AIMS Medical Science

AIMS Medical Science, 12(1): 38–62.
DOI: 10.3934/medsci.2025004
Received: 05 July 2024
Revised: 03 December 2024
Accepted: 10 December 2024
Published: 19 February 2025

http://www.aimspress.com/journal/medicalScience

Review

Type and duration of antithrombotic therapy after treatment of severely calcified lesions

Giulia Alagna, Alessia Cascone, Antonino Micari, Giancarlo Trimarchi, Francesca Campanella, Giovanni Taverna, Saro Pistorio and Giuseppe Andò*

Department of Clinical and Experimental Medicine, University of Messina, 98124 Messina, Italy

* **Correspondence:** Email: giuseppe.ando@unime.it.

Abstract: The presence of coronary artery calcification (CAC) increases with age, leading to a higher number and complexity of percutaneous coronary intervention (PCI) procedures in older patients. Chronic kidney disease (CKD) and diabetes are also associated with the development of CAC. These significant comorbidities, combined with PCI of severely calcified lesions, pose major challenges due to technical difficulties and potentially compromise both short- and long-term outcomes. Patients undergoing PCI for heavily calcified lesions should receive optimal anticoagulation and antiplatelet therapy according to current guidelines. However, data on the potential use of more potent P2Y12 inhibitors (ticagrelor, prasugrel) instead of clopidogrel as standard practice in elective PCI of CAC are limited. This is due to varying classifications used to define complex PCI in meta-analyses, and the extreme heterogeneity of the populations studied in terms of clinical presentation. The duration of antiplatelet therapy with aspirin and a P2Y12 inhibitor can be prolonged in selected patients. However, there is increasing evidence supporting the validity of P2Y12 inhibitor monotherapy after standard DAPT, adopting an aspirin-free and tailored de-escalation strategy.

Keywords: severely calcified lesions; coronary artery calcifications; complex percutaneous coronary intervention; dual antiplatelet therapy; P2Y12 inhibitors

1. Epidemiology of coronary artery calcifications (CAC)

The prevalence of calcium deposits in the coronary arteries typically begins after age 40, and its prevalence gradually increases with age. Coronary artery calcifications are found in 93% of men and

75% of women over the age of 70 [1]. Chronic kidney disease (CKD) and diabetes are strongly associated with the development of CAC, with severe CAC affecting between 6% and 20% of patients undergoing percutaneous coronary interventions (PCI) [2]. Among CKD patients, the overall prevalence of CAC, defined by an Agatston score >0, is 60% [3]. Furthermore, the prevalence and severity of CAC are higher in patients with kidney failure with replacement therapy (KFRT) [4]. CAC significantly increases the complexity of PCI. Previous studies have shown that severe CAC of target lesions is linked to adverse outcomes following PCI [5,6]. Also, calcific coronary artery disease is more common in octogenarians, potentially resulting in lower PCI success rates compared to younger patients [7], as well as a greater number and complexity of PCI procedures. Therefore, PCI of severely calcific lesions thus poses substantial technical challenges, potentially compromising both short- and long-term outcomes.

2. Definitions

The European Society of Cardiology (ESC) has proposed the following criteria to identify complex PCI (C-PCI): at least three stents implanted, at least three treated lesions, bifurcation injury with two stents implanted, total stent length >60 mm, or chronic total occlusion (CTO) [8] (Table 1). However, this definition does not account for several procedural criteria such as the assessment of the level of lesion calcifications, the potential use of rotational atherectomy (RA), orbital atherectomy (OA), laser ablation atherectomy, or coronary lithotripsy, involvement of the left main (LM) artery with its hemodynamic and prognostic implications, and the need for intervention on a coronary bypass, which carries a higher risk of embolization and thrombosis. The Society of Cardiovascular Angiography and Interventions (SCAI) has proposed a more comprehensive definition of C-PCI that combines patient-related risk factors and the severity of coronary artery disease (CAD) [9]. However, this definition still lacks practical criteria, such as the use of atherectomy devices and the total stent length. The absence of a universal definition of C-PCI is a significant challenge in randomized trials, making it very difficult to obtain homogeneous samples for sub-analyses. C-PCI usually requires longer or more aggressive procedures and can result in higher rates of periprocedural complications than non-complex procedures, such as myocardial injury or type 4 myocardial infarction (MI), which are associated with a worse long-term outcome [10–12]. Consequently, the most potent P2Y12 inhibitors, prasugrel and ticagrelor, are often used off-label in patients with chronic coronary syndrome (CCS) undergoing C-PCI, despite the lack of solid evidence. Data comparing ticagrelor with clopidogrel in patients with stable CAD are limited, and ticagrelor has rarely been specifically evaluated in patients treated with RA [13–16]. The use of RA remains infrequent, accounting for 3–5% in selected high-volume centers, which explains the difficulty in designing randomized trials for RA. During RA, the interaction between platelets and atheromatous debris is a potential mechanism for the release of cardiac enzymes and troponin. During plaque ablation, the burr could damage the endothelial cell barrier, exposing collagen and platelet recruitment and activation [17,18]. This calcium debulking technique is associated with slow-flow phenomena and distal embolization, which leads to the release of CK-MB [19–21].

Table 1. Definitions of complex PCI.

Study	Journal	Year	Definition of complex PCI
Chieffo et al. [22]	Am Heart J	2013	At least one of the following: - Bifurcation - CTO - Long lesion - Small vessel
Kirtane et al. [23]	Circulation	2016	At least one of the following: - Multivessel disease - LM stenosis/bifurcation - Calcific disease - Stent under-expansion or in-stent restenosis - CTO - Poor hemodynamic status or left ventricular function
Giustino et al. [24]	J Am Coll Cardiol	2016	At least one of the following: - 3 vessels treated - ≥3 stents implanted - ≥3 lesions treated - Bifurcation with 2 stents implanted - Total stent length >60 mm - CTO
Yeh et al. [25]	J Am Coll Cardiol	2017	At least one of the following: - >2 lesions per vessel - Bifurcation with side branch (SB) ≥2.5 mm - Unprotected LM - Total stent length ≥30 mm - Thrombus-containing lesion
Valgimigli et al. [8]	Eur Heart J	2017	At least one1 of the following: - ≥3 stents implanted - ≥3 lesions treated - Bifurcation with 2 stents implanted - Total stent length >60 mm - CTO
Généreux et al. [26]	Int J Cardiol	2018	At least one of the following: - ≥3 stents implanted - Bifurcation with 2 stents implanted - LM lesion - RA use for severely calcified lesions - PCI of saphenous vein graft

Continued on next page

Study	Journal	Year	Definition of complex PCI
Chandrasekhar et al. [27]	Can J Cardiol	2018	At least one of the following: - Bifurcation treated with any technique - LM lesion - Total stent length ≥30 mm - Moderate or severely target calcified lesion
Lipiecki et al. [28]	EuroIntervention	2018	At least one of the following: - 3 vessels treated - ≥3 stents implanted - ≥3 lesions treated - Bifurcation with 2 stents implanted - Total stent length ≥60 mm - CTO - Restenosis or saphenous vein graft lesion
Costa et al. [29]	J Am Coll Cardiol	2019	At least one of the following: - 3 vessels treated - ≥3 stents implanted - ≥3 lesions treated - Bifurcation with 2 stents implanted - Total stent length >60 mm - CTO
Choi et al. [30]	JACC Cardiovasc Interv	2019	At least one of the following: - Multivessel PCI - ≥3 stents implanted - Bifurcation with SB ≥2.5 mm size - Unprotected LM - CTO (≥3 months) - Heavy calcified lesion (requiring RA system) - In-stent restenosis - Long lesion (implanted stent length ≥38 mm)
Riley et al. [9]	Catheter Cardiovasc Interv	2020	At least one of the following: - 3 vessels treated - Saphenous vein graft - Unprotected LM - Bifurcation with severe SB lesion - Severe calcification - CTO - Mechanical circulatory support - Coronary thrombosis - Last remaining conduit - Severe tortuosity

Note: PCI: Percutaneous coronary intervention; CTO: Chronic total occlusion; LM: Left main; RA: Rotational atherectomy.

3. Assessment of ischemic and bleeding risk in high-risk patients

Beyond the issue of procedural complexity, it should be noted that octogenarians are more frequently prone to hemorrhagic events with dual antiplatelet therapy (DAPT) and anticoagulant therapy [31–34]. Their comorbidities are crucial determinants of the risk of ischemic complications. The primary predictors of ischemia include diabetes mellitus, acute coronary syndrome (ACS) or myocardial infarction at presentation, previous PCI (including C-PCI), myocardial infarction, cerebrovascular accident, smoking, CKD, and peripheral arterial disease (PAD). The main predictors of bleeding are age, CKD, cirrhosis, anemia or low hemoglobin levels, C-PCI [35], oral anticoagulants, previous bleeding and/or transfusions, and cancer. Patients undergoing C-PCI are therefore more likely to receive prolonged DAPT or more potent P2Y12 inhibitors, which may contribute to their higher bleeding rates [34,36]. The duration of DAPT may be extended beyond the standard period of 6 months after PCI in CCS [37] or 12 months in ACS with or without PCI [38,39]. Notably, clopidogrel is the preferred P2Y12 inhibitor in addition to aspirin in patients with CCS, while prasugrel (for those undergoing PCI) and ticagrelor (regardless of revascularization) are preferred over clopidogrel in patients with ACS. The ESC guidelines recommend prasugrel over ticagrelor in patients undergoing PCI. The duration of DAPT may be adjusted based on the patient's ischemic and bleeding risk. In patients at increased risk of both ischemic and hemorrhagic complications, bleeding risk should guide the decision-making over the duration of DAPT more than ischemic risk or PCI complexity [29]. Specific scores, tailored to the patient's individual clinical characteristics, can also guide the duration of antiplatelet therapy. The DAPT score [8] assesses thrombotic risk and predicts which patients are eligible for prolonged DAPT after PCI, while the PRECISE-DAPT score [29] assesses the risk of bleeding and helps identify patients for whom antiplatelet therapy needs to be shortened. Other risk stratification tools for predicting ischemia, bleeding, or their interplay in patients with CAD on dual antiplatelet therapy include the PARIS score, BleeMACS bleeding risk score, and ARC-HBR criteria [29,40–42]. However, data on the potential use of more potent P2Y12 inhibitors (ticagrelor, prasugrel) instead of clopidogrel as standard practice in patients with CAC undergoing elective PCI are scarce. Another major limitation of randomized trials investigating the best antiplatelet strategy for patients undergoing C-PCI is the exclusion of patients with moderately and severely calcific lesions from enrollment [43]. After completing DAPT, patients should resume single antiplatelet therapy (SAPT). Aspirin has been the standard of care for SAPT in most patients with CAD. However, emerging evidence in the post-PCI context instead supports the use of a P2Y12 inhibitor as chronic monotherapy [44–48].

4. Individual patient data meta-analysis on coronary calcification and long-term outcomes

The duration and efficacy of DAPT, significantly influenced by the aforementioned risk factors, may be affected by platelet reactivity testing when available. The ADAPT-DES (assessment of dual antiplatelet therapy with drug-eluting stents) study [49] was a prospective, multicenter, observational study aimed at examining the relationship between platelet reactivity to clopidogrel and stent thrombosis (ST) after the implantation of drug-eluting stents (DES). A sub-analysis within ADAPT-DES assessed how the extent and complexity of PCI influenced clinical outcomes two years post-DES implantation and whether these outcomes were affected by clinical presentation (CAD vs. ACS) and/or high platelet reactivity (HPR) to clopidogrel [26]. The definition of C-PCI (C-PCI)

included either elective or emergency PCI involving one or more of the following criteria: the implantation of three or more DES, bifurcation PCI with two stents, PCI of LM, PCI of saphenous vein grafts (SVG), and the use of rotational atherectomy for heavily calcified lesions. Successful DES PCI was performed on 8582 patients, 2255 (26.3%) of whom underwent C-PCI. The most common types of C-PCI involved the implantation of three or more stents, PCI for SVGs, and PCI for LM. Compared to non-C-PCI, patients undergoing C-PCI were generally older, more often male, and had a higher prevalence of both cardiovascular and non-cardiovascular comorbidities. These patients also more frequently presented with stable CAD over ACS, had more extensive CAD, and showed lower ejection fractions compared to the non-C-PCI group. There were no notable differences in platelet reactivity units (PRU) on clopidogrel or in the prevalence of HPR after C-PCI and non-C-PCI procedures. Likewise, the two groups showed no significant difference in DAPT use over the two-year follow-up period. However, patients undergoing C-PCI were more frequently treated with warfarin during the study period. Compared to non-C-PCI, C-PCI patients had higher rates of two-year all-cause mortality, MACE, ST, MI, ischemia-driven target lesion revascularization (ID-TLR), and major bleeding events. Landmark analyses at intervals of 0–6 months and 6 months to 2 years highlighted differences in event patterns depending on the type of C-PCI performed. In the first 6-month period, ST rates were highest for RA in severely calcific lesions, followed by bifurcation stenting, the implantation of three or more DES, and SVG intervention. Between 6 months and 2 years, ST rates continued to rise, particularly for patients undergoing bifurcation PCI and SVG intervention. No significant differences in MACE or ST rates were found between LM PCI and non-C-PCI during these periods. Across all ischemic events, procedural complexity did not interact with HPR, indicating that the potential benefits of extended potent antiplatelet therapy in patients with stable CAD and undergoing complex PCI may be particularly relevant when HPR is present with clopidogrel, which could increase adverse event risk. Nonetheless, major bleeding events within two years were also more frequent among C-PCI patients and were associated with even higher mortality than ischemic events, underscoring the treatment challenges in this population. Given that the ischemic risk period was generally longer within the first six months post-PCI (with exceptions for SVG and bifurcation PCI), a tailored DAPT intensification strategy over six months for selected patients with stable CAD undergoing C-PCI may yield net clinical benefits by balancing ischemic and bleeding risk [24]. In 2018, the efficacy of prasugrel and ticagrelor in patients without ACS was unproven; prasugrel only became available toward the end of the ADAPT-DES study, while ticagrelor was not yet in use. It remains unclear whether different outcomes might have been observed if patients had been treated with these potent P2Y12 inhibitors. Finally, multivariable models did not adjust for DAPT duration; however, no significant differences in DAPT regimens were noted between groups. It is also important to note that no interaction was detected between diabetes and procedural complexity, suggesting that the adverse effects of C-PCI may not be influenced by this comorbidity. A meta-analysis [50] encompassing 18 randomized controlled trials (RCTs) found that moderate or severe CACs were present in one or more target lesions in 6211 patients (31.3%). Patients with moderate or severe CACs were generally older and showed a higher prevalence of baseline comorbidities, such as insulin-dependent diabetes mellitus, hyperlipidemia, and a history of coronary artery bypass grafting (CABG). These patients also had a greater incidence of multivessel disease and lower thrombolysis in myocardial infarction (TIMI) flow at baseline. After adjusting for baseline and procedural factors, the presence of moderate or severe CACs was independently associated with a heightened 5-year risk of patient-oriented composite endpoint (POCE), target lesion failure (TLF), all-cause and cardiac

mortality, target vessel MI, and ID-TLR, with a trend toward increased MI risk. The benefits of second-generation DES over first-generation DES were similar for patients both with and without moderate or severe CAC in target lesions. Landmark analysis indicated that second-generation DES was linked with reduced rates of POCE, TLF, and ST during both the 0–1 year and 1–5 year intervals. CACs serve as a marker of atherosclerosis and correlate with the overall extent of plaque burden [51]. They are linked to an elevated risk of cardiovascular adverse events unrelated to the stent, as well as certain non-cardiac complications [52,53]. Additionally, CAC presence has been associated with higher rates of all-cause and cardiovascular mortality, as well as reinfarction involving target lesions, regardless of whether first- or second-generation DES was used [54–58]. The extensive meta-analysis, with a follow-up of up to 5 years, confirmed and expanded upon these observations. However, it did not account for variations in minimum DAPT duration across the studies, which is a limitation of the multivariate analysis. Furthermore, the use of various interventional devices and techniques—such as rotational or orbital atherectomy or cutting or scoring balloons to debulk CACs before stent implantation—was not considered. Consequently, the results of this post-hoc analysis should be interpreted with caution.

5. ALPHEUS study

The ALPHEUS randomized open-label trial aimed to assess whether ticagrelor offers superior efficacy over clopidogrel in reducing periprocedural myocardial necrosis in patients with CAD undergoing high-risk elective PCI, including PCI for severely calcified lesions classified as ACC/AHA type B2 or C lesions [59]. Criteria defining C-PCIs included procedures meeting at least one of nine criteria: multiple stents implantations, use of a guide-wire and/or extension catheter, total stent length greater than 60 mm, bifurcation stenting, LM stenting, CTO PCI, atherectomy, or PCI of arterial or venous coronary graft. Patients were randomly assigned in a 1:1 ratio to receive either ticagrelor (180 mg loading dose, followed by 90 mg twice daily for 30 days) or clopidogrel (300–600 mg loading dose, followed by 75 mg daily for 30 days). The primary efficacy endpoint was a composite of type 4a or 4b MI or major myocardial injury within 48 hours post-PCI, while the primary safety endpoint was major bleeding, assessed within the same timeframe or at hospital discharge if earlier. Clinical outcomes were evaluated at both 48 hours and 30 days. The risk of bleeding was similar between the two groups when assessed with the DAPT score, though slightly different when evaluated with PARIS score, with more patients with a low risk of bleeding in the ticagrelor group [40,60]. At 48 hours, the primary composite efficacy endpoint occurred in 35% of patients in the ticagrelor group and 36% of patients in the clopidogrel group, with no significant difference observed in secondary efficacy outcomes at the 30 days. Primary safety events were rare and comparable between groups. Despite ticagrelor's greater platelet inhibition, it did not demonstrate superiority over clopidogrel in reducing periprocedural MI or myocardial injury within 48 hours of high-risk PCI in patients with CAD. Moreover, clinical outcomes at 30 days did not differ between groups, though ticagrelor was associated with a slightly higher bleeding risk compared to clopidogrel over this period. The inability of ticagrelor to prevent PCI-related myocardial necrosis in patients with high-risk CAD contrasts with its efficacy in ACS management [61]. The initiation of drug therapy prior to PCI in ALPHEUS participants ensured consistent results regardless of pre-procedural timing. These findings align with those of similar studies, such as the SASSICAIA study [62], which found no advantage in using ticagrelor or prasugrel over clopidogrel to reduce periprocedural complications in elective PCI. Recent de-escalation

studies, which suggested safety benefits with single antiplatelet therapy in elective PCI over DAPT for more than 30 days, further support clopidogrel's role as standard therapy alongside aspirin in elective PCI [63]. The ancillary study of the ALPHEUS [64] aimed to evaluate the frequency and outcomes of C-PCIs in CAD patients and compare ticagrelor and clopidogrel efficacy. The population was stratified based on PCI complexity into non-C-PCI, low, intermediate, and high complexity groups. Treatment beyond 30 days was at the physician's discretion. The primary endpoint remained the composite of periprocedural MI (type 4a or 4b) and major myocardial injury within 48 hours, with secondary endpoints including MACE at 48 hours and one month, myocardial injury rates, procedural complications, and major bleeding events (BARC 3 or 5) at one month [65]. No significant interaction was found between randomized antiplatelet treatment and PCI complexity for the primary 48-hour endpoint. Although numerically higher rates of type 4a MI and major myocardial injury were observed in the complex PCI group, treatment assignment did not significantly impact outcomes, except for lower primary endpoint rates in patients treated with clopidogrel for two-stent bifurcation and those treated with ticagrelor for LM stenting. In conclusion, despite ticagrelor's potent platelet inhibition, it did not reduce rates of periprocedural MI and major myocardial injury compared to clopidogrel in CAD patients undergoing high-risk elective PCI, consistent across different types and complexities of PCI. These findings support clopidogrel's use alongside aspirin as standard therapy for elective PCI while encouraging exploration of other strategies to mitigate periprocedural infarction risk.

6. TIRATROP study

Recent studies have incorporated the use of RA for severely calcified lesions within the definition of C-PCI [26,66]. The TIRATROP (TIcagrelor in Rotational Atherectomy to reduce TROPonin enhancement) study was the first to compare ticagrelor with clopidogrel in patients undergoing RA for calcific lesions. It was a randomized, double-blind, multicenter controlled trial conducted between 2015 and 2018, involving 180 patients with severely calcified lesions necessitating RA for debulking. Patients were randomized to receive either clopidogrel (300 mg loading dose, followed by 75 mg daily) or ticagrelor (180 mg loading dose, followed by 90 mg twice daily) [67]. Given that RA is associated with arterial trauma and platelet activation, patients undergoing RA are expected to benefit from more potent antiplatelet therapy. This study aimed to assess whether ticagrelor, currently indicated to reduce ischemic cardiovascular events in ACS, would demonstrate superiority over clopidogrel in reducing troponin release post-procedure [38,68]. The primary endpoint of the study was troponin release within the first 24 hours, assessed using the area under the curve analysis of troponin levels over time. Secondary endpoints included procedural and hospital complications in the safety population. The overall population represented a high-risk cohort, with an average age of 76 ± 10 years, 76.3 % male, 35.3% diabetic, and 12.7% active smokers. Three-vessel CAD or its equivalent was present in 44% of patients, and LM stenosis in 23.7%. Most patients had only one calcific lesion targeted by RA. In the entire cohort, the incidence of type 4 MI and myocardial lesions as per the fourth universal definition of MI guidelines was 72.3% and 99.4%, respectively. No significant differences in troponin release were observed between the ticagrelor and clopidogrel groups based on the initial diagnosis at hospitalization. Only one patient experienced MI in the clopidogrel arm. Severe bleeding, defined by BARC criteria, occurred in both groups. There were no ST events in either treatment arm. Few events were reported post-discharge, with no significant differences between the groups. Therefore, the TIRATROP study failed to demonstrate ticagrelor's superiority over clopidogrel in limiting myocardial

injury extent during RA procedures. In fact, the results indicate that ticagrelor did not show superior efficacy in preventing ischemic complications of RA, such as on no-reflow/slow flow. This study found no difference between ticagrelor and clopidogrel in elective PCI regarding ischemic endpoints in a high-risk population, despite the marked pharmacodynamic differences between the two treatments. Given that the inclusion criteria focused on calcific lesions, this study involved a more homogeneous population compared to the ALPHEUS Study. The TIRATROP cohort also represented a population at very high risk for ischemic complications, with a higher incidence of transient myocardial ischemia, slow flow/no-flow and non-Q-wave MI reported during RA procedures [69]. Despite this increased ischemic risk, ticagrelor did not reduce myocardial necrosis in TIRATROP. Additionally, besides platelet aggregation, microembolization of atheromatous debris and thermal damage have been suggested as contributors to the heightened risk of periprocedural myocardial lesions during RA procedures [70]. The prognostic significance of troponin release post-PCI remains under discussion, with some meta-analyses and recent data indicating a link between long-term mortality and post-PCI troponin elevation [11,71]. The predictive value of troponin increases with its rise from baseline [72]. Patients with multiple lesions treated with RA showed greater troponin release, while those with CKD and inflammatory reactions exhibited higher cardiac troponin prevalence, potentially due to reduced clearance and myocardial damage. Although this study lacked statistical power to detect clinical differences between ticagrelor and clopidogrel, few bleeding events were reported during hospitalization, with no disparities observed between treatment regimens. In conclusion, the TIRATROP study suggests that ticagrelor does not offer superiority over clopidogrel in reducing troponin release after RA procedures. Furthermore, the findings indicate that RA-induced myocardial injury is unaffected by the level of P2Y12 inhibition. In addition, a 2023 Taiwanese study involving 411 patients examined profiles and short- to medium-term procedural outcomes of RA in patients over 80 years old compared to younger patients [7] Among the patients, 73.5% had hypertension, 58.6% had diabetes, and 10.7% had peripheral artery disease (PAD). Nearly all lesions treated were severely calcified, with both groups having a high baseline SYNTAX score [73]. Following stent implantation, DAPT with aspirin (100 mg/day) and either clopidogrel (75 mg/day) or ticagrelor (90 mg twice daily) was continued for at least 12 months in case of DES or three months for bare-metal stents (BMS). Octogenarians exhibited higher rates of all-cause and cardiovascular mortality during the first year, along with increased major adverse cardiovascular events (MACE) in the initial month. Conversely, non-octogenarians had more frequent target lesion revascularization (TLR) and target vessel revascularization (TVR) at 12 months. Thus, decisions on DAPT duration and intensity are crucial during the first year post-PCI in elderly patients with comorbidities.

7. Data from SIDNEY-2 and other meta-analysis in complex PCI

There are several criticisms regarding the prolonged duration of dual antiplatelet therapy (DAPT) in high-risk patients, despite its potential to reduce the risk of stent thrombosis and spontaneous atherothrombotic events [74]. Extending DAPT increases the risk of major bleeding, negatively impacting prognosis [24,75]. Several studies suggest that the complexity of PCI alone is insufficient justification for prolonging DAPT; instead, bleeding risk assessment should be an integral part of decision-making [76]. The Sidney-2 (Single Versus Dual Antiplatelet Therapy-2) meta-analysis [77] demonstrated that monotherapy with a P2Y12 inhibitor after 1–3 months of DAPT was associated with similar cardiovascular event risks and a 50% lower risk of bleeding compared to standard DAPT

following PCI. This effect was consistent across 4685 patients undergoing C-PCI, defined by criteria including treatment of 3 vessels, ≥3 implanted stents, ≥3 treated lesions, bifurcation with ≥2 implanted stents, total stent length >60 mm, or CTO. The primary efficacy endpoint included all-cause mortality, MI, and stroke, while the key safety endpoint was BARC 3 or 5 bleeding. Patients undergoing C-PCI are at increased risk of ischemic events and often receive prolonged DAPT to ensure long-term protection against atherothrombosis [74,78,79]. This approach is supported by a retrospective analysis of 9577 patients from six RCTs, which found that continuing DAPT for ≥1 year, rather than switching to aspirin monotherapy after 3 or 6 months, resulted in greater ischemic risk reduction among C-PCI patients [24]. However, a study involving 14963 patients from eight trials indicated that long-term DAPT provided ischemic benefits only when high-risk bleeding characteristics were absent [29]. Additionally, a sub-analysis of a trial involving high bleeding risk patients showed that 1-month DAPT followed by single antiplatelet therapy (mainly P2Y12 inhibitor alone) and standard DAPT resulted in similar rates of major adverse cardiac or cerebral events in both C-PCI and non-C-PCI patients [76,80]. Evidence supports discontinuation of aspirin after 1–3 months of DAPT and transitioning to P2Y12 inhibitor monotherapy, effectively balancing bleeding and ischemic risks post-PCI. This strategy has been associated with comparable rates of fatal and ischemic events and a lower risk of bleeding compared to standard DAPT [78] and is endorsed by international guidelines [8,74,79]. However, post-hoc analyses from individual studies [66,81–84] have not definitively resolved concerns regarding the safety and efficacy trade-offs of early transition to P2Y12 inhibitor monotherapy in C-PCI patients, particularly concerning potential harm in high-risk subsets. In the meta-analysis of Gragnano et al., the average age of patients was 64.9 years, with C-PCI patients more likely to be male or diabetic and presenting more frequently with non-ST segment elevation acute myocardial infarction (NSTEMI) and less often with ST segment elevation myocardial infarction (STEMI) compared to non-C-PCI patients. C-PCI patients had significantly higher ischemic risks and numerically higher bleeding rates than non-C-PCI patients. P2Y12 inhibitor monotherapy was associated with similar risks of fatal and ischemic events compared to DAPT across PCI complexities, P2Y12 inhibitor types, and clinical presentations. P2Y12 monotherapy significantly reduced major bleeding and net adverse cardiovascular events (NACE) relative to DAPT, with consistent hemorrhagic benefits observed across C-PCI and non-C-PCI groups. These results were confirmed by all subgroup and sensitivity analyses, which consistently showed that P2Y12 inhibitor monotherapy maintained ischemic protection without compromising safety. Increasing or prolonging DAPT entails a trade-off between reduced ischemic risk and increased bleeding risk, both of which impact subsequent mortality. Oral P2Y12 inhibitor monotherapy post-PCI, whether for C-PCI or non-C-PCI patients, has not been associated with adverse outcomes, showing similar rates of fatal and ischemic events to DAPT, with no increased risk of MI or ST [66]. Consistency in treatment effects was observed across different C-PCI criteria and procedural complexities, indicating a potential shift in practice toward early initiation of P2Y12 inhibitor monotherapy after PCI. Nonetheless, further research is needed to assess whether the type of P2Y12 inhibitor could affect the risk-benefit ratio between monotherapy and standard DAPT after C-PCI and non-C-PCI. The SIDNEY-2 findings should be interpreted with caution due to potential limitations, such as incomplete data on CTO procedures in two studies [84,85] and limited information on atherectomy device use available in only one study [66]. These factors may have influenced treatment effects, with subgroup analyses lacking sufficient power to detect heterogeneity due to small sample sizes. Further investigation is needed to explore how different P2Y12 inhibitor types may affect the risk-benefit balance of monotherapy versus standard DAPT following both C-PCI and non-C-PCI.

8. Complex PCI in STOPDAPT-3 trial

Recent RCTs suggest that a strategy involving a short duration of dual antiplatelet therapy (DAPT) for 1–3 months followed by P2Y12 inhibitor monotherapy reduces major bleeding events without increasing cardiovascular events after percutaneous coronary intervention (PCI) [86–90]. An aspirin-free regimen could therefore be a viable option for antiplatelet therapy in patients undergoing complex PCI (C-PCI), given their high risk of periprocedural bleeding. However, findings from the STOPDAPT-3 Study (ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-3) indicated that compared to standard DAPT, an aspirin-free strategy did not reduce major bleeding 1 month post-PCI, although it was not inferior for cardiovascular events [91]. These results were consistent in the C-PCI subgroup analysis of STOPDAPT-3, where the aspirin-free strategy using a reduced dose of prasugrel showed cardiovascular benefits compared to DAPT. The study included patients with severely calcified lesions, defined according to criteria from the European Society of Cardiology and Japanese Circulation Society [8,24,92]. Patients undergoing C-PCI were typically older, predominantly male, and had higher rates of comorbidities such as diabetes, left ventricular dysfunction, and chronic kidney disease compared to those without C-PCI. Subgroup analyses revealed no significant differences in cardiovascular and bleeding outcomes between aspirin-free and standard DAPT strategies, regardless of C-PCI status, without notable interactions. Importantly, there was no indication of increased cardiovascular events with the aspirin-free strategy in C-PCI patients, though these findings should be considered hypothesis-generating due to subgroup analysis limitations. Previous studies have highlighted the higher cardiovascular risk among C-PCI patients, particularly in the first month post-PCI. A 2016 meta-analysis by Giustino et al. [24] demonstrated that prolonged DAPT (12–24 months) reduced adverse cardiac events and coronary thrombotic events compared to shorter durations (3–6 months) in C-PCI across six RCTs where aspirin was primarily used after DAPT discontinuation. More recent findings by Gragnano et al. [77] and Yamamoto et al. in 2024 support the use of P2Y12 inhibitor monotherapy after short DAPT periods (1–3 months) without increased ischemic risks in C-PCI patients [93,94]. Moreover, Yamamoto et al. [95] reported a sub-analysis comparing low-dose prasugrel monotherapy versus DAPT immediately post-PCI, demonstrating no reduction in bleeding with the aspirin-free strategy due to procedure-related bleeding, which may be less responsive to aspirin omission or additional therapies [24]. Patients were randomized to receive either monotherapy with prasugrel 3.75 mg or dual antiplatelet therapy (DAPT) with aspirin plus prasugrel 3.75 mg for one month following percutaneous coronary intervention (PCI). The primary endpoints were major bleeding (defined as BARC 3 or 5) and cardiovascular events (a composite of cardiovascular death, myocardial infarction, stent thrombosis, or ischemic stroke), tested for non-inferiority at one month. The study found no significant reduction in bleeding risk with the aspirin-free strategy, which may be due to procedure-related bleeding, accounting for a substantial proportion of total bleeding and potentially less influenced by aspirin omission. Additionally, the efficacy of adjunctive therapies could have contributed to these findings. Notably, there was no discernible difference in cardiovascular events between the two treatment strategies among patients undergoing complex PCI (C-PCI). A sub-analysis identified an increased incidence of coronary events with prasugrel monotherapy, notably a three-fold higher risk of defined or probable sub-acute stent thrombosis. This observation is likely attributable to inadequate platelet inhibition. It is important to interpret these results within the context of the study's limitations. Nevertheless, the findings suggest that the complexity of PCI procedures may not significantly impact the efficacy of P2Y12 inhibitor

monotherapy compared to DAPT post-PCI. These conclusions are supported by a meta-analysis conducted by Gragnano et al. in 2023 [77], which extends previous observations to the first month post-PCI [95]. Furthermore, the study underscores the importance of selecting the appropriate P2Y12 inhibitor for aspirin-free strategies. Low-dose prasugrel may not consistently achieve sufficient P2Y12 receptor blockade, potentially explaining the higher incidence of coronary events observed in the aspirin-free group of STOPDAPT-3 [96]. These findings are consistent with those from STOPDAPT-2, which demonstrated an increased risk of coronary events with clopidogrel monotherapy initiated one-month post-PCI for acute coronary syndrome [97]. In contrast, standard doses of ticagrelor or prasugrel reliably achieve high levels of P2Y12 inhibition [98], potentially obviating the need for aspirin for antithrombotic protection. In the Sidney-3 meta-analysis [96], ticagrelor monotherapy following 1–3 months of DAPT post-PCI significantly reduced major bleeding and was non-inferior to standard DAPT in preventing cardiovascular events. Clopidogrel monotherapy also reduced bleeding but did not achieve non-inferiority to DAPT for fatal and ischemic events.

9. Antiplatelet de-escalation strategies

The 2023 ARC Consensus Document [99] focuses on de-escalation strategies. De-escalation by switch consists of the switch from aspirin plus a potent P2Y12 inhibitor to aspirin and clopidogrel. De-escalation by discontinuation consists of changing from DAPT to a monotherapy with either aspirin or prasugrel or ticagrelor. By reducing the intensity of platelet inhibition, de-escalation is an approach aimed at reducing the risk of hemorrhagic complications when they are considered greater than the risk of thrombotic complications. In fact, the escalation of antiplatelet therapy is intended to reduce thrombotic or ischemic complications by increasing the intensity of platelet inhibition at a time when this risk is considered greater than the risk of bleeding complications. The ESC Guidelines [38] report that in the case of de-escalation by switch of P2Y12 inhibitors, switching from prasugrel or ticagrelor to clopidogrel should be considered to reduce the risk of bleeding (CoR IIb, LoE A), but no earlier than one month. For patients with CCS, the ESC recommends balancing ischemic and bleeding risks when considering DAPT continuation beyond six months. In low-bleeding-risk patients with high ischemic risk, prolonged DAPT might be beneficial (CoR IIa, LoE A) [100]. Over the years, several studies have been conducted (TOPIC [101], PHARMCLO [102], TALOS-AMI [103], TROPICAL-ACS [104], POPULAR-GENETICS [105]) on de-escalation by switch therapy in ACS patients where the key message is virtually the same; namely, that guided de-escalation of antiplatelet treatment was not inferior to standard treatment with more potent P2Y12 inhibitors at one year after PCI in terms of net clinical benefit. There are also three de-escalation studies for discontinuation in ACS patients (SMART-DATE [106], REDUCE ACS [107], DAPT STEMI [108]) in which DAPT was evaluated compared to aspirin alone, and three studies (TICO [90], STOPDAPT-2 ACS [97], T-PASS [109]) on DAPT compared to the P2Y12 inhibitor alone. Finally, ULTIMATE-DAPT Trial [110] in 1-month DAPT followed by ticagrelor SAPT. In the case of de-escalation by discontinuation of P2Y12 inhibitors, ESC guidelines recommend discontinuing aspirin preferably after 3–6 months of DAPT events in patients with low ischemic risk (CoR IIA, LoE A) and discontinuing aspirin or P2Y12 inhibitor monotherapy after one month of DAPT in patients at high risk of bleeding (CoR IIb, LoE B). In a 2022 network meta-analysis [46], Andò et al. demonstrated that P2Y12 inhibitor monotherapy after discontinuation of DAPT after PCI is associated with a significantly lower risk for MI and a similar risk for major bleeding, suggesting a potentially relevant net clinical benefit compared

to aspirin monotherapy. This network meta-analysis was updated in 2024 [47] with the data of Gragnano et al. [111] and Chiarito et al. [112], and direct evidence showed that P2Y12 inhibitors were associated with a lower risk of MI and a risk of bleeding similar to aspirin; the robustness of the data increased with the selectivity of the population.

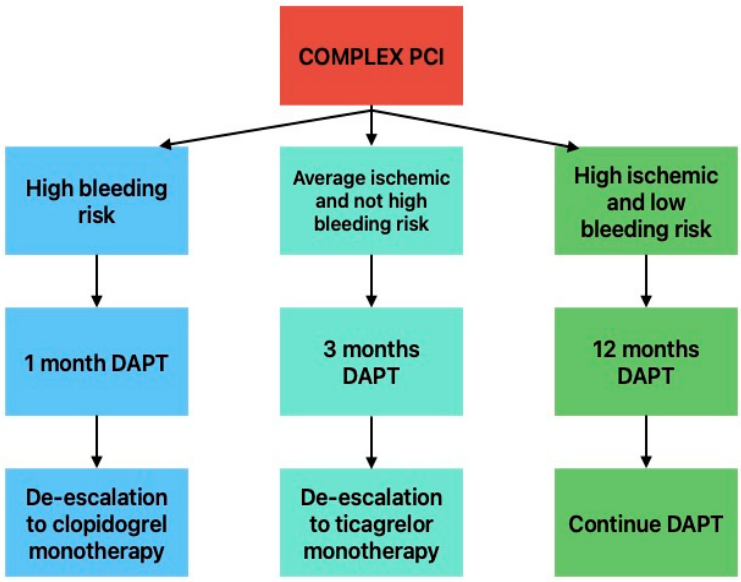

Figure 1. Potential strategies for DAPT after complex PCI (Modified from Bhatt (2023) [113]).

10. Conclusions

The selection of the study population poses a significant limitation on the available scientific evidence to date (Table 2). Notably, the exclusion of severely calcified lesions from criteria defining C-PCI in certain studies remains pivotal. This heterogeneity among patient subsets encompasses various clinical presentations (ACS and CCS) as well as the differentiation between C-PCI and non-C-PCI cases. However, patients with severe calcified coronary artery disease commonly share comorbidities such as diabetes and CKD, often associated with aging. In this context, personalized antiplatelet therapy has emerged as a paradigm to optimize the balance between safety and efficacy by tailoring treatment to each patient's individual needs and risk profile. Patients at high risk of ischemic events but at low risk of bleeding may benefit from a more aggressive antiplatelet regimen. Conversely, those at high risk of bleeding and low risk of ischemic events require a less intensive and cautious approach. For patients at low risk of both ischemic events and bleeding, the potential benefits of antiplatelet therapy may not justify the risks. Patients at high risk for both ischemic and bleeding events necessitate a delicate balance, as managing their condition involves carefully assessing the trade-off between risks and benefits.

Table 2. Summary of the discussed studies.

Study	Clinical presentation	Definition of C-PCI	P2Y12 inhibitor therapy	Results
ADAPT-DES	- ACS - CAD	At least one of the following: - ≥3 stents implanted - Bifurcation with 2 DES implanted - Rotational atherectomy - LM PCI - SVG PCI	Clopidogrel	No significant differences in PRU on clopidogrel or in the prevalence of HPR after C-PCI and non-C-PCI procedures. No significant differences in the use of DAPT during 2 years of follow-up. SVG PCI, 2-stent bifurcation treatment, and implantation of ≥3 stents were independently associated with MACE Patients undergoing extensive and more complex PCI experienced worse outcomes after successful PCI
GUEDENEY et al.	- ACS - CAD	Severity of CAC assessed using quantitative coronary angiography: moderate-lesion CAC as radiopaque densities noted during cardiac motion involving only one side of the vascular wall; severe-lesion CAC as radiopaque densities noted without cardiac motion generally involving both sides of the arterial wall.	Clopidogrel, ticagrelor	Treatment with contemporary second-generation DES was associated with consistently improved long-term outcomes in patients with and without moderate or severe CAC.

Continued on next page

Study	Clinical presentation	Definition of C-PCI	P2Y12 inhibitor therapy	Results
ALPHEUS	- CAD	At least one of the following: - Stent length >60 mm - Bifurcation with two DES implanted - LM - Bypass graft - CTO - Atherectomy or guiding catheter extensions - Multiwire technique - Multiple DES	Clopidogrel, Ticagrelor	Patients undergoing a C-PCI have higher rates of periprocedural and cardiovascular events that are not reduced by ticagrelor as compared with clopidogrel. The minimum duration of DAPT varied between the different studies considered and this potential confounding factor was not included in the multivariate analysis.
TIRATROP	- ACS (NSTEMI) - CAD	- Rotational atherectomy	Clopidogrel, ticagrelor	Greater platelet inhibition does not affect periprocedural myocardial necrosis in the setting of RA.
SIDNEY-2	- ACS - CAD	At least one of the following: - 3 treated vessels - ≥3 implanted DES - ≥3 treated lesions - Bifurcation with two DES implanted - Total stent length >60 mm - CTO	Clopidogrel, ticagrelor, prasugrel	P2Y12 inhibitor monotherapy after 1–3 months of DAPT was associated with a similar risk of cardiovascular events and a 50% lower risk of bleeding greater than standard DAPT after PCI.
STOP-DAPT 3	- ACS - CAD	At least one of the following: - ≥ 3 stents implanted - ≥ 3 lesions treated - Bifurcation lesion with two stents implanted - Total stent length >60 mm - CTO	Prasugrel	No difference in cardiovascular events between the two treatment strategies in patients undergoing C-PCI

Note: ACS: Acute coronary syndrome; CAD: Coronary artery disease; LM PCI: Left main PCI; SVG PCI: Saphenous vein graft PCI; DES: Drug-eluting stent; PRU: Platelet reactivity unit; HPR; High platelet reactivity; DAPT: Dual antiplatelet therapy; MACE: Major adverse cardiovascular events; CAC: Coronary artery calcification; RA: Rotation atherectomy; CTO: Chronic total occlusion.

Author contributions

Giulia Alagna prepared the original draft of the article. Alessia Cascone, Antonino Micari, Giancarlo Trimarchi, Francesca Campanella, Giovanni Taverna and Saro Pistorio reviewed the article for important intellectual content and contributed to literature review. Giuseppe Andò provided supervision and is responsible for the final decision to submit. All authors have approved its publication.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Acknowledgments

The authors are institutionally funded by the University of Messina. No external funding has been requested in preparing the article.

Conflict of interest

The authors declare no conflict of interest.

References

1. Wong ND, Kouwabunpat D, Vo AN, et al. (1994) Coronary calcium and atherosclerosis by ultrafast computed tomography in asymptomatic men and women: relation to age and risk factors. *Am Heart J* 127: 422–430. https://doi.org/10.1016/0002-8703(94)90133-3
2. Kedhi E, Généreux P, Palmerini T, et al. (2014) Impact of coronary lesion complexity on drug-eluting stent outcomes in patients with and without diabetes mellitus: analysis from 18 pooled randomized trials. *J Am Coll Cardiol* 63: 2111–2118. https://doi.org/10.1016/j.jacc.2014.01.064
3. Wang XR, Zhang JJ, Xu XX, et al. (2019) Prevalence of coronary artery calcification and its association with mortality, cardiovascular events in patients with chronic kidney disease: a systematic review and meta-analysis. *Ren Fail* 41: 244–256. https://doi.org/10.1080/0886022X.2019.1595646
4. Roy SK, Cespedes A, Li D, et al. (2011) Mild and moderate pre-dialysis chronic kidney disease is associated with increased coronary artery calcium. *Vasc Health Risk Manag* 7: 719–724. https://doi.org/10.2147/VHRM.S24536
5. Généreux P, Madhavan MV, Mintz GS, et al. (2014) Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes. Pooled analysis from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trials. *J Am Coll Cardiol* 63: 1845–1854. https://doi.org/10.1016/j.jacc.2014.01.034
6. Madhavan MV, Tarigopula M, Mintz GS, et al. (2014) Coronary artery calcification: pathogenesis and prognostic implications. *J Am Coll Cardiol* 63: 1703–1714. https://doi.org/10.1016/j.jacc.2014.01.017

7. Hu YC, Chen WJ, Lai CH, et al. (2023) Rotablation for octogenarians in a modern Cathlab: short- and intermediate-term results. *Acta Cardiol Sin* 39: 424–434. https://doi.org/10.6515/ACS.202305_39(3).20220926B
8. Valgimigli M, Bueno H, Byrne RA, et al. (2018) 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 39: 213–260. https://doi.org/10.1093/eurheartj/ehx419
9. Riley RF, Henry TD, Mahmud E, et al. (2020) SCAI position statement on optimal percutaneous coronary interventional therapy for complex coronary artery disease. *Catheter Cardiovasc Interv* 96: 346–362. https://doi.org/10.1002/ccd.28994
10. Zeitouni M, Silvain J, Guedeney P, et al. (2018) Periprocedural myocardial infarction and injury in elective coronary stenting. *Eur Heart J* 39: 1100–1109. https://doi.org/10.1093/eurheartj/ehx799
11. Ndrepepa G, Colleran R, Braun S, et al. (2016) High-sensitivity troponin T and mortality after elective percutaneous coronary intervention. *J Am Coll Cardiol* 68: 2259–2268. https://doi.org/10.1016/j.jacc.2016.08.059
12. Prasad A, Singh M, Lerman A, et al. (2006) Isolated elevation in troponin T after percutaneous coronary intervention is associated with higher long-term mortality. *J Am Coll Cardiol* 48: 1765–1770. https://doi.org/10.1016/j.jacc.2006.04.102
13. Xu Q, Sun Y, Zhang Y, et al. (2017) Effect of a 180 mg ticagrelor loading dose on myocardial necrosis in patients undergoing elective percutaneous coronary intervention: a preliminary study. *Cardiol J* 24: 15–24. https://doi.org/10.5603/CJ.a2017.0002
14. Bonello L, Laine M, Thuny F, et al. (2016) Platelet reactivity in patients receiving a maintenance dose of P2Y12-ADP receptor antagonists undergoing elective percutaneous coronary intervention. *Int J Cardiol* 216: 190–193. https://doi.org/10.1016/j.ijcard.2016.04.165
15. Orme RC, Parker WAE, Thomas MR, et al. (2018) Study of two dose regimens of ticagrelor compared with clopidogrel in patients undergoing percutaneous coronary intervention for stable coronary artery disease. *Circulation* 138: 1290–1300. https://doi.org/10.1161/CIRCULATIONAHA.118.034790
16. Khan MR, Koshy AN, Tanner R, et al. (2024) Real-world comparison of clopidogrel with ticagrelor and prasugrel in patients with chronic coronary disease who underwent atherectomy. *Am J Cardiol* 217: 1–4. https://doi.org/10.1016/j.amjcard.2024.02.006
17. Dehmer GJ, Nichols TC, Bode AP, et al. (1997) Assessment of platelet activation by coronary sinus blood sampling during balloon angioplasty and directional coronary atherectomy. *Am J Cardiol* 80: 871–877. https://doi.org/10.1016/s0002-9149(97)00538-9
18. Bau J, Gutensohn K, Kuck KH, et al. (2000) Flow-cytometric analysis of platelet activation during rotablation. *Z Kardiol* 89: 15–20. https://doi.org/10.1007/s003920050003 (Article in German)
19. Kini A, Kini S, Marmur JD, et al. (1999) Incidence and mechanism of creatine kinase-MB enzyme elevation after coronary intervention with different devices. *Catheter Cardiovasc Interv* 48: 123–129. https://doi.org/10.1002/(sici)1522-726x(199910)48:2<123::aid-ccd1>3.0.co;2-o
20. Sharma SK, Dangas G, Mehran R, et al. (1997) Risk factors for the development of slow flow during rotational coronary atherectomy. *Am J Cardiol* 80: 219–222. https://doi.org/10.1016/s0002-9149(97)00325-1

21. Kini A, Marmur JD, Duvvuri S, et al. (1999) Rotational atherectomy: improved procedural outcome with evolution of technique and equipment. Single-center results of first 1000 patients. *Catheter Cardiovasc Interv* 46: 305–311. https://doi.org/10.1002/(SICI)1522-726X(199903)46:3<305::AID-CCD9>3.0.CO;2-U
22. Chieffo A, Latib A, Caussin C, et al. (2013) A prospective, randomized trial of intravascular-ultrasound guided compared to angiography guided stent implantation in complex coronary lesions: the AVIO trial. *Am Heart J* 165: 65–72. https://doi.org/10.1016/j.ahj.2012.09.017
23. Kirtane AJ, Doshi D, Leon MB, et al. (2016) Treatment of higher-risk patients with an indication for revascularization: evolution within the field of contemporary percutaneous coronary intervention. *Circulation* 134: 422–431. https://doi.org/10.1161/CIRCULATIONAHA.116.022061
24. Giustino G, Chieffo A, Palmerini T, et al. (2016) Efficacy and safety of dual antiplatelet therapy after complex PCI. *J Am Coll Cardiol* 68: 1851–1864. https://doi.org/10.1016/j.jacc.2016.07.760
25. Yeh RW, Kereiakes DJ, Steg PG, et al. (2017) Lesion complexity and outcomes of extended dual antiplatelet therapy after percutaneous coronary intervention. *J Am Coll Cardiol* 70: 2213–2223. https://doi.org/10.1016/j.jacc.2017.09.011
26. Généreux P, Giustino G, Redfors B, et al. (2018) Impact of percutaneous coronary intervention extent, complexity and platelet reactivity on outcomes after drug-eluting stent implantation. *Int J Cardiol* 268: 61–67. https://doi.org/10.1016/j.ijcard.2018.03.103
27. Chandrasekhar J, Baber U, Sartori S, et al. (2018) Associations between complex PCI and prasugrel or clopidogrel use in patients with acute coronary syndrome who undergo PCI: from the PROMETHEUS study. *Can J Cardiol* 34: 319–329. https://doi.org/10.1016/j.cjca.2017.12.023
28. Lipiecki J, Brunel P, Morice MC, et al. (2018) Biolimus A9 polymer-free coated stents in high bleeding risk patients undergoing complex PCI: evidence from the LEADERS FREE randomised clinical trial. *EuroIntervention* 14: e418–e425. https://doi.org/10.4244/EIJ-D-18-00293
29. Costa F, Van Klaveren D, Feres F, et al. (2019) Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. *J Am Coll Cardiol* 73: 741–754. https://doi.org/10.1016/j.jacc.2018.11.048
30. Choi KH, Song YB, Lee JM, et al. (2019) Impact of intravascular ultrasound-guided percutaneous coronary intervention on long-term clinical outcomes in patients undergoing complex procedures. *JACC Cardiovasc Interv* 12: 607–620. https://doi.org/10.1016/j.jcin.2019.01.227
31. Henson KD, Popma JJ, Leon MB, et al. (1993) Comparison of results of rotational coronary atherectomy in three age groups (< 70, 70 to 79 and > or = 80 years). *Am J Cardiol* 71: 862–864. https://doi.org/10.1016/0002-9149(93)90839-5
32. Gravina Taddei CF, Weintraub WS, King 3rd S, et al. (1999) Early and intermediate outcomes after rotational atherectomy in octogenarian patients. *Am J Geriatr Cardiol* 8: 169–172.
33. Sandhu K, Nadar SK (2015) Percutaneous coronary intervention in the elderly. *Int J Cardiol* 199: 342–355. https://doi.org/10.1016/j.ijcard.2015.05.188
34. Shanmugam VB, Harper R, Meredith I, et al. (2015) An overview of PCI in the very elderly. *J Geriatr Cardiol* 12: 174–184. https://doi.org/10.11909/j.issn.1671-5411.2015.02.012
35. Urban P, Gregson J, Owen R, et al. (2021) Assessing the risks of bleeding vs thrombotic events in patients at high bleeding risk after coronary stent implantation: the ARC–high bleeding risk trade-off model. *JAMA Cardiol* 6: 410–419. https://doi.org/10.1001/jamacardio.2020.6814

36. Mohamed MO, Polad J, Hildick-Smith D, et al. (2020) Impact of coronary lesion complexity in percutaneous coronary intervention: one-year outcomes from the large, multicentre e-Ultimaster registry. *EuroIntervention* 16: 603–612. https://doi.org/10.4244/EIJ-D-20-00361
37. Knuuti J, Wijns W, Saraste A, et al. (2020) 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 41: 407–477. https://doi.org/10.1093/eurheartj/ehz425
38. Byrne RA, Rossello X, Coughlan JJ, et al. (2023) 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J* 44: 3720–3826. https://doi.org/10.1093/eurheartj/ehad191
39. Lis P, Rajzer M, Klima Ł (2024) The Significance of coronary artery calcification for percutaneous coronary interventions. *Healthcare* 12: 520. https://doi.org/10.3390/healthcare12050520
40. Baber U, Mehran R, Giustino G, et al. (2016) Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from Paris. *J Am Coll Cardiol* 67: 2224–2234. https://doi.org/10.1016/j.jacc.2016.02.064
41. Raposeiras-Roubín S, Faxén J, Íñiguez-Romo A, et al. (2018) Development and external validation of a post-discharge bleeding risk score in patients with acute coronary syndrome: the BleeMACS score. *Int J Cardiol* 254: 10–15. https://doi.org/10.1016/j.ijcard.2017.10.103
42. Urban P, Mehran R, Colleran R, et al. (2019) Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J* 40: 2632–2653. https://doi.org/10.1093/eurheartj/ehz372
43. Caiazzo G, Di Mario C, Kedhi E, et al. (2023) Current management of highly calcified coronary lesions: an overview of the current status. *J Clin Med* 12: 4844. https://doi.org/10.3390/jcm12144844
44. Koo BK, Kang J, Park KW, et al. (2021) Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. *Lancet* 397: 2487–2496. https://doi.org/10.1016/S0140-6736(21)01063-1
45. Capodanno D, Angiolillo DJ (2023) Long-term P2Y12 inhibitor or aspirin as single antiplatelet therapy in patients with previous percutaneous coronary intervention. *Circulation* 147: 118–121. https://doi.org/10.1161/CIRCULATIONAHA.122.063004
46. Andò G, De Santis GA, Greco A, et al. (2022) P2Y12 inhibitor or aspirin following dual antiplatelet therapy after percutaneous coronary intervention: a network meta-analysis. *JACC Cardiovasc Interv* 15: 2239–2249. https://doi.org/10.1016/j.jcin.2022.08.009
47. Andò G, Lombardo L, Alagna G, et al. (2024) Monotherapy with P2Y12-inhibitors after dual antiplatelet therapy: filling gaps in evidence. *Int J Cardiol* 401: 131893. https://doi.org/10.1016/j.ijcard.2024.131893
48. Alagna G, Mazzone P, Contarini M, et al. (2023) Dual antiplatelet therapy with parenteral P2Y12 inhibitors: rationale, evidence, and future directions. *J Cardiovasc Dev Dis* 10: 163. https://doi.org/10.3390/jcdd10040163
49. Stone GW, Witzenbichler B, Weisz G, et al. (2013) Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet* 382: 614–623. https://doi.org/10.1016/S0140-6736(13)61170-8

50. Guedeney P, Claessen BE, Mehran R, et al. (2020) Coronary calcification and long-term outcomes according to drug-eluting stent generation. *JACC Cardiovasc Interv* 13: 1417–1428. https://doi.org/10.1016/j.jcin.2020.03.053
51. Sangiorgi G, Rumberger JA, Severson A, et al. (1998) Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. *J Am Coll Cardiol* 31: 126–133. https://doi.org/10.1016/s0735-1097(97)00443-9
52. Criqui MH, Denenberg JO, Ix JH, et al. (2014) Calcium density of coronary artery plaque and risk of incident cardiovascular events. *JAMA* 311: 271–278. https://doi.org/10.1001/jama.2013.282535
53. Généreux P, Madhavan MV, Mintz GS, et al. (2014) Relation between coronary calcium and major bleeding after percutaneous coronary intervention in acute coronary syndromes (from the acute catheterization and urgent intervention triage strategy and harmonizing outcomes with revascularization and stents in acute myocardial infarction trials). *Am J Cardiol* 113: 930–935. https://doi.org/10.1016/j.amjcard.2013.11.053
54. Généreux P, Redfors B, Witzenbichler B, et al. (2017) Two-year outcomes after percutaneous coronary intervention of calcified lesions with drug-eluting stents. *Int J Cardiol* 231: 61–67. https://doi.org/10.1016/j.ijcard.2016.12.150
55. Giustino G, Mastoris I, Baber U, et al. (2016) Correlates and impact of coronary artery calcifications in women undergoing percutaneous coronary intervention with drug-eluting stents: from the Women in Innovation and Drug-Eluting Stents (WIN-DES) collaboration. *JACC Cardiovasc Interv* 9: 1890–1901. https://doi.org/10.1016/j.jcin.2016.06.022
56. Lee MS, Yang T, Lasala J, et al. (2016) Impact of coronary artery calcification in percutaneous coronary intervention with paclitaxel-eluting stents: two-year clinical outcomes of paclitaxel-eluting stents in patients from the ARRIVE program. *Catheter Cardiovasc Interv* 88: 891–897. https://doi.org/10.1002/ccd.26395
57. Huisman J, van der Heijden LC, Kok MM, et al. (2016) Impact of severe lesion calcification on clinical outcome of patients with stable angina, treated with newer generation permanent polymer-coated drug-eluting stents: a patient-level pooled analysis from TWENTE and DUTCH PEERS (TWENTE II). *Am Heart J* 175: 121–129. https://doi.org/10.1016/j.ahj.2016.02.012
58. Bourantas CV, Zhang YJ, Garg S, et al. (2014) Prognostic implications of coronary calcification in patients with obstructive coronary artery disease treated by percutaneous coronary intervention: a patient-level pooled analysis of 7 contemporary stent trials. *Heart* 100: 1158–1164. https://doi.org/10.1136/heartjnl-2013-305180
59. Silvain J, Lattuca B, Beygui F, et al. (2020) Ticagrelor versus clopidogrel in elective percutaneous coronary intervention (ALPHEUS): a randomised, open-label, phase 3b trial. *Lancet* 396: 1737–1744. https://doi.org/10.1016/S0140-6736(20)32236-4
60. Yeh RW, Secemsky EA, Kereiakes DJ, et al. (2016) Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA* 315: 1735–1749. https://doi.org/10.1001/jama.2016.3775
61. Wallentin L, Becker RC, Budaj A, et al. (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 361: 1045–1057. https://doi.org/10.1056/NEJMoa0904327

62. Mehilli J, Baquet M, Hochholzer W, et al. (2020) Randomized comparison of intensified and standard P2Y12-receptor-inhibition before elective percutaneous coronary intervention: the SASSICAIA trial. *Circ Cardiovasc Interv* 13: e008649. https://doi.org/10.1161/CIRCINTERVENTIONS.119.008649
63. Harrington RA, Stone GW, McNulty S, et al. (2009) Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med* 361: 2318–2329. https://doi.org/10.1056/NEJMoa0908628
64. Lattuca B, Mazeau C, Cayla G, et al. (2024) Ticagrelor vs clopidogrel for complex percutaneous coronary intervention in chronic coronary syndrome. *JACC Cardiovasc Interv* 17: 359–370. https://doi.org/10.1016/j.jcin.2023.12.011
65. Mehran R, Rao SV, Bhatt DL, et al. (2011) Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 123: 2736–2747. https://doi.org/10.1161/CIRCULATIONAHA.110.009449
66. Dangas G, Baber U, Sharma S, et al. (2020) Ticagrelor with or without aspirin after complex PCI. *J Am Coll Cardiol* 75: 2414–2424. https://doi.org/10.1016/j.jacc.2020.03.011
67. Lhermusier T, Motreff P, Bataille V, et al. (2023) Ticagrelor in rotational atherectomy to reduce TROPonin enhancement: the TIRATROP study, a randomized controlled trial. *J Clin Med* 12: 1445. https://doi.org/10.3390/jcm12041445
68. Amsterdam EA, Wenger NK, Brindis RG, et al. (2014) 2014 AHA/ACC guideline for the management of patients with Non-ST-Elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 64: e139–e228. https://doi.org/10.1016/j.jacc.2014.09.017
69. Ellis SG, Popma JJ, Buchbinder M, et al. (1994) Relation of clinical presentation, stenosis morphology, and operator technique to the procedural results of rotational atherectomy and rotational atherectomy-facilitated angioplasty. *Circulation* 89: 882–892. https://doi.org/10.1161/01.cir.89.2.882
70. Reisman M, Shuman BJ, Harms V (1998) Analysis of heat generation during rotational atherectomy using different operational techniques. *Cathet Cardiovasc Diagn* 44: 453–455. https://doi.org/10.1002/(sici)1097-0304(199808)44:4<453::aid-ccd21>3.0.co;2-i
71. Nienhuis MB, Ottervanger JP, Bilo HJG, et al. (2008) Prognostic value of troponin after elective percutaneous coronary intervention: a meta-analysis. *Catheter Cardiovasc Interv* 71: 318–324. https://doi.org/10.1002/ccd.21345
72. Tricoci P, Leonardi S, White J, et al. (2013) Cardiac troponin after percutaneous coronary intervention and 1-year mortality in non-ST-segment elevation acute coronary syndrome using systematic evaluation of biomarker trends. *J Am Coll Cardiol* 62: 242–251. https://doi.org/10.1016/j.jacc.2013.04.043
73. Safarian H, Alidoosti M, Shafiee A, et al. (2014) The SYNTAX score can predict major adverse cardiac events following percutaneous coronary intervention. *Heart Views* 15: 99–105. https://doi.org/10.4103/1995-705X.151081
74. Lawton JS, Tamis-Holland JE, Bangalore S, et al. (2022) 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. *Circulation* 145: e4–e17. https://doi.org/10.1161/CIR.0000000000001039

75. Leonardi S, Gragnano F, Carrara G, et al. (2021) Prognostic implications of declining hemoglobin content in patients hospitalized with acute coronary syndromes. *J Am Coll Cardiol* 77: 375–388. https://doi.org/10.1016/j.jacc.2020.11.046
76. Valgimigli M, Smits PC, Frigoli E, et al. (2022) Duration of antiplatelet therapy after complex percutaneous coronary intervention in patients at high bleeding risk: a MASTER DAPT trial sub-analysis. *Eur Heart J* 43: 3100–3114. https://doi.org/10.1093/eurheartj/ehac284
77. Gragnano F, Mehran R, Branca M, et al. (2023) P2Y12 inhibitor monotherapy or dual antiplatelet therapy after complex percutaneous coronary interventions. *J Am Coll Cardiol* 81: 537–552. https://doi.org/10.1016/j.jacc.2022.11.041
78. Valgimigli M, Gragnano F, Branca M, et al. (2021) P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials. *BMJ* 373: n1332. https://doi.org/10.1136/bmj.n1332
79. Collet JP, Thiele H, Barbato E, et al. (2021) 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 42: 1289–1367. https://doi.org/10.1093/eurheartj/ehaa575
80. Valgimigli M, Frigoli E, Heg D, et al. (2021) Dual antiplatelet therapy after PCI in patients at high bleeding risk. *N Engl J Med* 385: 1643–1655. https://doi.org/10.1056/NEJMoa2108749
81. Serruys PW, Takahashi K, Chichareon P, et al. (2019) Impact of long-term ticagrelor monotherapy following 1-month dual antiplatelet therapy in patients who underwent complex percutaneous coronary intervention: insights from the Global Leaders trial. *Eur Heart J* 40: 2595–2604. https://doi.org/10.1093/eurheartj/ehz453
82. Yamamoto K, Watanabe H, Morimoto T, et al. (2021) Very Short dual antiplatelet therapy after drug-eluting stent implantation in patients who underwent complex percutaneous coronary intervention: insight from the STOPDAPT-2 trial. *Circ Cardiovasc Interv* 14: e010384. https://doi.org/10.1161/CIRCINTERVENTIONS.120.010384
83. Lee SJ, Lee YJ, Kim BK, et al. (2021) Ticagrelor monotherapy versus ticagrelor with aspirin in acute coronary syndrome patients with a high risk of ischemic events. *Circ Cardiovasc Interv* 14: e010812. https://doi.org/10.1161/CIRCINTERVENTIONS.121.010812
84. Roh JW, Hahn JY, Oh JH, et al. (2021) P2Y12 inhibitor monotherapy in complex percutaneous coronary intervention: a post-hoc analysis of SMART-CHOICE randomized clinical trial. *Cardiol J* 28: 855–863. https://doi.org/10.5603/CJ.a2021.0101
85. Franzone A, McFadden E, Leonardi S, et al. (2019) Ticagrelor alone versus dual antiplatelet therapy from 1 month after drug-eluting coronary stenting. *J Am Coll Cardiol* 74: 2223–2234. https://doi.org/10.1016/j.jacc.2019.08.1038
86. Vranckx P, Valgimigli M, Jüni P, et al. (2018) Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet* 392: 940–949. https://doi.org/10.1016/S0140-6736(18)31858-0
87. Watanabe H, Domei T, Morimoto T, et al. (2019) Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA* 321: 2414–2427. https://doi.org/10.1001/jama.2019.8145

88. Hahn JY, Song YB, Oh JH, et al. (2019) Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA* 321: 2428–2437. https://doi.org/10.1001/jama.2019.8146
89. Mehran R, Baber U, Sharma SK, et al. (2019) Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med* 381: 2032–2042. https://doi.org/10.1056/NEJMoa1908419
90. Kim BK, Hong SJ, Cho YH, et al. (2020) Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA* 323: 2407–2416. https://doi.org/10.1001/jama.2020.7580
91. Natsuaki M, Watanabe H, Morimoto T, et al. (2024) An aspirin-free versus dual antiplatelet strategy for coronary stenting: STOPDAPT-3 randomized trial. *Circulation* 149: 585–600. https://doi.org/10.1161/CIRCULATIONAHA.123.066720
92. Nakamura M, Kimura K, Kimura T, et al. (2020) JCS 2020 guideline focused update on antithrombotic therapy in patients with coronary artery disease. *Circ J* 84: 831–865. https://doi.org/10.1253/circj.CJ-19-1109
93. Ueki Y, Karagiannis A, Zanchin C, et al. (2019) Validation of high-risk features for stent-related ischemic events as endorsed by the 2017 DAPT guidelines. *JACC Cardiovasc Interv* 12: 820–830. https://doi.org/10.1016/j.jcin.2018.12.005
94. Yamamoto K, Shiomi H, Morimoto T, et al. (2021) Ischemic and bleeding risk after complex percutaneous coronary intervention in patients with or without high bleeding risk. *Catheter Cardiovasc Interv* 97: E758–E770. https://doi.org/10.1002/ccd.29335
95. Yamamoto K, Natsuaki M, Watanabe H, et al. (2024) An aspirin-free strategy for immediate treatment following complex percutaneous coronary intervention. *JACC Cardiovasc Interv* 17: 1119–1130. https://doi.org/10.1016/j.jcin.2024.03.017
96. Valgimigli M, Gragnano F, Branca M, et al. (2024) Ticagrelor or clopidogrel monotherapy vs dual antiplatelet therapy after percutaneous coronary intervention: a systematic review and patient-level meta-analysis. *JAMA Cardiol* 9: 437–448. https://doi.org/10.1001/jamacardio.2024.0133
97. Watanabe H, Morimoto T, Natsuaki M, et al. (2022) Comparison of clopidogrel monotherapy after 1 to 2 months of dual antiplatelet therapy with 12 months of dual antiplatelet therapy in patients with acute coronary syndrome: the STOPDAPT-2 ACS randomized clinical trial. *JAMA Cardiol* 7: 407–417. https://doi.org/10.1001/jamacardio.2021.5244
98. Capodanno D, Baber U, Bhatt DL, et al. (2022) P2Y12 inhibitor monotherapy in patients undergoing percutaneous coronary intervention. *Nat Rev Cardiol* 19: 829–844. https://doi.org/10.1038/s41569-022-00725-6
99. Capodanno D, Mehran R, Krucoff MW, et al. (2023) Defining strategies of modulation of antiplatelet therapy in patients with coronary artery disease: a consensus document from the academic research consortium. *Circulation* 147: 1933–1944. https://doi.org/10.1161/CIRCULATIONAHA.123.064473
100. Vrints C, Andreotti F, Koskinas KC, et al. (2024) 2024 ESC guidelines for the management of chronic coronary syndromes. *Eur Heart J* 45: 3415–3537. https://doi.org/10.1093/eurheartj/ehae177

101. Cuisset T, Deharo P, Quilici J, et al. (2017) Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. *Eur Heart J* 38: 3070–3078. https://doi.org/10.1093/eurheartj/ehx175
102. Notarangelo FM, Maglietta G, Bevilacqua P, et al. (2018) Pharmacogenomic approach to selecting antiplatelet therapy in patients with acute coronary syndromes: the PHARMCLO trial. *J Am Coll Cardiol* 71: 1869–1877. https://doi.org/10.1016/j.jacc.2018.02.029
103. Kim CJ, Park MW, Kim MC, et al. (2021) Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): an investigator-initiated, open-label, multicentre, non-inferiority, randomised trial. *Lancet* 398: 1305–1316. https://doi.org/10.1016/S0140-6736(21)01445-8
104. Sibbing D, Aradi D, Jacobshagen C, et al. (2017) A randomised trial on platelet function-guided de-escalation of antiplatelet treatment in ACS patients undergoing PCI. Rationale and design of the Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes (TROPICAL-ACS) trial. *Thromb Haemost* 117: 188–195. https://doi.org/10.1160/TH16-07-0557
105. Claassens DMF, Vos GJA, Bergmeijer TO, et al. (2019) A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. *N Engl J Med* 381: 1621–1631. https://doi.org/10.1056/NEJMoa1907096
106. Lee JM, Cho DK, Hahn JY, et al. (2016) Safety of 6-month duration of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndromes: rationale and design of the Smart Angioplasty Research Team-safety of 6-month duration of Dual Antiplatelet Therapy after percutaneous coronary intervention in patients with acute coronary syndromes (SMART-DATE) prospective multicenter randomized trial. *Am Heart J* 182: 1–8. https://doi.org/10.1016/j.ahj.2016.07.022
107. Camaro C, Damen SAJ, Brouwer MA, et al. (2016) Randomized evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with the COMBO dual therapy stent: rationale and design of the REDUCE trial. *Am Heart J* 178: 37–44. https://doi.org/10.1016/j.ahj.2016.04.016
108. Kedhi E, Fabris E, van der Ent M, et al. (2018) Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (DAPT-STEMI): randomised, multicentre, non-inferiority trial. *BMJ* 363: k3793. https://doi.org/10.1136/bmj.k3793
109. Hong SJ, Lee SJ, Suh Y, et al. (2024) Stopping aspirin within 1 month after stenting for ticagrelor monotherapy in acute coronary syndrome: the T-PASS randomized noninferiority trial. *Circulation* 149: 562–573. https://doi.org/10.1161/CIRCULATIONAHA.123.066943
110. Ge Z, Kan J, Gao X, et al. (2024) Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes (ULTIMATE-DAPT): a randomised, placebo-controlled, double-blind clinical trial. *Lancet* 403: 1866–1878. https://doi.org/10.1016/S0140-6736(24)00473-2
111. Gragnano F, Cao D, Pirondini L, et al. (2023) P2Y12 inhibitor or aspirin monotherapy for secondary prevention of coronary events. *J Am Coll Cardiol* 82: 89–105. https://doi.org/10.1016/j.jacc.2023.04.051

112. Chiarito M, Sanz-Sánchez J, Cannata F, et al. (2020) Monotherapy with a P2Y12 inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. *Lancet* 395: 1487–1495. https://doi.org/10.1016/S0140-6736(20)30315-9
113. Bhatt DL (2023) Optimal antiplatelet therapy revisited: When is a single better than a double?. *J Am Coll Cardiol* 81: 553–556. https://doi.org/10.1016/j.jacc.2022.11.040

AIMS Press