bleeding endpoint were determined to be 2.91 % (8 out of 275 patients) and 1.09 % (3 out of 275 patients) respectively. Additionally, our study also provided insights into the incidences of secondary outcomes, which included all-cause death (0.73 % [2 out of 275 patients]), cardiovascular death (0.36 % [1 out of 275 patients]), stroke (0.49 % [2 out of 275 patients]), myocardial infarction (1.82 % [5 out of 275 patients]), stent thrombosis (2 % [0.73 out of 275 patients]), repeat coronary revascularization (2.55 % [7 out of 275 patients]), and major or minor bleeding endpoint (10.91 % [30 out of 275 patients]).

3.4. Aspirin-free P2Y12 inhibitor monotherapy versus DAPT after PCI

The STOPDAPT-3 study was the first prospective, multicenter, open-label, adjudicator-blinded RCT assessing the effect of aspirin-free P2Y12 inhibitor monotherapy versus DAPT in 5966 patients with ACS (75 %) regardless of high bleeding risk or non-ACS (25 %) with high bleeding risk with planned PCI. The primary analysis at 1 month after randomization was to compare the outcomes between the aspirin-free P2Y12 inhibitor monotherapy and 1-month DAPT strategies. At 1 month, the group of patients not taking aspirin was not superior to the DAPT group for the primary bleeding endpoint (HR = 0.95, 95 % CI: 0.75–1.20; $P_{superiority} = 0.66$). On the other hand, the group not taking aspirin was found to be non-inferior to the DAPT group for the primary ischemic endpoint (HR = 1.12, 95 % CI: 0.87–1.45; $P_{noninferiority} = 0.01$). There were no significant differences observed in net adverse clinical outcomes or other secondary outcomes including death, stroke, and myocardial infarction between the two groups (Table 2). However, there was an increased incidence of unplanned coronary revascularization in the no-aspirin group (1.05 %) compared to the DAPT group (0.57 %), with an HR of 1.83 (95%CI: 1.01–3.30). Additionally, there was a higher incidence of subacute definite or probable stent thrombosis in the no-aspirin group (0.58 %) compared to the DAPT group (0.17 %), with an HR of 3.04 (95 % CI: 1.26–9.23).

4. Discussion

Based on single-arm studies, it has been suggested that aspirin-free P2Y12 inhibitor monotherapy without DAPT after PCI is both safe and feasible in specific patients with ACS or CAD. However, the STOPDAPT-3 trial highlighted the need for further investigation into the safety and efficacy of this aspirin-free approach in comparison to standard DAPT strategies following PCI. More research is required to definitively determine the benefits and risks associated with this alternative treatment approach.

In the present study, evidence from single-arm pilot prospective studies (OPTICA, MACT, ASET-JAPAN, and ASET-BRAZIL) suggested that in ACS patients with P2Y12 monotherapy following aspirin withdrawal immediately after PCI, the occurrence rates of the primary ischemic endpoint and primary major bleeding endpoint were 2.91 % and 1.09 % respectively, whereas both the incidence rates of the primary ischemic and bleeding endpoints were 0.25 % among individuals with stable CAD. These findings demonstrated the safety and feasibility of aspirin-free P2Y12 monotherapy immediately after PCI in patients presenting with ACS or stable CAD. However, only the STOPDAPT-3 trial compared the prasugrel monotherapy and 1-month DAPT strategies after PCI. There were no differences in the primary ischemic or bleeding endpoints and most secondary outcomes (death, stroke, and myocardial infarction) between the two studied groups. However, the findings in the STOPDAPT-3 trial indicated a potential increased risk of coronary revascularization and stent thrombosis in the group not taking aspirin. Further studies are still needed to confirm the safety and efficacy of aspirin-free P2Y12 inhibitor monotherapy without initial DAPT following PCI, especially compared to standard DAPT strategies.

Aspirin irreversibly inhibits cyclooxygenase-1, thereby reducing thromboxane A2 (TXA2) production and platelet aggregation. In contrast, P2Y12 inhibitors block the ADP receptor P2Y12 on platelet membranes, inhibiting the amplification of platelet activation. In patients with ACS after PCI, the DAPT strategy plays a crucial role in minimizing the risk of recurrent ischemic events. Current guidelines recommend at least 12 months of DAPT after PCI, with a combination of aspirin and a P2Y12 inhibitor (preferably ticagrelor or prasugrel). However, the effectiveness of this strategy comes at the cost of increased bleeding risks. In the early stages following PCI, when the risk of ischemia is highest, the benefits of DAPT for preventing ischemic complications are significant, with most bleeding events occurring during the maintenance phase of DAPT treatment. Therefore, balancing the risks of ischemic and bleeding events is crucial in antiplatelet therapy for patients undergoing PCI. Recent evidence RCTs such as GLOBAL LEADERS, TWILIGHT, TICO, T-PASS, SMART-CHOICE, and STOPDAPT-2 supports the potential benefits of a shorter duration (ranging from 1 to 3 months) of DAPT followed by a switch to aspirin-free P2Y12 inhibitor monotherapy in patients undergoing PCI. These trials have shed light on the advantages of this approach, emphasizing that it can lead to reduced bleeding risks without an increase in ischaemic events, as compared to continuing DAPT after PCI. Several meta-analyses [9–12,21] have also confirmed these findings by pooling the results of these RCTs, supporting the use of P2Y12 inhibitor monotherapy following a short DAPT period after PCI as a reasonable alternative strategy for selected patients with ACS or stable CAD.

The challenge of discerning the efficacy of antiplatelet therapy from its potential harm is a nuanced and critical aspect of patient care post-PCI. The benefits of preventing ischemic events must be carefully weighed against the risks of increased bleeding, which can be particularly significant in patients with high bleeding risk profiles. The balance is further complicated by the variability in individual patient responses to antiplatelet agents, emphasizing the need for a personalized approach to therapy. While current guidelines recommend DAPT to maximize ischemic prevention, the pursuit of tailored antiplatelet strategies is essential to mitigate bleeding risks. Future research should continue to explore the complex relationship between the efficacy and harm of antiplatelet therapy to guide clinical decision-making and optimize patient outcomes.

While recent studies suggest that modified aspirin-free antiplatelet therapy approaches after PCI [22–25], specifically reducing DAPT duration and transitioning to P2Y12 inhibitor monotherapy [26], may offer advantages in terms of bleeding risk reduction, the impacts of initiating aspirin-free P2Y12 inhibitor monotherapy immediately after PCI are not yet fully understood and require further investigation. The ASET-BRAZIL pilot study was groundbreaking as it first provided evidence that prasugrel monotherapy immediately after PCI in stable CAD patients was effective and had no overt safety concerns, paving the new way for further exploration and research in the field of antiplatelet therapy post-PCI. Subsequently, the ASET-JAPAN pilot study with a similar study design also presented the safety and feasibility of administering aspirin-free prasugrel monotherapy as an antiplatelet therapy after PCI. It is noted that the ASET-BRAZIL and ASET-JAPAN trials enrolled low ischemic and bleeding risk patients with stable CAD requiring PCI. Furthermore, the OPTICA and MACT pilot studies extend the positive preliminary feasibility findings of P2Y12 inhibitor monotherapy immediately after PCI to ACS patients. When compared to traditional DAPT strategies, the STOPDAPT-3 trial demonstrated that aspirin-free strategy using low-dose prasugrel monotherapy without initial DAPT following PCI had similar cardiovascular events and bleeding endpoints, but seemingly increased the risks of 1-month coronary events among Japanese patients with ACS or high bleeding risk. However, the STOPDAPT-3 trial involved low-dose prasugrel, and it is not known whether similar results would be obtained with a standard dose of prasugrel or other P2Y12 inhibitors (ticagrelor and clopidogrel).

Currently, there is a lack of sufficient research focusing on the implementation of an early aspirin-free strategy. The only randomized controlled study conducted so far has failed to demonstrate any benefits associated with this approach. However, from a rational perspective, such a strategy could be beneficial for patients at a high risk of bleeding by reducing initial bleeding incidents, as long as the risk of ischemic events does not increase. Unfortunately, in the STOPDAPT-3 trial, there was no observed reduction in bleeding, and instead, certain ischemic events such as subacute stent thrombosis and the necessity for urgent revascularization procedures actually increased. Thus, this trial can be considered a complete failure when evaluating the effectiveness of an immediate aspirin-free strategy post-PCI. Two ongoing trials (NEOMINDSET [27] and LEGACY [28]) on aspirin-free P2Y12 inhibitor monotherapy after a very short DAPT duration in ACS patients undergoing PCI may provide more insights.

The evidence for the specific involvement of TXA2 versus ADP-mediated platelet activation in PCI is still being elucidated, especially when ischemic heart disease is complicated with atrial fibrillation [29–31]. Currently, the clinical practice of DAPT is justified, as it targets both pathways comprehensively. However, the quest for predictive biomarkers to tailor antiplatelet therapy to individual patient responses remains a significant goal. Until such biomarkers are identified and validated, DAPT continues to be the recommended approach to balance the prevention of ischemic events and the risk of bleeding post-PCI.

5. Limitations

Our present review should acknowledge several limitations. First, we included 4 single-arm pilot studies and 1 RCT, our analysis was primarily descriptive in nature. Further meta-analysis could include ongoing trials to perform statistical comparisons between aspirin-free P2Y12 inhibitor monotherapy and standard DAPT after PCI. Second, due to insufficient data, we did not conduct the necessary subgroup analysis based on study design, age, gender, geographical location, coronary artery severity, and type and dose of P2Y12 inhibitors. Third, the MACT trial also added colchicine on the basis of ticagrelor or prasugrel P2Y12 inhibitors on the day after PCI, which might affect the findings. Finally, although the selected patients ranged from stable CAD to ACS, the effect of aspirin-free P2Y12 inhibitor monotherapy after PCI in patients with both high bleeding and ischaemic risks needs further investigation.

6. Conclusions

Although evidence from single-arm pilot prospective studies suggests the safety and feasibility of aspirin-free P2Y12 inhibitor monotherapy without initial DAPT after PCI in selected patients with ACS or stable CAD, the safety and efficacy of this aspirin-free approach compared with standard DAPT strategies following PCI still need further investigation.

Ethical approval

Not required.

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Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Shenglong Yu: Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **Linjuan Guo:** Writing – original draft, Software, Methodology, Formal analysis, Data curation. **Huizhuang Guo:** Writing – review & editing,

Validation, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35741.

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