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STATE OF THE ART REVIEW
Interventional cardiology

Aspirin or $P2Y_{12}$ inhibitor monotherapy in atherosclerotic cardiovascular disease?

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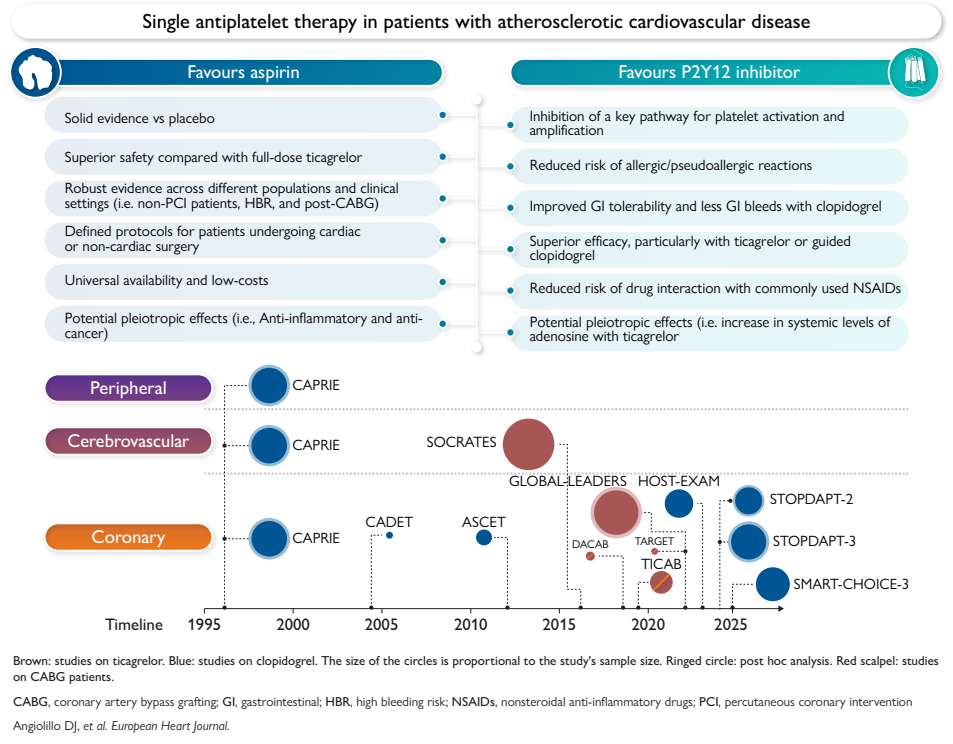
Graphical Abstract



Brown: studies on ticagrelor. Blue: studies on clopidogrel. The size of the circles is proportional to the study's sample size. Ringed circle: post hoc analysis. Red scalpel: studies on CABG patients.

CABG, coronary artery bypass grafting; GI, gastrointestinal; HBR, high bleeding risk; NSAIDs, nonsteroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention

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Upper section: factors favouring aspirin vs $P2Y_{12}$ inhibitor monotherapy in patients with atherosclerotic cardiovascular disease. Lower section: time course of pivotal studies on aspirin vs $P2Y_{12}$ inhibitor monotherapy in patients with atherosclerotic disease.

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Abstract

Antiplatelet therapy is the cornerstone of treatment in patients with established atherosclerotic disease. The use of a single antiplatelet agent is commonly recommended for the long-term management of these patients. Although aspirin has represented the mainstay of antiplatelet therapy for decades, emerging evidence suggests that $P2Y_{12}$ inhibitors may be more than just a viable alternative to aspirin and may be preferred over aspirin. This review examines the current evidence comparing the efficacy and safety of aspirin vs $P2Y_{12}$ inhibitors in reducing cardiovascular events in patients with atherosclerotic disease. Special attention is given to the practical challenges and considerations surrounding the use of aspirin vs $P2Y_{12}$ inhibitor monotherapy, including interindividual variability in drug response, side effects, costs, and real-world implementation. By evaluating the strengths and limitations of these treatment options, this article aims to guide clinicians in optimizing the selection of single antiplatelet strategies for long-term secondary prevention in patients with atherosclerotic disease.

Keywords $P2Y_{12}$ inhibitor • Clopidogrel • Aspirin • Cardiovascular • Ticagrelor • Prasugrel

Antiplatelet therapy in atherosclerotic disease: rationale and historical overview

Atherosclerosis is a systemic disease characterized by the progressive accumulation of fibrofatty plaques within the arterial walls.[1] The rupture or erosion of atherosclerotic plaques triggers superimposed thrombosis—a process known as atherothrombosis— which causes acute obstruction or occlusion of the artery, representing the primary pathological mechanism underlying acute cardiovascular (CV) events.[2,3] Given the central role of platelets in atherosclerotic thrombotic complications, antiplatelet therapy plays a key role in the treatment and prevention of ischaemic events in patients with atherosclerotic CV disease (ASCVD).[4,5]

The first randomized controlled trial (RCT) evaluating the effects of antiplatelet therapy in patients with ASCVD was published in 1974, few years after the discovery that aspirin exerts antiplatelet effects through the inhibition of the cyclooxygenase-1 (COX-1) enzyme and hence preventing thromboxane A_2 (TXA_2) synthesis.[6,7] In this RCT, 1239 patients with recent (mean of 10 weeks) myocardial infarction (MI) were treated with single daily dose of aspirin 300 mg or placebo.[8] Although the results were statistically inconclusive, aspirin use was associated with a relative reduction in the risk of mortality of 12% at 6 months and 25% at 12 months compared with placebo, calling for additional RCTs on the use of aspirin in this setting.[8] In 1988, a few years after demonstrating that low doses (<100 mg daily) of aspirin are sufficient to achieve full antiplatelet effects, the large *Second International Study of Infarct Survival* (ISIS-2) randomized 17 187 patients with acute MI to receive either 1-h intravenous streptokinase, oral aspirin (160 mg/day), both treatments combined, or placebo.[9,10] The study demonstrated that aspirin alone reduced vascular mortality at 35 days by 20% compared with placebo and that its effects were additive to streptokinase, leading in combination to a 39% relative risk reduction in vascular mortality at 35 days.[10] Since then, a vast body of scientific evidence has established the efficacy of low-dose aspirin in the management of patients with a CV event, particularly coronary artery disease (CAD) and cerebrovascular disease, and to a lesser extent, peripheral artery disease (PAD).[11–15] The profound impact of low-dose aspirin in ASCVD raised doubts about the feasibility of conducting RCTs without its inclusion as background therapy. Consequently, no study has since tested another antiplatelet therapy against placebo.[16] Moreover, its acceptable safety profile, widespread availability, and low cost have reinforced its role as the dominant antiplatelet agent worldwide.[17]

Oral $P2Y_{12}$ inhibitors, including ticlopidine, clopidogrel, prasugrel, and ticagrelor, are a class of antiplatelet agents that block the $P2Y_{12}$ receptor, a key mediator of platelet activation and amplification of the aggregation response.[18] Ticlopidine has been abandoned for clinical use due to its association with rare but serious adverse effects, including neutropenia, thrombotic thrombocytopenic purpura, and aplastic anaemia. Therefore, it will not be discussed in this article. $P2Y_{12}$ inhibitors are commonly used in adjunct to aspirin, also known as dual antiplatelet therapy (DAPT). Due to the synergistic inhibitory effects achieved by blocking two distinct pathways of platelet activation, DAPT has proven highly effective in reducing CV events following acute coronary syndrome (ACS), percutaneous coronary interventions (PCIs), or stroke.[4,19–22] The *Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events* (CAPRIE) double-blind trial compared aspirin 325 mg with clopidogrel 75 mg monotherapy in 19 185 patients with ASCVD manifested as either recent MI (<35 days), recent ischaemic stroke, or symptomatic PAD.[23] Compared with aspirin, clopidogrel was associated with a modest, albeit significant ($P = .04$), 8.7% relative risk reduction in major adverse cardiovascular events (MACEs, composite of vascular death, MI, and ischaemic stroke) over 1.9 years mean follow-up period, with no differences in the risk of bleeding but significantly less hospitalization for gastrointestinal (GI) bleeding.[23,24] A subgroup analysis suggested that clopidogrel benefits were primarily observed in patients with PAD, rather than in those with a history of MI or stroke.[23] In light of these findings, aspirin continued to be the single antiplatelet therapy (SAPT) of choice in patients with ASCVD, with the only exception of PAD, for over 40 years.

Recently, there has been emerging evidence suggesting that $P2Y_{12}$ inhibitors may be more than just as a viable alternative to aspirin and may be preferred over aspirin. This might be attributed to the different antiplatelet efficacy achieved by inhibiting the $P2Y_{12}$ signalling pathway.[25,26] This review examines the current evidence comparing the efficacy and safety of aspirin vs $P2Y_{12}$ inhibitor monotherapy in patients with ASCVD. Special attention is given to the practical challenges and considerations surrounding their use, including interindividual variability in drug response, side effects, costs, and real-world implementation. By evaluating the strengths and limitations of these treatment options, this article aims to guide clinicians in optimizing the selection of single antiplatelet strategies for long-term secondary prevention in patients with established atherosclerotic disease.

Antiplatelet therapy for long-term secondary prevention: unmet needs

Patients with ASCVD remain at risk for ischaemic recurrences. Up to one in six patients will experience another event within 6 years despite

standard secondary prevention strategies, contributing to increased mortality and substantial healthcare costs.[27] Thus, defining the optimal antiplatelet regimen—on top of other established treatments (i.e. statins)—for the long-term prevention of ischaemic recurrences in patients with ASCVD is of critical importance. Intensifying antithrombotic therapies have been extensively tested to reduce the residual thrombotic risk associated with aspirin monotherapy. These include the prolongation of DAPT regimens after ACS or PCI, adjunctive use of antiplatelet therapies blocking alternative targets such as the protease-activated receptor-1 (PAR-1) receptor (i.e. vorapaxar), or the addition of low-dose anticoagulation (e.g. rivaroxaban at vascular dose of 2.5 mg twice daily) to antiplatelet therapy, also known as dual pathway inhibition (DPI), and the use of alternative antithrombotic therapies such as vitamin K antagonists.[28–32] However, these strategies have all resulted in increased bleeding, at least partially offsetting the achieved ischaemic benefit, leading to an uncertain net clinical benefit.[33,34] These observations emphasize the importance of balancing risks and benefits when choosing a long-term antithrombotic regimen and the inherent risks of combining multiple agents.

Recent RCTs comparing a $P2Y_{12}$ inhibitor to aspirin have sparked debate on whether they should replace aspirin as the standard long-term SAPT.[25,35] The growing emphasis on de-escalating antiplatelet therapy from DAPT to SAPT a few months after an acute CV event or PCI has intensified the debate on whether aspirin or the $P2Y_{12}$ inhibitor should be preferred after DAPT discontinuation.[36,37] The evidence supporting de-escalation to $P2Y_{12}$ inhibitor monotherapy, in particular ticagrelor, has further raised the clinical dilemma of how to manage these patients in the long term given that most data on this strategy is limited to within 1 year after PCI.[36–39] However, it may also be argued that studies on aspirin monotherapy have been limited to just a few years, which may question whether this is the best suited treatment for lifelong management in patients with atherosclerotic disease.[39] Moreover, it remains to be determined whether antiplatelet therapy can be safely discontinued at some point during long-term management. A careful understanding of the pharmacology of antiplatelet agents and the available evidence from RCTs and meta-analyses may allow to better define which is the ideal drug to implement in clinical practice on a case-by-case basis.

Pharmacologic considerations

Aspirin at a low-dose regimen selectively and irreversibly acetylates platelet COX-1, blocking the conversion of arachidonic acid to TXA_2, an important mediator of platelet activation and aggregation (*Figure 1*).[17] As platelets lack nuclei, COX-1 inhibition persists for their lifespan (7–10 days), and low daily doses (75–100 mg daily) are sufficient to inhibit the newly synthesized pool of circulating platelets, maintaining sustained antiplatelet effects. The antiplatelet effect is mostly achieved after GI absorption in the portal circulation, allowing selective targeting of platelet COX-1 while sparing COX-2 activity in other tissues, limiting GI and vascular side effects.[9,17]

$P2Y_{12}$ receptor plays a key role in platelet activation and amplification (*Figure 1*). There are two classes of clinically approved oral $P2Y_{12}$ inhibitors: thienopyridine and cyclopentyltriazolopyrimidine (CPTP). These agents have different pharmacokinetic (PK) and pharmacodynamic (PD) profiles, which culminate in blockade of the $P2Y_{12}$ receptor.[5,26] Thienopyridines (i.e. ticlopidine, clopidogrel, and prasugrel) are prodrugs that require hepatic metabolism to generate an active metabolite and irreversibly block the $P2Y_{12}$ receptor, while CPTP (i.e. ticagrelor) is direct acting (no metabolism required) and reversibly blocks the $P2Y_{12}$ receptor[40,41] (*Figure 1*). The first approved $P2Y_{12}$ inhibitor was the thienopyridine ticlopidine, which was soon replaced by the second-generation agent clopidogrel due to its superior safety and tolerability profile.[42] Although clopidogrel remains the most commonly used $P2Y_{12}$ inhibitor worldwide, its efficacy may be limited by interindividual variability in its PK/PD effects.[41,43] Clopidogrel is a prodrug that requires a two-step conversion in the liver by the cytochrome P450 (CYP) system.[41] The gene encoding for the CYP2C19 enzyme, which is involved in both metabolic steps, is highly polymorphic. Subjects who are carriers of loss-of-function (LoF) alleles for this gene have reduced active metabolite formation and display more often high platelet reactivity (HPR).[41,44,45] In addition to genetic factors, clopidogrel response is also modulated by clinical factors, including age, body mass index, kidney function, and diabetes mellitus.[46] Notably, up to 30% of clopidogrel-treated patients may display HPR, especially if assessed early after treatment initiation, a condition characterized by increased risk of thrombotic complications.[43,47,48] The third-generation thienopyridine prasugrel has a more favourable metabolism compared with clopidogrel yielding higher concentration of active metabolite formation and more potent platelet inhibition.[40] The CPTP ticagrelor is not a prodrug and, similar to prasugrel, provides more potent and consistent $P2Y_{12}$ receptor inhibition compared with clopidogrel.[40] Moreover, ticagrelor inhibits the adenosine transporter Type 1 equilibrative nucleoside transporter (ENT1), which provides protection for adenosine from intracellular metabolism, thus potentially increasing its systemic concentration and biological activity.[49] Increased circulating levels of adenosine associated with ticagrelor have been suggested to contribute to its overall benefits (e.g. vasodilatation, reduce ischaemic/reperfusion injury, and modulate inflammation) as well as its side effects (e.g. dyspnoea, reduce glomerular filtration, and electrical conduction disturbances).[49] However, in a randomized cross-over trial, ticagrelor was not associated with increased circulating adenosine levels.[50] Additionally, ticagrelor-induced dyspnoea has been linked to higher ticagrelor plasma concentrations and greater platelet inhibition, rather than elevated adenosine levels, suggesting that a direct $P2Y_{12}$ receptor–mediated effect on the central nervous system may underlie this adverse event.[51] The PD properties of prasugrel and ticagrelor lead to greater efficacy compared with clopidogrel in ACS patients, but at the expense of an increased risk of bleeding.[52,53]

Rationale for using a $P2Y_{12}$ inhibitor in lieu of aspirin

The safety and efficacy of aspirin vs placebo were established in earlier trials conducted under clinical conditions and treatment protocols that differ significantly from current practice. As such, it is reasonable to question whether those findings would hold true today and to suggest that they warrant re-evaluation in a contemporary setting.

The central role of platelet $P2Y_{12}$ receptor signalling in platelet activation and amplification suggests that the antithrombotic effects of $P2Y_{12}$ blockade may be superior to that achieved by aspirin through the inhibition of TXA_2-induced platelet activation.[26,54–56] These considerations are especially evident in patients using the newer generation $P2Y_{12}$ inhibitors (i.e. prasugrel or ticagrelor), which are also characterized by more predictable effects than clopidogrel, supporting the rationale for considering these agents to better tackle the residual thrombotic risk in patients with ASCVD.[55,57]

Factors favouring $P2Y_{12}$ inhibitor over aspirin

Evidence from early trials comparing aspirin and clopidogrel, along with aspirin's classification as a non-steroidal anti-inflammatory drug

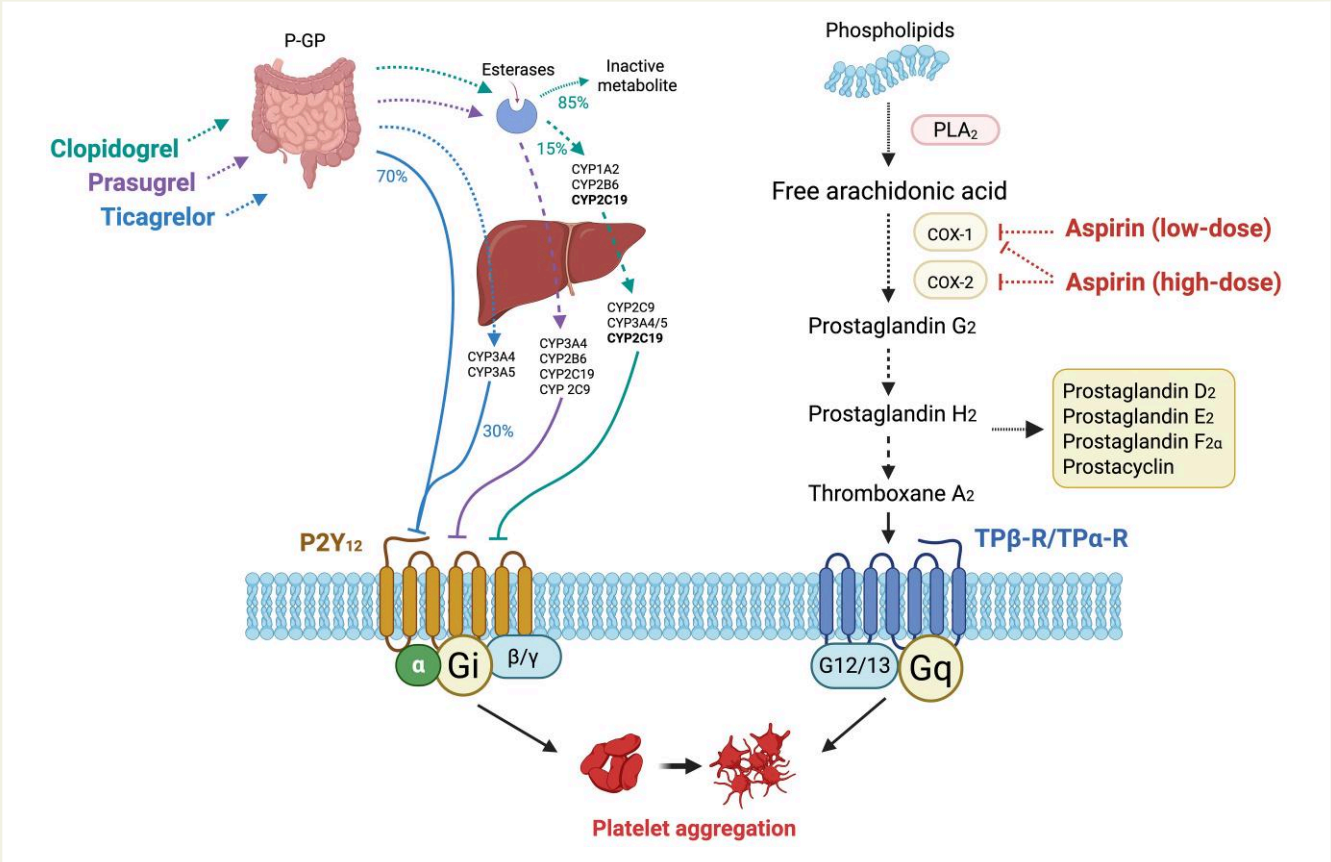

Figure 1 Mechanism of action and pharmacology of oral $P2Y_{12}$ inhibitors and aspirin. The three oral $P2Y_{12}$ inhibitors—clopidogrel, prasugrel, and ticagrelor—are absorbed in the intestine via the P-glycoprotein efflux transporter. Clopidogrel, a prodrug, undergoes extensive first-pass metabolism: ~85% is inactivated by esterases in the blood and liver, while only about 15% is converted to its active metabolite through a two-step oxidative process mediated by hepatic cytochrome P450 enzymes. CYP2C19 is involved in both steps, playing a key role in clopidogrel active metabolite formation. In contrast, prasugrel's activation also involves esterases, but it is more efficiently converted to its active form through a single cytochrome P450-dependent step. Ticagrelor differs mechanistically in that it is not a prodrug; it directly and reversibly inhibits the $P2Y_{12}$ receptor via allosteric binding. Approximately 20%–30% of its antiplatelet activity is attributed to an active metabolite generated by cytochrome P450 metabolism, which retains similar potency to the parent compound. Aspirin acts by modulating the arachidonic acid pathway. Arachidonic acid, released from membrane phospholipids via phospholipase A2, is metabolized by cyclooxygenase-1 and cyclooxygenase-2 enzymes into prostaglandin G_2 and subsequently into prostaglandin H_2. Low-dose aspirin selectively acetylates cyclooxygenase-1, thereby inhibiting its activity, while higher doses also inhibit cyclooxygenase-2. Prostaglandin H_2 serves as a precursor for various prostanoids, including thromboxane A_2, a potent mediator of platelet activation. Thromboxane A_2 acts via the thromboxane receptor, a member of the G protein–coupled receptor family. Both the $P2Y_{12}$ and thromboxane receptors belong to the Gi subclass of purinergic G protein–coupled receptors, mediating intracellular signalling that promotes platelet aggregation and thrombus formation. P-gp, P-glycoprotein; CYP, cytochrome P450; PLA2, phospholipase A2; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; PGG_2, prostaglandin G_2; PGH_2, prostaglandin H_2; TXA_2, thromboxane A_2; TP, thromboxane receptor; GPCR, G protein–coupled receptor

(NSAID), has contributed to the longstanding notion that aspirin has GI toxicity. In fact, NSAIDs at anti-inflammatory doses are associated with GI toxicity due to COX-1 and COX-2 inhibition in the GI mucosa, which disrupts the protective role of prostanoids.[17] In the CAPRIE trial, the risk of GI bleeding was significantly higher with aspirin than with clopidogrel (.72% vs .52%), though the absolute risk remained low.[23] It is important to note that aspirin was used at a higher dose (325 mg) than currently recommended (75–100 mg), and it is well-established that the risk of GI side effects is dose dependent. However, low-dose aspirin has minimal impact on COX-1 and COX-2 activity in the GI mucosa due to its short half-life and the rapid resynthesis of acetylated COX isozymes in nucleated epithelial cells.[17] Notably, studies using serial capsule endoscopy found no significant difference in bleeding or ulceration in the stomach or small intestine in patients treated with low-dose aspirin vs placebo or clopidogrel monotherapy.[58,59] These observations may challenge the conventional belief that aspirin is more ulcerogenic than clopidogrel. A recent meta-analysis comparing aspirin vs $P2Y_{12}$ inhibitors in patients with ASCVD concluded that aspirin was associated with significant higher rates of GI bleeding (1.56% vs 1.22%), with a number needed to harm of 152.[60] It remains unclear what roleaspirin dose played in GI bleeding in this meta-analysis, considering that the CAPRIE trial was also included. Collectively, evidence from RCTs suggests a modest but significant increase in GI bleeding risk with aspirin compared with clopidogrel monotherapy, the most extensively evaluated $P2Y_{12}$ inhibitor. Since GI bleeding is the most common type of bleeding in patients with ASCVD treated with antiplatelet therapy, these observations may favour the use of $P2Y_{12}$ inhibitors, particularly clopidogrel, over aspirin, especially in those with a history of GI bleed or at increased bleeding risk.[61]

Aspirin-induced GI toxicity affects treatment adherence,[62,63] and poor adherence to aspirin is associated with an increased risk of ischaemic recurrences.[64] Enteric-coated aspirin formulations were developed to minimize GI toxicity by preventing aspirin release in the stomach.[65] However, studies have not demonstrated enteric-coated aspirin formulations to reduce bleeding and ulcers.[66] Moreover, their clinical benefits have been challenged given that enteric coating reduces drug absorption and bioavailability, resulting in delayed onset of action and variable antiplatelet efficacy.[65,67,68] Enteric coating leading to impaired drug bioavailability in addition to poor compliance has been considered as the main contributor to variability in aspirin-induced effects, including 'aspirin resistance'.[67,68] However, carefully conducted PD studies in compliant subjects specifically using COX-1-specific assays to assess aspirin-induced effects have shown that resistance is rare.[68,69] On the other hand, variability in aspirin-induced antiplatelet effects has been shown when assessed by non-COX-1-specific assays, with patients showing heightened levels of platelet reactivity to be at increased ischaemic risk.[70–73] However, these clinical findings have been largely confined to assays not specific to measuring the effects of aspirin on its therapeutic target (i.e. COX-1 enzyme), debating how to best address this laboratory finding.[74] Novel formulations, including a phospholipid–aspirin complex liquid, have been designed to reduce GI toxicity, provide reliable absorption and bioavailability, and prevent drug interactions with food intake.[75,76] However, whether this translates into superior efficacy and safety remains unknown.

Aspirin intolerance or hypersensitivity can be a significant limitation to its use in clinical practice.[77,78] Aspirin intolerance is a Type A drug reaction, characterized by predictable adverse effects related to its pharmacological action. These side effects, including dyspepsia and bleeding, are primarily linked to aspirin-induced GI toxicity.[77] Aspirin intolerance is as frequent as 2%–20% and is more common in East Asians.[77,78] In contrast, aspirin hypersensitivity (AH) is a Type B drug reaction, occurring in predisposed individuals with increased susceptibility. It is unpredictable and not directly related to aspirin's mechanism of action.[77] Aspirin hypersensitivity is estimated to affect 1%–5% of the general population and up to 25% of individuals with asthma. Common manifestations include respiratory and cutaneous symptoms, typically due to pseudo-allergic reactions, though true allergic reactions are rare.[77] For patients with AH or intolerance, P2Y$_{12}$ inhibitors are the most recommended alternatives.

Aspirin has few but potentially significant drug interactions. In particular, the concomitant use of NSAIDs may reduce aspirin's antiplatelet effects, as NSAIDs reversibly bind COX-1 preventing aspirin from binding and leading to a rebound in platelet reactivity once their effect wears off.[79,80] The use of NSAIDs is common and increasing in Western countries.[81] Moreover, although aspirin is often administered with food to minimize GI toxicity, its absorption can be influenced by food intake. This practice may impact aspirin bioavailability and contribute to variability in antiplatelet effects.[82]

Finally, while low-dose aspirin administered once daily has proven effective for most patients, it may be insufficient for patients with accelerated platelet turnover, such as those with diabetes mellitus, essential thrombocythaemia, and following coronary artery bypass grafting (CABG), or individuals with higher body weight. These patients may require multiple daily dosing to achieve sustained TXA$_2$ inhibition.[83–86]

Clinical evidence

Key clinical studies comparing P2Y$_{12}$ inhibitor vs aspirin monotherapy in patients with different manifestations of ASCVD are summarized in *Table 1* and *Graphical Abstract*.

Coronary artery disease

Among patients with CAD, all trials comparing aspirin vs P2Y$_{12}$ inhibitor monotherapy were performed in the context of secondary prevention. These trials can be broadly categorized based on the timing of monotherapy initiation—either as an upfront (default monotherapy) strategy or following a short course of DAPT as part of a de-escalation approach.

Default monotherapy

Of the 19 185 patients with stable ASCVD included in the CAPRIE trial who were randomized to aspirin 325 mg daily or clopidogrel 75 daily and followed up for a mean of 1.9 years, 6302 had a recent MI (<35 days),[23] in whom clopidogrel was associated with a minimal, non-significant, increase in MACE [5.0% vs 4.8%; relative risk reduction (RRR) = −3.7%], compared with aspirin.[23] Moreover, in a broader subgroup analysis of CAPRIE including all patients with established CAD (prior MI patients; $n = 8446$), irrespective of the qualifying event for trial inclusion, no significant differences were observed between aspirin and clopidogrel for the primary composite endpoint of CV death, MI, or stroke (HR .94; 95% CI .83–1.07), nor for major bleeding (HR .80; 95% CI .54–1.20).[87] It should be acknowledged that these findings from CAPRIE stem from a subgroup analysis of an older study, in which the clinical management and adjunctive therapies for MI differ substantially from current standards. Additionally, high doses of aspirin were used, in contrast to the low-dose regimens recommended today. Nonetheless, this trial remains the largest ever comparing aspirin and clopidogrel in patients with CAD and the only one available in a non-Asian population (*Graphical Abstract*).

Eight years later, the small *Clopidogrel and Aspirin: Determination of the Effects on Thrombogenicity* (CADET) double-blind trial randomly allocated 184 patients with recent MI (within 3–7 days) to aspirin 75 mg daily or clopidogrel 75 mg daily.[88] The laboratory endpoints including fibrinogen, D-dimer, von Willebrand factor, Factor VIII, C-reactive protein (CRP), tissue plasminogen activator antigen did not differ between groups. There were very few clinical events during follow-up, with a numerical reduction of MI with clopidogrel (6 vs 1).[88]

Aspirin Non-responsiveness and Clopidogrel Clinical Endpoint Trial (ASCET) randomized 1001 patients with angiographically documented CAD who underwent testing with the Platelet Function Analyzer (PFA-100) to assess residual platelet reactivity (RPR) in response to aspirin to continue with aspirin 160 mg daily or change to clopidogrel 75 mg daily.[70] The study was designed to show a 40% reduction in the composite endpoint of death, MI, ischaemic stroke, and unstable angina in patients with low on-aspirin RPR as compared with patients with high on-aspirin RPR at 2 years.[70] No formal sample size calculation was performed for the comparison between aspirin and clopidogrel.[70] The study was double blinded for the PD results but open label for clinical outcomes. The frequency of high RPR on aspirin treatment was 25.9%. There was a non-significant increase in the primary endpoint in patients with high vs low on-treatment RPR (13.3% vs 9.9%; $P = .31$).[70] Among patients randomized to aspirin or clopidogrel, there was no difference in the primary endpoint between groups (10.8% vs 10.4%; $P = .87$). However, there was an increase in any bleeding in the clopidogrel group compared with the aspirin group (15.8% vs 10.2%; $P = .008$), driven by minor bleeding.[70]

It is important to note that none of these three trials were designed to assess the comparative safety or efficacy of aspirin vs clopidogrel in patients with CAD. The first RCT specifically designed to explore this hypothesis did not become available until 2021.

The *Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-Extended Antiplatelet Monotherapy* (HOST-EXAM) open-label

Table 1 Key clinical studies comparing $P2Y_{12}$ inhibitor vs aspirin in atherosclerotic cardiovascular disease

Trial, year	Design	Enrolment site	Clinical setting	Sample	Intervention	Control	Primary outcome	$P2Y_{12}$ inhibitor better than aspirin?	Follow-up
CAPRIE, 1996 (1)	Double blind	North America, Australia/New Zealand, Europe	Established symptomatic and recent atherosclerotic cerebrovascular, coronary, and peripheral artery disease	19 185	Clopidogrel 75 mg	Aspirin 325 mg	A composite of ischaemic stroke, MI, or vascular death tested for superiority	*MACE*: yes, (driven by PAD patients) *Bleeding*: no	1–3 years
CADET, 2004 (2)	Double blind	Europe	Coronary artery disease: patients with an acute myocardial infarction within the previous 3–7 days	184	Clopidogrel 75 mg	Aspirin 75 mg	Laboratory outcomes (fibrinogen, D-dimer, von Willebrand factor, Factor VIII, C-reactive protein, tissue plasminogen activator antigen)		6 months
ASCET, 2012 (3)	Open label (double blinded for the PD results)	Europe	Coronary artery disease: angiographically documented High on-aspirin residual platelet reactivity assessed by the PFA100	1001	Clopidogrel 75 mg	Aspirin 160 mg	A composite of death, MI, ischaemic stroke, and unstable angina (stratified according to high on-aspirin platelet reactivity) with no formal sample size calculation	*MACE*: no *Bleeding*: No, increased bleeding	24 months
SOCRATES, 2016 (4)	Double blind	North America, South America, Europe, Australia, China, Japan, East Asia, Russia	Cerebrovascular disease: acute non-severe stroke or TIA	13 199	Ticagrelor 90 mg bid	Aspirin 100 mg	A composite of stroke, MI, or death tested for superiority	*MACE*: no *Bleeding*: no	90 days
DACAB, 2018 (5)	Open label	China	Coronary artery disease: post-CABG	322	Ticagrelor 90 mg bid	Aspirin 100 mg	Saphenous vein graft patency tested for superiority	*MACE*: no *Bleeding*: no	12 months
TICAB, 2019 (6)	Double blind	Europe	Coronary artery disease: post-CABG	1852 (out of 3850 planned)	Ticagrelor 90 mg bid	Aspirin 100 mg	A composite of CV death, MI, repeat revascularization, and stroke tested for superiority although the trial was prematurely halted	*MACE*: no *Bleeding*: no	12 months
GLOBAL LEADERS, 2022 (7)	*Post hoc* analysis	North America, Australia, Singapore, Europe	Coronary artery disease: 12 months after index PCI	11 121	Ticagrelor 90 mg bid	Aspirin 75–100 mg	Ischaemic events (all-cause death, any MI, or any stroke) and major bleeding events (BARC Type 3 or 5 bleeding)	*MACE*: yes *Bleeding*: no, increased bleeding	12 months
TARGET, 2022 (8)	Double blind	North America	Coronary artery disease: post-CABG	250	Ticagrelor 90 mg bid	Aspirin 81 mg	Saphenous vein graft patency tested for superiority	*MACE*: no *Bleeding*: no	12 months

Continued

Table 1 *Continued*

Trial, year	Design	Enrolment site	Clinical setting	Sample	Intervention	Control	Primary outcome	P2Y$_{12}$ inhibitor better than aspirin?	Follow-up
HOST-EXAM, 2021 (9)	Open label	East Asia	Coronary artery disease: patients with previous PCI who maintained DAPT without clinical events for 6–18 months	5530	Clopidogrel 75 mg	Aspirin 100 mg	A composite of all-cause death, non-fatal MI, stroke, hospitalization for angina, or BARC ≥ 3 bleeding tested for superiority	*MACE*: yes *Bleeding*: yes	24 months
STOPDAPT-2, 2024 (10)	Pre-specified landmark analysis (1–5 years) of an open-label trial	Japan	Coronary artery disease: patients with ACS and CCS who underwent PCI	3005	Clopidogrel 75 mg	Aspirin 81–200 mg	A composite of CV death, MI, stroke, or definite ST) or TIMI major or minor bleeding	*MACE*: no *Bleeding*: no	5 years
STOPDAPT-3, 2024 (11)	Pre-specified landmark analysis (30 days–1 year) of an open-label trial	Japan	Coronary artery disease: patients after 1 month from ACS or those with HBR undergoing PCI	5833	Clopidogrel 75 mg	Aspirin 81–100 mg	Co-primary endpoints were the cardiovascular endpoint defined as a composite of CV death, MI, definite ST, or ischaemic stroke and BARC 3 or 5 bleeding	*MACE*: no *Bleeding*: no	12 months
SMART-CHOICE 3, (12)	Open label	East Asia	Coronary artery disease: patients at high risk of recurrent ischaemic events (previous MI or medication-treated diabetes, or complex coronary lesions) who completed a standard duration of DAPT after PCI	5506	Clopidogrel 75 mg	Aspirin 81–100 mg	Composite of death from any cause, MI, or stroke tested for superiority	*MACCE*: yes *Bleeding*: no	27 months

ACS, acute coronary syndrome; CCS, chronic coronary syndrome; CV, cardiovascular; MACEs, major adverse cardiovascular events; ST, stent thrombosis; MI, myocardial infarction; BARC, Bleeding Academic Research Consortium; TIMI, Thrombolysis in Myocardial Infarction; PCI, percutaneous coronary intervention; HBR, high bleeding risk; CABG, coronary artery bypass grafting; TIA, transient ischaemic attack; PCI, percutaneous coronary intervention; PD, pharmacodynamic.

trial randomized 5530 patients from South Korea who maintained DAPT without clinical events for 6–18 months after PCI with drug-eluting stents (DESs) to receive monotherapy with clopidogrel 75 mg once daily or aspirin 100 mg once daily for 24 months.[89] The primary endpoint—a composite of all-cause death, MI, stroke, readmission due to ACS, and Bleeding Academic Research Consortium (BARC) bleeding Type 3 or greater—was significantly reduced with clopidogrel compared with aspirin at 24 months (5.7% vs 7.7%; $P = .003$). This reduction in the primary endpoint was mainly driven by haemorrhagic stroke, readmission due to ACS, and BARC ≥ 3 bleeding. However, clopidogrel reduced the thrombotic composite endpoint [composite of CV death, MI, ischaemic stroke, readmission due to ACS, and definite or probable stent thrombosis (ST); 3.7% vs 5.5%; $P = .003$], stroke (.7% vs 1.6%; $P = .002$), BARC ≥ 3 bleeding (1.2% vs 2.0%; $P = .035$), and BARC ≥ 2 bleeding (2.3% vs 3.3%; $P = .036$), compared with aspirin.[89] Notably, there was a trend towards increased all-cause death (1.9% vs 1.3%; $P = .101$) and CV death (.7% vs .5%; $P = .374$) in the clopidogrel arm. However, an extended follow-up analysis at 5.8 years showed that the benefit in favour of clopidogrel over aspirin in terms of ischaemic and bleeding events remained consistent, with no differences in mortality.[56,90] This study used a primary endpoint including soft outcomes and exclusively included East Asian patients, a population with a higher bleeding risk and a lower incidence of ischaemic events compared with other ancestries.[91]

In 2024, two sub-analyses of open-label RCTs performed in Japan provided further evidence on the use of clopidogrel vs aspirin in CAD patients.[92,93] The 5-year analysis of the STOPDAPT-2 compared clopidogrel 75 mg daily following 1 month of DAPT with aspirin 81–200 mg daily following 12 months of DAPT after PCI for 5 years in 3005 patients (38% with ACS).[92] The primary endpoint [composite of CV death, MI, stroke, ST, or thrombolysis in myocardial infarction (TIMI) major or minor bleeding] and TIMI major bleeding were similar between groups (11.7% vs 13.5%; $P = .13$ and 4.4% vs 4.9%; $P = .51$, respectively).[92] Results were consistent at the 1-year landmark analysis, although clopidogrel was numerically, but not significantly, superior to aspirin for CV events (6.7% vs 8.6%; HR .77; 95% CI .59–1.01; $P = .06$), driven by a reduction in MI (2.5% vs 4.1%; HR .61; 95% CI .40–.92; $P = .02$), without difference in major bleeding (3.9% vs. 3.3%; HR 1.23; 95% CI .84–1.81; $P = .31$).[92] In STOPDAPT-3, patients with ACS or high bleeding risk undergoing PCI were randomly assigned to 1-month DAPT with aspirin and low-dose prasugrel (3.75 mg daily) followed by aspirin monotherapy or 1-month low-dose prasugrel monotherapy followed by clopidogrel monotherapy. In the 30-day landmark analysis of the trial, comparing aspirin monotherapy (81–100 mg daily) vs clopidogrel monotherapy (75 mg daily) between 30 days and 1 year in 5833 patients (75% with ACS),[93] the incidence of the CV endpoint (composite of CV death, MI, definite ST, or ischaemic stroke; incidence rate by 100 person-year 4.5 vs 4.5; $P = .97$), and bleeding endpoint (BARC 3–5 bleeding; incidence rate by 100 person-year 2.0 vs 1.9; $P = .92$) were similar between the aspirin and clopidogrel groups.[93]

The use of the $P2Y_{12}$ inhibitor ticagrelor 90 mg b.i.d. vs aspirin 100 mg daily in patients with CAD was tested in a *post hoc* analysis of the GLOBAL LEADERS trial, including 11 121 patients (45% with ACS) who were free from events at the end of the first year post-PCI and adherent to their assigned antiplatelet therapy.[94] In this *post hoc* analysis, during the second year of the trial, the ischaemic composite endpoint was lower with ticagrelor monotherapy compared with aspirin monotherapy (1.9% vs 2.6%; HR .74; 95% CI .58–.96; $P = .022$), which was primarily driven by a reduced risk of MI. In contrast, BARC Type 3 or 5 bleeding was numerically higher with ticagrelor monotherapy (.5% vs .3%; unadjusted HR 1.80, 95% CI .99–3.30; $P = .055$; adjusted HR 1.89, 95% CI 1.03–3.45; $P = .040$).[94] Notably, clinical endpoints have not been adjudicated in the GLOBAL LEADERS trial. The pre-specified *Global Leaders Adjudication Substudy* (GLASSY) was an independent Clinical Event Committee that prospectively adjudicated all the investigator-reported, eventually not reporting, events of 7585 patients from the top 20 recruiting sites of the GLOBAL LEADERs trial. At 1-year landmark, the composite of CV death or MI [1.4% vs 2.0%; rate ratio (RR) .69; 95% CI .48–.98], as well as the rates of MI (.6% vs 1.2%; RR .54; 95% CI .33–.88) and definite ST (.05% vs .3%; RR .14; 95% CI .03–.63) were lower in the experimental arm after 1-year time point. The rates of BARC 2 bleeding (but not BARC 3 or higher) were higher with experimental treatment (1.7% vs .9%; RR 1.93; 95% CI 1.26–2.96).[95]

A *post hoc* analysis of the CAPRIE trial suggested that clopidogrel could be more effective and safe than aspirin among patients with a history of CABG.[96] Two small trials conducted in CABG patients comparing ticagrelor vs aspirin monotherapy did not confirm the previously noted advantage for clopidogrel over aspirin,[97,98] acknowledging neither of the two was powered for clinical endpoints. In the *Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery* (DACAB) open-label trial, 322 patients (66% with ACS) were randomized to ticagrelor 90 mg b.i.d. or aspirin 100 mg daily within 24 h post-CABG using saphenous vein graft.[97] There was no difference in the primary endpoint of saphenous vein graft patency 1 year after CABG between groups (82.9% vs 76.5%; $P = .10$). There were two major bleeding events in the ticagrelor group and no major bleeding events in the aspirin group.[97] The subsequent *Ticagrelor Antiplatelet Therapy to Reduce Graft Events and Thrombosis* (TARGET) double-blind trial ($n = 250$) did not detect any advantage of ticagrelor vs aspirin.[99] The larger *Ticagrelor in Coronary Artery Bypass* (TICAB) double-blind trial comparing ticagrelor 90 mg bid vs aspirin 100 mg daily was stopped prematurely after enrolling 1852 (31% with ACS) of the 3850 planned.[98] Twelve months after CABG, there were no difference between groups in the primary efficacy (composite of CV death, MI, repeat revascularization, and stroke; 9.7% vs 8.2%; $P = .28$) or safety (BARC 3, 4, and 5; 3.7% vs 3.2%; $P = .53$) endpoints.[98]

An individual participant-level meta-analysis (IPD-MA) of 24 325 patients from seven RCTs comparing $P2Y_{12}$ inhibitor vs aspirin monotherapy for the secondary prevention of coronary events was recently published.[87] The study found that the primary outcome of CV death, MI, and stroke was significantly lower with $P2Y_{12}$ inhibitor monotherapy (ticagrelor = 38%; clopidogrel = 62%) compared with aspirin (3.6% vs 4.0%; HR .88; 95% CI .79–.97; $P = .012$), with the benefit driven primarily by a 24% relative reduction in the risk of MI at 2 years. The number needed to treat at 2 years was 126. In a *post hoc* subgroup analysis, patients from Asian institutions appeared to benefit more from $P2Y_{12}$ inhibitors for the primary endpoint ($p_{int} = .034$) than those from Europe and North America.[87,100] There was no difference in major bleeding between groups (.76% vs .87%; $P = .23$), whereas the risk of GI bleeding and haemorrhagic stroke was significantly lower with $P2Y_{12}$ inhibitor than with aspirin monotherapy.[87] Another recent IPD-MA focusing on patients with a history of PCI and including the STOPDAPT-2 trial found similar results.[101]

The *SMart Angioplasty Research Team: CHoice of Optimal Anti-Thrombotic Strategy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents 3* (SMART-CHOICE 3) open-label trial randomized 5506 high-risk patients who had completed standard DAPT after PCI to clopidogrel or aspirin monotherapy.[102] Patients were enrolled at 26 sites in South Korea, and high risk of recurrent ischaemic events was defined by clinical (previous MI or medication-treated diabetes) or procedural characteristics (complex coronary lesions). Although the event rate

was lower than anticipated, which resulted in approximately half the number of the expected primary events, there was still a significant reduction in the primary endpoint (composite of death from any cause, MI, or stroke) with clopidogrel compared with aspirin (HR .71; 95% CI .54–.93; $P = .013$) at a median follow-up of 2.3 years. Moreover, there was a numerical reduction in death from any cause (2.4% vs 4.0%), CV death (1.5% vs 2.0%), MI (1.0% vs 2.2%), and ST (0% vs .2%) with clopidogrel compared with aspirin but no difference in stroke (1.3% vs 1.3%), BARC 2, 3, or 5 bleeding (3.0% vs 3.0%), or major bleeding (BARC 3 or 5, 1.6% vs 1.3%) between groups.[102] The open-label design, lower-than-anticipated event rate for the primary outcome, selective inclusion of East Asian patients, imbalance in all-cause mortality between groups, and the delayed divergence of Kaplan–Meier curves—favouring clopidogrel over aspirin only after the second year, when the proportion of patients still alive or under follow-up had decreased from 71% to 35%—represent limitations of this trial.[103]

An updated IPD-MA, which also included SMART-CHOICE 3, recently compared clopidogrel vs aspirin monotherapy in patients with established CAD, most of whom had undergone PCI. Using data from 28,982 patients across seven randomised trials, over a median follow-up of 2.3 years, the risk of MACCE was significantly lower with clopidogrel than with aspirin (HR 0.86; 95% CI 0.77-0.96; $P = 0.0082$), with trial sequential analysis confirming the robustness of this finding. MI and stroke, including ischemic and hemorrhagic stroke, were lower with clopidogrel. No differences were observed between clopidogrel and aspirin in major bleeding (HR 0.94; 95% CI 0.74-1.21; $P = 0.64$) or all-cause mortality (HR 0.99; 95% CI 0.89-1.09; $P = 0.79$).[104] Latest European guidelines on CCS support the use of clopidogrel 75 mg with a Class I, Level of evidence (LoE) A, in alternative to aspirin monotherapy in patients with a prior MI or PCI.[105] Conversely, North American guidelines on CCS recommend the use of clopidogrel as an alternative to low-dose aspirin only in individuals who cannot tolerate aspirin therapy (*Table 2*).[106]

This divergence in recommendations likely stems from the distinct supporting evidence referenced by each guideline. European guidelines have incorporated data from East Asian populations (e.g. HOST-EXAM and SMART-CHOICE 3), while North American guidelines have primarily relied on studies conducted in Western populations (e.g. CAPRIE and GLOBAL LEADERS). Additionally, the absence of outcome stratification based on drug responsiveness remains a limitation when comparing clopidogrel with aspirin.

Monotherapy after a short course of dual antiplatelet therapy (de-escalation by discontinuation)

No RCT has been designed to compare aspirin vs P2Y$_{12}$ inhibitor monotherapy following a short course of DAPT in patients with CAD undergoing PCI.[4] However, significant differences in the outcomes of RCTs evaluating short-term DAPT de-escalation a few months after ACS or PCI may arise depending on whether aspirin, clopidogrel, or ticagrelor is used as subsequent monotherapy.[107,108] Notably, no RCT has investigated prasugrel monotherapy after a short course of DAPT. Briefly, among studies comparing standard DAPT duration with short DAPT followed by aspirin or clopidogrel monotherapy, a numerical increase in ischaemic events was observed with the monotherapy strategy in ACS patients but not in those undergoing PCI for stable CAD.[109–112] On the other hand, trials using a strategy of ticagrelor monotherapy after a short course of DAPT showed at least comparable outcomes or even improved outcomes with ticagrelor.[113–119] These findings led the 2025 North American guidelines to provide a Class I, LoE A recommendation for a strategy of ticagrelor monotherapy after ≥1 month of uneventful DAPT to reduce bleeding in patients with or without high bleeding risk features.[120] Of note, this is currently the only Class I recommendation for de-escalation of antiplatelet therapy in patients with recent ACS.[105,120,121] European guidelines recommend SAPT, with a preference for P2Y$_{12}$ inhibitor monotherapy, in patients who are event-free 3–6 months after ACS and are not at high ischaemic risk, with a Class IIa, LoE A.[121] Both European and North American guidelines recommend, with a Class IIb, LoE B, the transition from DAPT to SAPT 1 month after ACS in high bleeding risk patients.[120,121]

Cerebrovascular disease

CAPRIE included 6421 patients with recent stroke (>1 week and <6 months). In this subgroup of patients, clopidogrel was associated with a modest reduction in MACE (7.1% vs 7.7%; RRR = 7.3%), compared with aspirin, at 1.9 years.[23] These findings should be interpreted with caution, as they derive from a subgroup analysis of the CAPRIE trial, which was conducted nearly 30 years ago and utilized high-dose rather than low-dose aspirin.

SOCRATES was a double-blind, multicentre, controlled trial, in which 13 199 patients with a non-severe ischaemic stroke or high-risk transient ischaemic attack (TIA) were randomly assigned within 24 h after symptom onset, to receive either ticagrelor 90 mg b.i.d. or aspirin 100 mg daily.[122] Ticagrelor was associated with no difference in the primary endpoint (6.7% vs 7.5%; $P = .07$) or in PLATO-defined major bleeding between groups.[122]

International guidelines recommend either aspirin or clopidogrel for long-term secondary prevention after ischaemic stroke or TIA[123] (*Table 2*).

The *Ticagrelor or Clopidogrel with Aspirin in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II* (CHANCE-2) trial was a double-blind, placebo-controlled trial randomizing 6412 patients with a minor ischaemic stroke or TIA who carried CYP2C19 LoF alleles to clopidogrel 75 mg or ticagrelor 90 mg b.i.d.[124] The primary endpoint of new stroke was lower in the ticagrelor compared with the clopidogrel group (6.0% vs 7.6%; HR .77; 95% CI .64 to .94; $P = .008$), with no difference in severe or moderate bleeding (.3% vs .3%) at 90 days.[124]

Peripheral artery disease

CAPRIE included 6452 patients with PAD defined as having intermittent claudication and ankle/arm systolic blood pressure ratio ≤ 85 in either leg at or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty with no persisting complications from intervention. At 1.9 years, clopidogrel significantly reduced MACE compared with aspirin, in this subgroup of patients (3.7% vs 4.9%; RRR = 23.8%).[23] As with other subgroups in the study, these findings should be interpreted considering several limitations, as discussed above. No further evidence from RCTs comparing P2Y$_{12}$ inhibitors with aspirin is currently available.

The large *Examining Use of Ticagrelor in Peripheral Artery Disease* (EUCLID) trial unexpectedly failed to demonstrate the superiority of ticagrelor over clopidogrel in reducing CV events among 13 885 patients with PAD undergoing P2Y$_{12}$ inhibitor monotherapy.[125] It should be noted that carriers of *CYP2C19* LoF alleles, were excluded from the study. Since the assessment of *CYP2C19* LoF alleles is not a clinical routine, it remains difficult to interpret this evidence for practice.[21] These findings have challenged the role of potent P2Y$_{12}$ inhibition in this cohort of patients, which instead appear to benefit more from a

Table 2 Recommendations by latest European or North American Guidelines on the use of $P2Y_{12}$ inhibitor vs aspirin monotherapy for secondary prevention across the spectrum of patients with atherosclerotic vascular disease

Guidelines	Recommendations	Class	level of evidence
Coronary artery disease			
2024 ESC guidelines on chronic coronary syndrome[1]	In CCS patients with a prior MI or PCI, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy	I	A
	In CCS patients without prior MI or revascularization but with evidence of significant obstructive CAD, aspirin 75–100 mg daily is recommended lifelong	I	B
	In CCS or stabilized post-ACS patients who underwent PCI and were initially treated with ticagrelor-based DAPT, who remain at high ischaemic risk and are not at high bleeding risk, ticagrelor monotherapy 90 mg b.i.d. may be considered as an alternative to dual or other single antiplatelet therapy	IIb	C
2023AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the management of patients with chronic coronary disease[2]	'Further clinical trials would be useful to guide recommendations regarding the long-term use of clopidogrel vs aspirin as SAPT in CCS' 'As an alternative to low-dose aspirin, clopidogrel may be used in individuals who cannot tolerate aspirin therapy, and many of the contemporary trials have used clopidogrel monotherapy after a short course of DAPT'		
Peripheral artery disease			
2024 ESC guidelines for the management of peripheral arterial and aortic diseases[3]	Use of antiplatelet therapy with clopidogrel alone (75 mg daily) may be considered over aspirin to reduce MI, stroke, and vascular death	IIb	B
2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the management of lower extremity peripheral artery disease[4]	In patients with symptomatic PAD, single antiplatelet therapy with clopidogrel alone (75 mg daily) is recommended to reduce the risk of MACE	I	B
Stroke or transient ischaemic attack			
2022 European Stroke Organisation (ESO) guideline on pharmacological interventions for long-term secondary prevention after ischaemic stroke or transient ischaemic attack[5]	'Overall, we conclude that the evidence favours use of antiplatelet monotherapy, and indirect data suggest that clopidogrel is preferable to aspirin' 'We did not specifically address the choice of antiplatelet but given the limited differences in direct comparisons between aspirin and other antiplatelets, we believe that there is likely equivalent benefit from other antiplatelets such as clopidogrel'		
2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association[6]	No mention		

ACS, acute coronary syndrome; MI, myocardial infarction; MACEs, major adverse cardiovascular events; PCI, percutaneous coronary interventions; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; CCS, chronic coronary syndrome; CABG, coronary artery bypass grafting; PAD, peripheral artery disease; b.i.d., bis in die.

DPI-based approach, consisting in the combination of low-dose aspirin with a vascular dose of rivaroxaban (2.5 mg b.i.d.).[126–128] Of interest aspirin and $P2Y_{12}$ inhibitors have been compared in PD studies when used in adjunct to a vascular dose of rivaroxaban.[55,129] Although these PD studies have shown promising results for the use of a $P2Y_{12}$ inhibitor, particularly ticagrelor, the clinical evidence to support this approach remains scarce.[55,129]

International guidelines recommend either clopidogrel or low-dose aspirin for reducing MACE in patients with symptomatic PAD (Class I, LoE A). A Class IIb, LoE B, recommendation is given considering the use of clopidogrel over aspirin for reducing the risk of MI, stroke, and vascular death[130] (*Table 2*).

Clinical challenges with the use of $P2Y_{12}$ inhibitor monotherapy

The use of $P2Y_{12}$ inhibitor monotherapy instead of aspirin monotherapy in patients with ASCVD may raise challenges.

A major challenge in the use of $P2Y_{12}$ inhibitor monotherapy in lieu of aspirin monotherapy stems from the fact that this drug class encompasses pharmacologically heterogeneous agents, each with distinct PK and PD profiles.[5,26] Indeed, clopidogrel—unlike prasugrel and ticagrelor—is characterized by substantial interindividual variability in its response.[43,44] This variability is primarily attributed to differences in clopidogrel metabolism, leading to reduced levels of its active

metabolite and HPR in ~30% of treated patients, with ethnicity playing a significant role.[43,44] Poor clopidogrel responsiveness can be identified through platelet function testing or predicted by genetic testing for LoF polymorphisms in the *CYP2C19* gene (*2 and *3 alleles).[44,131] Guided selection of P2Y$_{12}$ inhibitors, wherein prasugrel or ticagrelor is selectively administered to patients with inadequate clopidogrel response, may improve outcomes in patients receiving DAPT.[132,133] However, no RCTs have specifically evaluated this approach in patients receiving SAPT. Given the well-characterized variability in clopidogrel metabolism and the more predictable PD profile of aspirin—where clinically significant aspirin resistance is rare—it is reasonable to hypothesize that interindividual differences in clopidogrel response may have influenced the outcomes of RCTs comparing aspirin and P2Y$_{12}$ inhibitors in unselected populations. Therefore, the greater predictability of aspirin's antiplatelet effects compared with clopidogrel may represent a notable advantage in the context of SAPT. To this extent, a recent international consensus document on the use of platelet function and genetic testing in patients undergoing PCI recommends that antiplatelet therapy should be tailored in high-risk patients receiving clopidogrel monotherapy.[44]

It may seem intuitive to address clopidogrel's interindividual variability by substituting it with prasugrel or ticagrelor. However, while these agents offer more consistent platelet inhibition, they are also more frequently associated with low platelet reactivity, which has been linked to an increased risk of bleeding without a proportional reduction in thrombotic events.[47]

As a result, their use as monotherapy may lead to a net increase in bleeding risk, potentially outweighing their ischaemic benefits. A potential strategy to mitigate this issue could involve the use of lower-dose regimens, such as ticagrelor 60 mg twice daily or prasugrel 5 mg daily.[134] However, these dosing strategies have not been formally tested in RCTs as monotherapy.

Another key limitation in the widespread adoption of P2Y$_{12}$ inhibitor monotherapy lies in the fact that much of the supporting evidence originates from studies conducted in East Asian populations. Since ethnicity significantly influences antiplatelet drug metabolism—particularly for clopidogrel—extrapolating these findings to non-Asian populations should be approached with caution.[91,135]

Aspirin may be characterized by lower cost and broader global availability than P2Y$_{12}$ inhibitors. Moreover, aspirin has been widely and empirically adopted across various clinical settings, while in comparison to aspirin, the amount of evidence on the safety and efficacy of P2Y$_{12}$ inhibitor monotherapy is not as robust. For instance, aspirin is empirically used in a number of different conditions, such as patients with high bleeding risk or patients undergoing percutaneous interventions including both vascular (i.e. carotid stenting or percutaneous transluminal angioplasty of PAD or other vascular districts) and structural interventions (i.e. transcatheter aortic valve implantation, left atrial appendage closure, and percutaneous mitral or tricuspid interventions) and CAD patients not undergoing PCI or undergoing CABG.[20,21,136–138]

Furthermore, the use of P2Y$_{12}$ inhibitors in women remains limited, as females have been consistently underrepresented in trials comparing P2Y$_{12}$ inhibitor vs aspirin monotherapy, comprising only about one in five participants.[89,102] Evidence from both PD and randomized trials suggest that women exhibit different responses to P2Y$_{12}$ inhibitor monotherapy compared with men, with females potentially deriving greater benefit from P2Y$_{12}$ inhibitor monotherapy.[139,140]

The perioperative management of P2Y$_{12}$ inhibitors remains challenging in patients undergoing cardiac or non-cardiac surgery. Current surgical protocols commonly recommend aspirin monotherapy in the perioperative period.[141] Additionally, many surgeons remain hesitant to perform procedures in patients actively receiving P2Y$_{12}$ inhibitors due to concerns regarding excessive bleeding. This further complicates the use of P2Y$_{12}$ monotherapy as a long-term strategy in clinical practice. To this extent, studies assessing the feasibility and safety of performing surgical procedures in patients on P2Y$_{12}$ monotherapy remain an unmet need.

Moreover, specific adverse effects associated with P2Y$_{12}$ inhibitors, particularly ticagrelor, may impact their clinical use compared with aspirin. For instance, ticagrelor is associated with dyspnoea in 5%–20% of treated patients, which can lead to drug discontinuation and reduced adherence.[142] Additionally, as a reversible P2Y$_{12}$ inhibitor, ticagrelor's PD profile is more susceptible to variability in patients with poor medication adherence, making its efficacy potentially less certain in these populations.[143]

Finally, after defining first its anti-inflammatory properties followed by its cardioprotective effects, aspirin has now entered a new wave of potential benefits as shown by its chemo-preventive effects against cancer, particularly solid tumours of the GI tract. Regular aspirin use has been associated with a reduced risk of oesophageal, gastric, and colorectal cancer.[144,145] To this extent, a recent study demonstrated that aspirin exerts anti-metastatic effects by alleviating T cell suppression induced by platelet-derived TXA_2.[146] However, P2Y$_{12}$ inhibitors, in particular ticagrelor, have also demonstrated pleiotropic effects, including cardioprotective effects against ischemia–reperfusion injury, anti-inflammatory, and antimicrobic effects.[49,147] These benefits were particularly evident in patients treated with ticagrelor and may explain the reduced incidence of death in ACS patients associated with ticagrelor use, although the underlying mechanisms remain unclear, as this was not replicated in other trials.[147–149] However, the clinical relevance of the pleiotropic effects of both aspirin and P2Y$_{12}$ inhibitors remains a subject of debate and warrants confirmation through more robust evidence.

Future perspectives and conclusions

Acknowledging and addressing the limitations of both aspirin and P2Y$_{12}$ inhibitors is key to enable a more personalized therapeutic approach, enhance patient compliance, and ultimately improve outcomes. For instance, the development of more tolerable formulations may mitigate GI toxicity of aspirin, while for P2Y$_{12}$ inhibitors, the use of lower-dose regimens of prasugrel or ticagrelor, or a guided selection strategy incorporating platelet function and genetic testing to help identify those in whom the efficacy of clopidogrel is impaired, could help tailor therapy more effectively. Recent evidence, mostly derived from East Asian populations, has added to prior data showing superior efficacy of P2Y$_{12}$ inhibitor monotherapy over aspirin monotherapy for the prevention of ischemic events in patients with atherosclerotic cardiovascular disease, without an excess risk of bleeding. Additional large-scale clinical trials conducted in contemporary populations across the world are warranted to further enhance our understanding of whether patients' characteristics, including ethnicity, age, sex, clinical setting (ACS vs CCS), individual response to P2Y$_{12}$ inhibitors, and type of P2Y$_{12}$ inhibitors, impact the choice of the optimal SAPT. A collaborative effort involving North America and Europe, potentially endorsed by regulatory agencies such as the Food and Drug Administration or European Medicines Agency, would be instrumental in generating robust evidence and guiding future clinical practice.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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References

1. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, *et al.* Atherosclerosis. *Nat Rev Dis Primers* 2019;**5**:56. https://doi.org/10.1038/s41572-019-0106-z
2. Viles-Gonzalez JF, Fuster V, Badimon JJ. Atherothrombosis: a widespread disease with unpredictable and life-threatening consequences. *Eur Heart J* 2004;**25**:1197–207. https://doi.org/10.1016/j.ehj.2004.03.011%J
3. Libby P. Pathogenesis of atherothrombotic events: from lumen to lesion and beyond. *Circulation* 2024;**150**:1217–9. https://doi.org/10.1161/circulationaha.124.070087
4. Angiolillo DJ, Galli M, Collet JP, Kastrati A, O'Donoghue ML. Antiplatelet therapy after percutaneous coronary intervention. *EuroIntervention* 2022;**17**:e1371–96. https://doi.org/10.4244/eij-d-21-00904
5. Angiolillo DJ, Ueno M, Goto S. Basic principles of platelet biology and clinical implications. *Circ J* 2010;**74**:597–607. https://doi.org/10.1253/circj.cj-09-0982
6. Kocsis JJ, Hernandovich J, Silver MJ, Smith JB, Ingerman C. Duration of inhibition of platelet prostaglandin formation and aggregation by ingested aspirin or indomethacin. *Prostaglandins* 1973;**3**:141–4. https://doi.org/10.1016/0090-6980(73)90081-6
7. Jafari E, Saleem A, Shaikh BS, Demers LM. Effect of aspirin on prostaglandin synthesis by human platelets. *Prostaglandins* 1976;**12**:829–35. https://doi.org/10.1016/0090-6980(76)90056-3
8. Elwood PC, Cochrane AL, Burr ML, Sweetnam PM, Williams G, Welsby E, *et al.* A randomized controlled trial of acetyl salicylic acid in the secondary prevention of mortality from myocardial infarction. *Br Med J* 1974;**1**:436–40. https://doi.org/10.1136/bmj.1.5905.436
9. Patrono C, Ciabattoni G, Patrignani P, Pugliese F, Filabozzi P, Catella F, *et al.* Clinical pharmacology of platelet cyclooxygenase inhibition. *Circulation* 1985;**72**:1177–84. https://doi.org/10.1161/01.CIR.72.6.1177
10. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988;**2**:349–60.
11. Patrono C, Baigent C. Role of aspirin in primary prevention of cardiovascular disease. *Nat Rev Cardiol* 2019;**16**:675–86. https://doi.org/10.1038/s41569-019-0225-y
12. Michelson AD. Antiplatelet therapies for the treatment of cardiovascular disease. *Nat Rev Drug Discov* 2010;**9**:154–69. https://doi.org/10.1038/nrd2957
13. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, *et al.* Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;**373**:1849–60. https://doi.org/10.1016/s0140-6736(09)60503-1
14. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke. *The Lancet* 1997;**349**:1569–81. https://doi.org/10.1016/S0140-6736(97)04011-7
15. Chen Z-M. CAST: randomised placebo-controlled trial of early aspirin use in 20 000 patients with acute ischaemic stroke. *The Lancet* 1997;**349**:1641–9. https://doi.org/10.1016/S0140-6736(97)04010-5
16. Galli M, Andreotti F, D'Amario D, Vergallo R, Vescovo GM, Giraldi L, *et al.* Antithrombotic therapy in the early phase of non-ST-elevation acute coronary syndromes: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2020;**6**:43–56. https://doi.org/10.1093/ehjcvp/pvz031
17. Patrono C. Low-dose aspirin for the prevention of atherosclerotic cardiovascular disease. *Eur Heart J* 2024;**45**:2362–76. https://doi.org/10.1093/eurheartj/ehae324
18. Wallentin L. P2y12 inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. *Eur Heart J* 2009;**30**:1964–77. https://doi.org/10.1093/eurheartj/ehp296
19. Greco A, Occhipinti G, Giacoppo D, Agnello F, Laudani C, Spagnolo M, *et al.* Antithrombotic therapy for primary and secondary prevention of ischemic stroke: JACC state-of-the-art review. *J Am Coll Cardiol* 2023;**82**:1538–57. : https://doi.org/10.1016/j.jacc.2023.07.025
20. Galli M, Gragnano F, Berteotti M, Marcucci R, Gargiulo G, Calabrò P, *et al.* Antithrombotic therapy in high bleeding risk, part I: percutaneous cardiac interventions. *JACC Cardiovasc Interv* 2024;**17**:2197–215. https://doi.org/10.1016/j.jcin.2024.08.022
21. Galli M, Gragnano F, Berteotti M, Marcucci R, Gargiulo G, Calabrò P, *et al.* Antithrombotic therapy in high bleeding risk, part II. *JACC Cardiovasc Interv* 2024;**17**:2325–36. https://doi.org/10.1016/j.jcin.2024.09.011
22. Cadroy Y, Bossavy JP, Thalamas C, Sagnard L, Sakariassen K, Boneu B. Early potent antithrombotic effect with combined aspirin and a loading dose of clopidogrel on experimental arterial thrombogenesis in humans. *Circulation* 2000;**101**:2823–8. : https://doi.org/10.1161/01.cir.101.24.2823
23. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *CAPRIE Steering Committee. Lancet* 1996;**348**:1329–39. doi: https://doi.org/10.1016/s0140-6736(96)09457-3
24. Bhatt DL, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Reduction in the need for hospitalization for recurrent ischemic events and bleeding with clopidogrel instead of aspirin. CAPRIE investigators. *Am Heart J* 2000;**140**:67–73. doi: https://doi.org/10.1067/mhj.2000.108239
25. Capodanno D, Mehran R, Valgimigli M, Baber U, Windecker S, Vranckx P, *et al.* Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol* 2018;**15**:480–96. doi: https://doi.org/10.1038/s41569-018-0049-1
26. Storey RF. Biology and pharmacology of the platelet P2Y12 receptor. *Curr Pharm Des* 2006;**12**:1255–9. doi: https://doi.org/10.2174/138161206776361318
27. Peters SAE, Colan LD, Dai Y, Zhao H, Bittner V, Farkouh ME, *et al.* Trends in recurrent coronary heart disease after myocardial infarction among US women and men between 2008 and 2017. *Circulation* 2021;**143**:650–60. https://doi.org/10.1161/CIRCULATIONAHA.120.047065
28. Capodanno D, Bhatt DL, Eikelboom JW, Fox KAA, Geisler T, Michael Gibson C, *et al.* Dual-pathway inhibition for secondary and tertiary antithrombotic prevention in cardiovascular disease. *Nat Rev Cardiol* 2020;**17**:242–57. : https://doi.org/10.1038/s41569-019-0314-y
29. Navarese EP, Andreotti F, Schulze V, Kołodziejczak M, Buffon A, Brouwer M, *et al.* Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. *Bmj* 2015;**350**:h1618. https://doi.org/10.1136/bmj.h1618
30. Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, *et al.* Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 2012;**366**:1404–13. https://doi.org/10.1056/NEJMoa1200933
31. H M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002;**347**:969–74. https://doi.org/10.1056/NEJMoa020496
32. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, *et al.* Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;**377**:1319–30. https://doi.org/10.1056/NEJMoa1709118
33. Navarese EP, Landi A, Oliva A, Piccolo R, Aboyans V, Angiolillo D, *et al.* Within and beyond 12-month efficacy and safety of antithrombotic strategies in patients with established coronary artery disease: two companion network meta-analyses of the 2022 joint clinical consensus statement of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Association for Acute CardioVascular Care (ACVC), and European Association of Preventive Cardiology (EAPC). *European Heart Journal—Cardiovascular Pharmacotherapy* 2023;**9**:271–90. https://doi.org/10.1093/ehjcvp/pvad016
34. V M, Aboyans V, Angiolillo D, Atar D, Capodanno D, Halvorsen S, *et al.* Antithrombotic treatment strategies in patients with established coronary atherosclerotic disease. *Eur Heart J—Cardiovasc Pharmacother* 2023;**9**:462–96. : https://doi.org/10.1093/ehjcvp/pvad032
35. Galli M, Capodanno D, Andreotti F, Crea F, Angiolillo DJ. Safety and efficacy of P2Y12 inhibitor monotherapy in patients undergoing percutaneous coronary interventions. *Expert Opin Drug Saf* 2021;**20**:9–21. https://doi.org/10.1080/14740338.2021.1850691
36. Capodanno D, Mehran R, Krucoff MW, Baber U, Bhatt DL, Capranzano P, *et al.* Defining strategies of modulation of antiplatelet therapy in patients with coronary artery disease: a consensus document from the academic research consortium. *Circulation* 2023;**147**:1933–44. https://doi.org/10.1161/circulationaha.123.064473
37. Galli M, Angiolillo DJ. De-escalation of antiplatelet therapy in acute coronary syndromes: why, how and when? *Front Cardiovasc Med* 2022;**9**:975969. https://doi.org/10.3389/fcvm.2022.975969
38. Galli M, Ortega-Paz L, Franchi F, Rollini F, Angiolillo DJ. Precision medicine in interventional cardiology: implications for antiplatelet therapy in patients undergoing percutaneous coronary intervention. *Pharmacogenomics* 2022;**23**:723–37. https://doi.org/10.2217/pgs-2022-0057
39. Gargiulo G, Windecker S, Vranckx P, Gibson CM, Mehran R, Valgimigli M. A critical appraisal of aspirin in secondary prevention: is less more? *Circulation* 2016;**134**:1881–906. https://doi.org/10.1161/circulationaha.116.023952
40. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. *Nat Rev Cardiol* 2015;**12**:30–47. https://doi.org/10.1038/nrcardio.2014.156
41. Pereira NL, Rihal CS, So DYF, Rosenberg Y, Lennon RJ, Mathew V, *et al.* Clopidogrel pharmacogenetics. *Circ Cardiovasc Interv* 2019;**12**:e007811. https://doi.org/10.1161/circinterventions.119.007811
42. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation* 2000;**102**:624–9. https://doi.org/10.1161/01.cir.102.6.624
43. Gurbel PA, Bliden KP, Hiatt BL, O'Connor M. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003;**107**:2908–13. https://doi.org/10.1161/01.Cir.0000072771.11429.83
44. Angiolillo DJ, Galli M, Alexopoulos D, Aradi D, Bhatt DL, Bonello L, *et al.* International consensus statement on platelet function and genetic testing in percutaneous coronary intervention: 2024 update. *JACC Cardiovasc Interv* 2024;**17**:2639–63. https://doi.org/10.1016/j.jcin.2024.08.027

45. Galli M, Franchi F, Rollini F, Cavallari LH, Capodanno D, Crea F, *et al.* Genetic testing in patients undergoing percutaneous coronary intervention: rationale, evidence and practical recommendations. *Expert Rev Clin Pharmacol* 2021;**14**:963–78. https://doi.org/10.1080/17512433.2021.1927709
46. Angiolillo DJ, Capodanno D, Danchin N, Simon T, Bergmeijer TO, Ten Berg JM, *et al.* Derivation, validation, and prognostic utility of a prediction rule for nonresponse to clopidogrel: the ABCD-GENE score. *JACC Cardiovasc Interv* 2020;**13**:606–17. https://doi.org/10.1016/j.jcin.2020.01.226
47. Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K, *et al.* Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. *Eur Heart J* 2015;**36**:1762–71. https://doi.org/10.1093/eurheartj/ehv104
48. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann F-J, Metzger DC, *et al.* Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *The Lancet* 2013;**382**:614–23. https://doi.org/10.1016/S0140-6736(13)61170-8
49. Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. *J Am Coll Cardiol* 2014;**63**:2503–9. https://doi.org/10.1016/j.jacc.2014.03.031
50. Ariotti S, Ortega-Paz L, van Leeuwen M, Brugaletta S, Leonardi S, Akkerhuis KM, *et al.* Effects of ticagrelor, prasugrel, or clopidogrel on endothelial function and other vascular biomarkers: a randomized crossover study. *JACC Cardiovasc Interv* 2018;**11**:1576–86. https://doi.org/10.1016/j.jcin.2018.04.022
51. Ortega-Paz L, Brugaletta S, Ariotti S, Akkerhuis KM, Karagiannis A, Windecker S, *et al.* Adenosine and ticagrelor plasma levels in patients with and without ticagrelor-related dyspnea. *Circulation* 2018;**138**:646–8. https://doi.org/10.1161/CIRCULATIONAHA.118.034489
52. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, *et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**:2001–15. https://doi.org/10.1056/NEJMoa0706482
53. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–57. https://doi.org/10.1056/NEJMoa0904327
54. Baber U, Zafar MU, Dangas G, Escolar G, Angiolillo DJ, Sharma SK, *et al.* Ticagrelor with or without aspirin after PCI: the TWILIGHT platelet substudy. *J Am Coll Cardiol* 2020;**75**:578–86. https://doi.org/10.1016/j.jacc.2019.11.056
55. Galli M, Franchi F, Rollini F, Been L, Jaoude PA, Rivas A, *et al.* Platelet P2Y12 inhibiting therapy in adjunct to vascular dose of rivaroxaban or aspirin: a pharmacodynamic study of dual pathway inhibition vs. dual antiplatelet therapy. *Eur Heart J Cardiovasc Pharmacother* 2022;**8**:728–37. https://doi.org/10.1093/ehjcvp/pvac022
56. Capodanno D, Angiolillo DJ. Long-term P2Y12 inhibitor or aspirin as single antiplatelet therapy in patients with previous percutaneous coronary intervention. *Circulation* 2023;**147**:118–21. https://doi.org/10.1161/CIRCULATIONAHA.122.063004
57. Armstrong PC, Leadbeater PD, Chan MV, Kirkby NS, Jakubowski JA, Mitchell JA, *et al.* In the presence of strong P2Y12 receptor blockade, aspirin provides little additional inhibition of platelet aggregation. *J Thromb Haemost* 2011;**9**:552–61. https://doi.org/10.1111/j.1538-7836.2010.04160.x
58. Laine L, Maller ES, Yu C, Quan H, Simon T. Ulcer formation with low-dose enteric-coated aspirin and the effect of COX-2 selective inhibition: a double-blind trial. *Gastroenterology* 2004;**127**:395–402. https://doi.org/10.1053/j.gastro.2004.05.001
59. Han Y, Liao Z, Li Y, Zhao X, Ma S, Bao D, *et al.* Magnetically controlled capsule endoscopy for assessment of antiplatelet therapy–induced gastrointestinal injury. *JACC* 2022;**79**:116–28. https://doi.org/10.1016/j.jacc.2021.10.028
60. Chiarito M, Sanz-Sánchez J, Cannata F, Cao D, Sturla M, Panico C, *et al.* Monotherapy with a P2Y(12) inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. *Lancet* 2020;**395**:1487–95. https://doi.org/10.1016/s0140-6736(20)30315-9
61. Galli M, Laborante R, Andreotti F, Vergallo R, Montone RA, Iaconelli A, *et al.* Bleeding complications in patients undergoing percutaneous coronary intervention. *Rev Cardiovasc Med* 2022;**23**:286. https://doi.org/10.31083/j.rcm2308286
62. Lavie CJ, Howden CW, Scheiman J, Tursi J. Upper gastrointestinal toxicity associated with long-term aspirin therapy: consequences and prevention. *Curr Probl Cardiol* 2017;**42**:146–64. https://doi.org/10.1016/j.cpcardiol.2017.01.006
63. Pratt S, Thompson VJ, Elkin EP, Næsdal J, Sörstadius E. The impact of upper gastrointestinal symptoms on nonadherence to, and discontinuation of, low-dose acetylsalicylic acid in patients with cardiovascular risk. *Am J Cardiovasc Drugs* 2010;**10**:281–8. https://doi.org/10.2165/11584410-000000000-00000
64. Sundström J, Hedberg J, Thuresson M, Aarskog P, Johannesen KM, Oldgren J. Low-dose aspirin discontinuation and risk of cardiovascular events: a Swedish nationwide, population-based cohort study. *Circulation* 2017;**136**:1183–92. https://doi.org/10.1161/circulationaha.117.028321
65. Kedir HM, Sisay EA, Abiye AA. Enteric-coated aspirin and the risk of gastrointestinal Side effects: a systematic review. *Int J Gen Med* 2021;**14**:4757–63. https://doi.org/10.2147/ijgm.S326929
66. Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet* 1996;**348**:1413–6. https://doi.org/10.1016/s0140-6736(96)01254-8
67. Bhatt DL, Grosser T, Dong JF, Logan D, Jeske W, Angiolillo DJ, *et al.* Enteric coating and aspirin nonresponsiveness in patients with type 2 diabetes Mellitus. *J Am Coll Cardiol* 2017;**69**:603–12. https://doi.org/10.1016/j.jacc.2016.11.050
68. Grosser T, Fries S, Lawson JA, Kapoor SC, Grant GR, FitzGerald GA. Drug resistance and pseudoresistance: an unintended consequence of enteric coating aspirin. *Circulation* 2013;**127**:377–85. https://doi.org/10.1161/circulationaha.112.117283
69. Tantry US, Bliden KP, Gurbel PA. Overestimation of platelet aspirin resistance detection by thrombelastograph platelet mapping and validation by conventional aggregometry using arachidonic acid stimulation. *J Am Coll Cardiol* 2005;**46**:1705–9. https://doi.org/10.1016/j.jacc.2005.05.090
70. Pettersen A, Seljeflot I, Abdelnoor M, Arnesen H. High on-aspirin platelet reactivity and clinical outcome in patients with stable coronary artery disease: results from ASCET (Aspirin Nonresponsiveness and Clopidogrel Endpoint Trial). *J Am Heart Assoc* 2012;**1**:e000703. https://doi.org/10.1161/jaha.112.000703
71. Mattiello T, Guerriero R, Lotti LV, Trifirò E, Felli MP, Barbarulo A, *et al.* Aspirin extrusion from human platelets through multidrug resistance protein-4-mediated transport: evidence of a reduced drug action in patients after coronary artery bypass grafting. *J Am Coll Cardiol* 2011;**58**:752–61. https://doi.org/10.1016/j.jacc.2011.03.049
72. FitzGerald R, Pirmohamed M. Aspirin resistance: effect of clinical, biochemical and genetic factors. *Pharmacol Ther* 2011;**130**:213–25. https://doi.org/10.1016/j.pharmthera.2011.01.011
73. Galli M, Terracina S, Schiera E, Mancone M, Frati L, Angiolillo DJ, *et al.* Interindividual variability in platelet reactivity among individuals with or without antiplatelet therapy: results from a large tertiary care hospital. *J Thromb Thrombolysis* 2025;**58**:71–83. https://doi.org/10.1007/s11239-024-03022-w
74. Patrono C, Rocca B. Aspirin: promise and resistance in the new millennium. *Arterioscler Thromb Vasc Biol* 2008;**28**:s25–32. https://doi.org/10.1161/atvbaha.107.160481
75. Franchi F, Schneider DJ, Prats J, Fan W, Rollini F, Been L, *et al.* Pharmacokinetic and pharmacodynamic profiles of a novel phospholipid-aspirin complex liquid formulation and low dose enteric-coated aspirin: results from a prospective, randomized, cross-over study. *J Thromb Thrombolysis* 2022;**54**:373–81. https://doi.org/10.1007/s11239-022-02687-5
76. Angiolillo DJ, Prats J, Deliargyris EN, Schneider DJ, Scheiman J, Kimmelstiel C, *et al.* Pharmacokinetic and pharmacodynamic profile of a novel phospholipid aspirin formulation. *Clin Pharmacokinet* 2022;**61**:465–79. https://doi.org/10.1007/s40262-021-01090-2
77. Galli M, Cortellini G, Occhipinti G, Rossini R, Romano A, Angiolillo DJ. Aspirin hypersensitivity in patients with atherosclerotic cardiovascular disease. *J Am Coll Cardiol* 2024;**84**:1748–66. https://doi.org/10.1016/j.jacc.2024.05.084
78. Grimaldi S, Migliorini P, Puxeddu I, Rossini R, De Caterina R. Aspirin hypersensitivity: a practical guide for cardiologists. *Eur Heart J* 2024;**45**:1716–26. https://doi.org/10.1093/eurheartj/ehae128
79. Evans AM, Nation RL, Sansom LN, Bochner F, Somogyi AA. Effect of racemic ibuprofen dose on the magnitude and duration of platelet cyclo-oxygenase inhibition: relationship between inhibition of thromboxane production and the plasma unbound concentration of S(+)-ibuprofen. *Br J Clin Pharmacol* 1991;**31**:131–8. https://doi.org/10.1111/j.1365-2125.1991.tb05500.x
80. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, *et al.* Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001;**345**:1809–17. https://doi.org/10.1056/NEJMoa003199
81. Davis JS, Lee HY, Kim J, Advani SM, Peng HL, Banfield E, *et al.* Use of non-steroidal anti-inflammatory drugs in US adults: changes over time and by demographic. *Open Heart* 2017;**4**:e000550. https://doi.org/10.1136/openhrt-2016-000550
82. Moore RA, Derry S, Wiffen PJ, Straube S. Effects of food on pharmacokinetics of immediate release oral formulations of aspirin, dipyrone, paracetamol and NSAIDs—a systematic review. *Br J Clin Pharmacol* 2015;**80**:381–8. https://doi.org/10.1111/bcp.12628
83. Rocca B, Tosetto A, Petrucci G, Rossi E, Betti S, Soldati D, *et al.* Long-term pharmacodynamic and clinical effects of twice- versus once-daily low-dose aspirin in essential thrombocythemia: the ARES trial. *Am J Hematol* 2024;**99**:1462–74. https://doi.org/10.1002/ajh.27418
84. Rothwell PM, Cook NR, Gaziano JM, Price JF, Belch JFF, Roncaglioni MC, *et al.* Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. *Lancet* 2018;**392**:387–99. https://doi.org/10.1016/s0140-6736(18)31133-4
85. Capodanno D, Patel A, Dharmashankar K, Ferreiro JL, Ueno M, Kodali M, *et al.* Pharmacodynamic effects of different aspirin dosing regimens in type 2 diabetes mellitus patients with coronary artery disease. *Circ Cardiovasc Interv* 2011;**4**:180–7. https://doi.org/10.1161/circinterventions.110.960187
86. Paikin JS, Hirsh J, Ginsberg JS, Weitz JI, Chan NC, Whitlock RP, *et al.* Multiple daily doses of acetyl-salicylic acid (ASA) overcome reduced platelet response to once-daily ASA after coronary artery bypass graft surgery: a pilot randomized controlled trial. *J Thromb Haemost* 2015;**13**:448–56. https://doi.org/10.1111/jth.12832

87. Gragnano F, Cao D, Pirondini L, Franzone A, Kim HS, von Scheidt M, *et al.* P2y(12) inhibitor or aspirin monotherapy for secondary prevention of coronary events. *J Am Coll Cardiol* 2023;**82**:89–105. https://doi.org/10.1016/j.jacc.2023.04.051
88. Woodward M, Lowe GD, Francis LM, Rumley A, Cobbe SM. A randomized comparison of the effects of aspirin and clopidogrel on thrombotic risk factors and C-reactive protein following myocardial infarction: the CADET trial. *J Thromb Haemost* 2004;**2**:1934–40. https://doi.org/10.1111/j.1538-7836.2004.01017.x
89. Koo B-K, Kang J, Park KW, Rhee T-M, Yang H-M, Won K-B, *et al.* Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. *The Lancet* 2021;**397**:2487–96. https://doi.org/10.1016/S0140-6736(21)01063-1
90. Kang J, Park KW, Lee H, Hwang D, Yang H-M, Rha S-W, *et al.* Aspirin versus clopidogrel for long-term maintenance monotherapy after percutaneous coronary intervention: the HOST-EXAM extended study. *Circulation* 2023;**147**:108–17. https://doi.org/10.1161/CIRCULATIONAHA.122.062770
91. Kwon O, Park DW. Antithrombotic therapy after acute coronary syndromes or percutaneous coronary interventions in East Asian populations. *JACC Asia* 2022;**2**:1–18. https://doi.org/10.1016/j.jacasi.2021.12.005
92. Watanabe H, Morimoto T, Natsuaki M, Yamamoto K, Obayashi Y, Nishikawa R, *et al.* Clopidogrel vs aspirin monotherapy beyond 1 year after percutaneous coronary intervention. *JACC* 2024;**83**:17–31. https://doi.org/10.1016/j.jacc.2023.10.013
93. Watanabe H, Natsuaki M, Morimoto T, Yamamoto K, Obayashi Y, Nishikawa R, *et al.* Aspirin vs. clopidogrel monotherapy after percutaneous coronary intervention: 1-year follow-up of the STOPDAPT-3 trial. *Eur Heart J* 2024;**45**:5042–54. https://doi.org/10.1093/eurheartj/ehae617
94. Ono M, Hara H, Kawashima H, Gao C, Wang R, Wykrzykowska JJ, *et al.* Ticagrelor monotherapy versus aspirin monotherapy at 12 months after percutaneous coronary intervention: a landmark analysis of the GLOBAL LEADERS trial. *EuroIntervention* 2022;**18**:e377–88. https://doi.org/10.4244/eij-d-21-00870
95. Franzone A, McFadden E, Leonardi S, Piccolo R, Vranckx P, Serruys PW, *et al.* Ticagrelor alone versus dual antiplatelet therapy from 1 month after drug-eluting coronary stenting. *J Am Coll Cardiol* 2019;**74**:2223–34. https://doi.org/10.1016/j.jacc.2019.08.1038
96. Bhatt DL, Chew DP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. *Circulation* 2001;**103**:363–8. https://doi.org/10.1161/01.cir.103.3.363
97. Zhao Q, Zhu Y, Xu Z, Cheng Z, Mei J, Chen X, *et al.* Effect of ticagrelor plus aspirin, ticagrelor alone, or aspirin alone on saphenous vein graft patency 1 year after coronary artery bypass grafting: a randomized clinical trial. *JAMA* 2018;**319**:1677–86. https://doi.org/10.1001/jama.2018.3197
98. Schunkert H, Boening A, von Scheidt M, Lanig C, Gusmini F, de Waha A, *et al.* Randomized trial of ticagrelor vs. aspirin in patients after coronary artery bypass grafting: the TiCAB trial. *Eur Heart J* 2019;**40**:2432–40. https://doi.org/10.1093/eurheartj/ehz185
99. Kulik A, Abreu AM, Boronat V, Kouchoukos NT, Ruel M. Ticagrelor versus aspirin and vein graft patency after coronary bypass: a randomized trial. *J Card Surg* 2022;**37**:563–70. https://doi.org/10.1111/jocs.16189
100. Bates ER. Clinically significant differences between P2Y12 inhibitor monotherapy and aspirin monotherapy have yet to be demonstrated. *J Am Coll Cardiol* 2024;**83**:e9–10. https://doi.org/10.1016/j.jacc.2023.09.833
101. Giacoppo D, Gragnano F, Watanabe H, Kimura T, Kang J, Park KW, *et al.* P2y(12) inhibitor or aspirin after percutaneous coronary intervention: individual patient data meta-analysis of randomised clinical trials. *Bmj* 2025;**389**:e082561. https://doi.org/10.1136/bmj-2024-082561
102. Choi KH, Park YH, Lee JY, Jeong JO, Kim CJ, Yun KH, *et al.* Efficacy and safety of clopidogrel versus aspirin monotherapy in patients at high risk of subsequent cardiovascular event after percutaneous coronary intervention (SMART-CHOICE 3): a randomised, open-label, multicentre trial. *Lancet* 2025;**405**:1252–63. https://doi.org/10.1016/s0140-6736(25)00449-0
103. Galli M, Patrono C. Weekly Journal Scan: is a SMART-CHOICE of clopidogrel monotherapy after coronary stenting supported by adequate evidence? *Eur Heart J* 2025;**46**:2831–2. https://doi.org/10.1093/eurheartj/ehaf290
104. Valgimigli M, Choi KH, Giacoppo D, Gragnano F, Kimura T, Watanabe H, *et al.* Clopidogrel versus aspirin for secondary prevention of coronary artery disease: a systematic review and individual patient data meta-analysis. *Lancet* 2025. https://doi.org/10.1016/s0140-6736(25)01562-4
105. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, *et al.* 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J* 2024;**45**:3415–537. https://doi.org/10.1093/eurheartj/ehae177
106. Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, *et al.* 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation* 2023;**148**:e9–119. https://doi.org/10.1161/CIR.0000000000001168
107. Valgimigli M, Gragnano F, Branca M, Franzone A, da Costa BR, Baber U, *et al.* Ticagrelor or clopidogrel monotherapy vs dual antiplatelet therapy after percutaneous coronary intervention: a systematic review and patient-level meta-analysis. *JAMA Cardiol* 2024;**9**:437–48. https://doi.org/10.1001/jamacardio.2024.0133
108. Galli M, Laudani C, Occhipinti G, Spagnolo M, Gragnano F, D'Amario D, *et al.* P2y12 inhibitor monotherapy after short DAPT in acute coronary syndrome: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2024;**10**:588–98. https://doi.org/10.1093/ehjcvp/pvae057
109. Hahn J-Y, Song YB, Oh J-H, Cho D-K, Lee JB, Doh J-H, *et al.* 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. *The Lancet* 2018;**391**:1274–84. https://doi.org/10.1016/S0140-6736(18)30493-8
110. Kedhi E, Fabris E, Mvd E, Buszman P, Birgelen CV, Roolvink V, *et al.* 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* 2018;**363**:k3793. https://doi.org/10.1136/bmj.k3793
111. Watanabe H, Morimoto T, Natsuaki M, Yamamoto K, Obayashi Y, Ogita M, *et al.* 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* 2022;**7**:407–17. https://doi.org/10.1001/jamacardio.2021.5244
112. Natsuaki M, Morimoto T, Yamamoto E, Shiomi H, Furukawa Y, Abe M, *et al.* One-year outcome of a prospective trial stopping dual antiplatelet therapy at 3 months after everolimus-eluting cobalt-chromium stent implantation: ShortT and OPtimal duration of Dual AntiPlatelet Therapy after everolimus-eluting cobalt-chromium stent (STOPDAPT) trial. *Cardiovasc Interv Ther* 2016;**31**:196–209. https://doi.org/10.1007/s12928-015-0366-9
113. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, *et al.* 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* 2018;**392**:940–9. https://doi.org/10.1016/s0140-6736(18)31858-0
114. Tomaniak M, Chichareon P, Onuma Y, Deliargyris EN, Takahashi K, Kogame N, *et al.* Benefit and risks of aspirin in addition to ticagrelor in acute coronary syndromes: a *post hoc* analysis of the randomized GLOBAL LEADERS trial. *JAMA Cardiol* 2019;**4**:1092–101. https://doi.org/10.1001/jamacardio.2019.3355
115. Baber U, Dangas G, Angiolillo DJ, Cohen DJ, Sharma SK, Nicolas J, *et al.* Ticagrelor alone vs. ticagrelor plus aspirin following percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: TWILIGHT-ACS. *Eur Heart J* 2020;**41**:3533–45. https://doi.org/10.1093/eurheartj/ehaa670
116. Hong S-J, Lee S-J, Suh Y, Yun KH, Kang TS, Shin S, *et al.* Stopping aspirin within 1 month after stenting for ticagrelor monotherapy in acute coronary syndrome: the T-PASS randomized noninferiority trial. *Circulation* 2024;**149**:562–73. https://doi.org/10.1161/CIRCULATIONAHA.123.066943
117. Hahn J-Y, Song YB, Oh J-H, Chun WJ, Park YH, Jang WJ, *et al.* 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* 2019;**321**:2428–37. https://doi.org/10.1001/jama.2019.8146
118. Ge Z, Kan J, Gao X, Raza A, Zhang J-J, Mohydin BS, *et al.* 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. *The Lancet* 2024;**403**:1866–78. https://doi.org/10.1016/S0140-6736(24)00473-2
119. Valgimigli M, Hong SJ, Gragnano F, Chalkou K, Franzone A, da Costa BR, *et al.* De-escalation to ticagrelor monotherapy versus 12 months of dual antiplatelet therapy in patients with and without acute coronary syndromes: a systematic review and individual patient-level meta-analysis of randomised trials. *Lancet* 2024;**404**:937–48. https://doi.org/10.1016/s0140-6736(24)01616-7
120. Rao SV, O'Donoghue ML, Ruel M, Rab T, Tamis-Holland JE, Alexander JH, *et al.* ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the management of patients with acute coronary syndromes. *JACC* 2025;**85**:2135–237. https://doi.org/10.1016/j.jacc.2024.11.009
121. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, *et al.* 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;**44**:3720–826. https://doi.org/10.1093/eurheartj/ehad191
122. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, *et al.* Ticagrelor versus aspirin in acute stroke or transient ischemic attack. *N Engl J Med* 2016;**375**:35–43. https://doi.org/10.1056/NEJMoa1603060
123. Dawson J, Béjot Y, Christensen LM, De Marchis GM, Dichgans M, Hagberg G, *et al.* European Stroke Organisation (ESO) guideline on pharmacological interventions for long-term secondary prevention after ischaemic stroke or transient ischaemic attack. *Eur Stroke J* 2022;**7**:I–ii. https://doi.org/10.1177/23969873221100032
124. Wang Y, Meng X, Wang A, Xie X, Pan Y, Johnston SC, *et al.* Ticagrelor versus clopidogrel in CYP2C19 loss-of-function carriers with stroke or TIA. *N Engl J Med* 2021;**385**:2520–30. https://doi.org/10.1056/NEJMoa2111749

125. Hiatt WR, Fowkes FGR, Heizer G, Berger JS, Baumgartner I, Held P, *et al.* Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med* 2017;**376**:32–40. https://doi.org/10.1056/NEJMoa1611688
126. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, *et al.* Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med* 2020;**382**:1994–2004. https://doi.org/10.1056/NEJMoa2000052
127. Kaplovitch E, Eikelboom JW, Dyal L, Aboyans V, Abola MT, Verhamme P, *et al.* Rivaroxaban and aspirin in patients with symptomatic lower extremity peripheral artery disease: a subanalysis of the COMPASS randomized clinical trial. *JAMA Cardiol* 2021;**6**:21–9. https://doi.org/10.1001/jamacardio.2020.4390
128. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, *et al.* Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *The Lancet* 2018;**391**:219–29. https://doi.org/10.1016/S0140-6736(17)32409-1
129. Galli M, Franchi F, Rollini F, Been L, Jaoude PA, Rivas A, *et al.* Pharmacodynamic profiles of dual-pathway inhibition with or without clopidogrel versus dual antiplatelet therapy in patients with atherosclerotic disease. *Thromb Haemost* 2022;**122**:1341–51. https://doi.org/10.1055/a-1730-8725
130. Mazzolai L, Teixido-Tura G, Lanzi S, Boc V, Bossone E, Brodmann M, *et al.* 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases. *Eur Heart J* 2024;**45**:3538–700. https://doi.org/10.1093/eurheartj/ehae179
131. Galli M, Franchi F, Rollini F, Angiolillo DJ. Role of platelet function and genetic testing in patients undergoing percutaneous coronary intervention. *Trends Cardiovasc Med* 2023;**33**:133–8. https://doi.org/10.1016/j.tcm.2021.12.007
132. Galli M, Benenati S, Capodanno D, Franchi F, Rollini F, D'Amario D, *et al.* Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *The Lancet* 2021;**397**:1470–83. https://doi.org/10.1016/S0140-6736(21)00533-X
133. Galli M, Benenati S, Franchi F, Rollini F, Capodanno D, Biondi-Zoccai G, *et al.* Comparative effects of guided vs. potent P2Y12 inhibitor therapy in acute coronary syndrome: a network meta-analysis of 61 898 patients from 15 randomized trials. *Eur Heart J* 2021;**43**:959–67. https://doi.org/10.1093/eurheartj/ehab836
134. Galli M, Costa F, Navarese EP. De-escalation versus shortening of dual antiplatelet therapy. *Eur Heart J Cardiovasc Pharmacother* 2024;**10**:267–9. https://doi.org/10.1093/ehjcvp/pvae019
135. Galli M, Laborante R, Occhipinti G, Zito A, Spadafora L, Biondi-Zoccai G, *et al.* Impact of ethnicity on antiplatelet treatment regimens for bleeding reduction in acute coronary syndromes: a systematic review and pre-specified subgroup meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2024;**10**:158–69. https://doi.org/10.1093/ehjcvp/pvad085
136. Mauro MS, Finocchiaro S, Calderone D, Rochira C, Agnello F, Scalia L, *et al.* Antithrombotic strategies for preventing graft failure in coronary artery bypass graft. *J Thromb Thrombolysis* 2024;**57**:547–57. https://doi.org/10.1007/s11239-023-02940-5
137. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med* 2018;**379**:1529–39. https://doi.org/10.1056/NEJMoa1804988
138. McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM, *et al.* Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med* 2018;**379**:1519–28. https://doi.org/10.1056/NEJMoa1803955
139. Valgimigli M, Gragnano F, Branca M, Franzone A, Baber U, Jang Y, *et al.* P2y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials. *Bmj* 2021;**373**:n1332. https://doi.org/10.1136/bmj.n1332
140. Galli M, Terracina S, Schiera E, De Corci S, Sangiorgi D, Mancone M, *et al.* Sex-related variations in platelet reactivity in presence or absence of antiplatelet therapy. *Eur Heart J Cardiovasc Pharmacother* May 14, 2025;**11**:509–517. https://doi.org/10.1093/ehjcvp/pvaf034 6
141. Lyons MD, Pope B, Alexander J. Perioperative management of antithrombotic therapy. *JAMA* 2024;**332**:420–1. https://doi.org/10.1001/jama.2024.5880
142. Angiolillo DJ, Cao D, Sartori S, Baber U, Dangas G, Zhang Z, *et al.* Dyspnea-related ticagrelor discontinuation after percutaneous coronary intervention. *JACC Cardiovasc Interv* 2023;**16**:2514–24. https://doi.org/10.1016/j.jcin.2023.08.019
143. Arora S, Shemisa K, Vaduganathan M, Qamar A, Gupta A, Garg SK, *et al.* Premature ticagrelor discontinuation in secondary prevention of atherosclerotic CVD: JACC review topic of the week. *J Am Coll Cardiol* 2019;**73**:2454–64. https://doi.org/10.1016/j.jacc.2019.03.470
144. Patrono C. Cyclooxygenase inhibitors and cancer: the missing pieces. *J Pharmacol Exp Ther* 2023;**386**:181–9. https://doi.org/10.1124/jpet.122.001631
145. Martling A, Hed Myrberg I, Nilbert M, Grönberg H, Granath F, Eklund M, *et al.* Low-Dose Aspirin for PI3K-Altered Localized Colorectal Cancer. *N Engl J Med* 2025;**393**:1051–1051. https://doi.org/10.1056/NEJMoa2504650 11
146. Yang J, Yamashita-Kanemaru Y, Morris BI, Contursi A, Trajkovski D, Xu J, *et al.* Aspirin prevents metastasis by limiting platelet TXA2 suppression of T cell immunity. *Nature* 2025;**640**:1052–61. https://doi.org/10.1038/s41586-025-08626-7
147. Triska J, Maitra N, Deshotels MR, Haddadin F, Angiolillo DJ, Vilahur G, *et al.* A comprehensive review of the pleiotropic effects of ticagrelor. *Cardiovasc Drugs Ther* 2024;**38**:775–97. https://doi.org/10.1007/s10557-022-07373-5
148. Galli M, Niccoli G, De Maria G, Brugaletta S, Montone RA, Vergallo R, *et al.* Coronary microvascular obstruction and dysfunction in patients with acute myocardial infarction. *Nat Rev Cardiol* 2024;**21**:283–98. https://doi.org/10.1038/s41569-023-00953-4
149. D'Amario D, Galli M, Restivo A, Canonico F, Vergallo R, Migliaro S, *et al.* Ticagrelor enhances the cardioprotective effects of ischemic preconditioning in stable patients undergoing percutaneous coronary intervention: the TAPER-S randomized study. *Eur Heart J Cardiovasc Pharmacother* 2024;**10**:190–200. https://doi.org/10.1093/ehjcvp/pvad092