Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention

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Abstract | In patients with manifestations of cardiovascular disease, acetylsalicylic acid (popularly known as aspirin) has been the mainstay of treatment for decades owing to its capacity to reduce the risk of ischaemic events. Accordingly, novel antithrombotic therapies have been traditionally tested on a background of acetylsalicylic acid therapy. Although the adjunctive use of such antithrombotic therapies can potentially further reduce the risk of ischaemic events, these agents are also inevitably associated with an increased risk of bleeding. However, acetylsalicylic acid also increases the risk of bleeding, challenging the paradigm that this agent should remain the cornerstone of antiplatelet treatment when alternative antithrombotic agents are also used. Many antithrombotic compounds are characterized by increased potency and consistent efficacy, which might lessen the need for concomitant acetylsalicylic acid. Accordingly, numerous investigations are testing the hypothesis that acetylsalicylic acid-sparing regimens based on newer antithrombotic agents might have an increased net benefit for individual patients owing to the reduction in bleeding risk, without a trade-off in efficacy. This Review summarizes the state of the art relating to antithrombotic approaches with and without acetylsalicylic acid for the prevention of cardiovascular disease and cardioembolic stroke. Discussion of the scientific rationale, from bench to bedside, for ongoing studies of acetylsalicylic acid-free pharmacological strategies is included.

The first recorded use of salicylate-containing plants dates back approximately 4,000 years to the Sumerians, who noted the pain-relieving properties of remedies derived from the willow tree on early clay tablets[1]. The modern formulation of the active agent, acetylsalicylic acid, was synthesized for the first time in 1853 by the chemist Charles Frédéric Gerhardt[2]. More than 150 years later, acetylsalicylic acid (commonly known by the brand name aspirin) is one of the most prescribed medications worldwide, especially after its antiplatelet effect was discovered in the 1970s[3].

At commercially available doses of 75–100 mg, acetylsalicylic acid exerts its antithrombotic and vascular protective properties through the inhibition of platelet cyclooxygenase 1 (COX1; also known as prostaglandin G/H synthase 1) and blockade of thromboxane A_2 generation[4]. These effects translate into clinical benefits that render acetylsalicylic acid the cornerstone of pharmacological therapies for cardiovascular atherothrombotic disease. In turn, most new antithrombotic treatment strategies aimed at further improvement of these outcomes have been developed with acetylsalicylic acid as a background therapy. Although sex-related differences in the cardiovascular effects of low-dose acetylsalicylic acid have been suggested, the totality of the evidence does not support the concept that the balance of benefits and risks of low-dose acetylsalicylic acid are influenced by sex[5]. The benefit of acetylsalicylic acid is also supported by observations that cardiovascular events increase after treatment discontinuation[6,7]. In current guidelines, acetylsalicylic acid consistently has a class I recommendation for secondary prevention of atherothrombotic and thromboembolic events across multiple presentations of cardiovascular disease[8–17] (TABLE 1).

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https://doi.org/10.1038/s41569-018-0049-1

Key points

- Most new antithrombotic treatment strategies aimed at further outcome improvement have been developed with acetylsalicylic acid as background therapy.
- Given that acetylsalicylic acid increases bleeding risk, a number of studies are exploring the possibility of avoiding this drug in the presence of other antithrombotic agents.
- Pharmacodynamic investigations indicate that no other antithrombotic agent can replace the cyclooxygenase 1-selective, platelet-inhibitory effects of acetylsalicylic acid; however, many newer antithrombotic therapies might have greater antithrombotic efficacy.
- Given the established role of acetylsalicylic acid in cardiovascular disease management and prevention, favourable results from large-scale clinical trials are warranted before acetylsalicylic acid-free strategies are recommended for routine clinical practice.
- Acetylsalicylic acid is cost effective and has favourable noncardiac effects, which are under ongoing investigation and need to be taken into account when considering acetylsalicylic acid-free approaches.

Although the use of acetylsalicylic acid for primary prevention remains controversial and is the subject of ongoing investigation[18], no other antiplatelet agent has proved beneficial for primary prevention.

Despite the undisputed benefits of acetylsalicylic acid in secondary prevention of cardiovascular disease, its status as the cornerstone of antithrombotic therapy has recently been challenged (FIG. 1). This challenge is based on three major arguments. First, intracranial and extracranial (especially gastrointestinal) bleeding events occur in a sizeable proportion of patients receiving acetylsalicylic acid, and these events are especially likely in elderly patients or those receiving long-term treatment. This effect is amplified in patients receiving combinations of acetylsalicylic acid with other antiplatelet agents, such as P2Y purinoceptor 12 ($P2Y_{12}$) inhibitors or proteinase-activated receptor (PAR)1 inhibitors or anticoagulant medications, including vitamin K antagonists and non-vitamin K antagonist oral anticoagulants (NOACs). Second, drugs for controlling blood pressure, lipid profiles, and blood glucose levels that are now established as effective in secondary prevention were not available at the time of the pivotal studies of acetylsalicylic acid. These drugs might decrease an individual's risk of cardiovascular events, which would mean that the relative benefits of acetylsalicylic acid therapy now translate into smaller absolute benefits than they did previously. This issue is probably amplified in the primary prevention setting, which might explain the small (if not trivial) benefit of long-term acetylsalicylic acid use observed in contemporary studies and meta-analyses of patients with cardiovascular risk factors or subclinical atherothrombosis[18]. Finally, the availability of new compounds with potent and consistent antithrombotic efficacy questions the traditionally pre-eminent role of acetylsalicylic acid. Numerous investigations are testing the hypothesis that new antithrombotic approaches that do not include acetylsalicylic acid have an increased net benefit for the patient owing to their capacity to reduce bleeding risk without impairing antithrombotic efficacy[19–22].

In light of these observations, interest has been growing in acetylsalicylic acid-free approaches for the prevention of cardiovascular disease and cardioembolic stroke. The goal of this manuscript is not to diminish the undisputed value of acetylsalicylic acid for secondary prevention in these settings. Data that support use of acetylsalicylic acid-free strategies are limited, and such strategies should not be advocated for use in routine clinical practice unless they are supported by clinical trial evidence. Nevertheless, insights on this emerging trend are needed. Therefore, in this Review, we summarize the state of the art of antithrombotic therapy (with or without acetylsalicylic acid) for cardiovascular disease and cardioembolic stroke prevention. We also focus on the scientific rationale, from bench to bedside, for the ongoing studies of 'acetylsalicylic acid-free' pharmacological strategies.

Benefits and risks

Cardiovascular disease prevention

Evidence supporting acetylsalicylic acid for secondary prevention dates back to 2009, with a meta-analysis of 16 trials (mostly published before the stent era) including a total of 17,000 individuals at high cardiovascular risk — mainly patients with prior myocardial infarction (MI) but also some with prior stroke or transient ischaemic attack. In the pooled analysis, acetylsalicylic acid treatment was associated with an 18% relative reduction in the annual incidence of major vascular events versus the control treatment (6.7% versus 8.2%; $P<0.0001$), including strokes (2.1% versus 2.5% per year; $P=0.002$) and coronary events (4.3% versus 5.3% per year; $P<0.0001$)[23]. However, acetylsalicylic acid was also associated with a significantly increased annual incidence of major bleeding events versus the control treatment (0.25% versus 0.06%; $P=0.01$)[23]. Among patients with a wide range of symptomatic vascular diseases (including previous MI, acute MI, previous stroke, acute stroke, or other high-risk conditions), in whom the annual risk of a serious vascular event is between 4% and 8%, treatment of 1,000 patients for 1 year with low-dose acetylsalicylic acid is calculated to prevent approximately 10–20 fatal

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and nonfatal ischaemic events. By contrast, the absolute harm associated with acetylsalicylic acid has been quantified as 1 or 2 major extracranial (mostly gastrointestinal) bleeding complications per 1,000 treated patients and 1–2 haemorrhagic strokes per 10,000 treated patients[24]. The incidence of such events could be higher among elderly individuals and those with cardiovascular risk factors that also increase the risk of bleeding, as well as in patients with a history of gastrointestinal bleeding or in those receiving concomitant treatment with NSAIDs or oral anticoagulants.

The role of acetylsalicylic acid in primary prevention of cardiovascular disease is not well established but has been reappraised in a 2016 meta-analysis of 11 trials, which included a total of 118,445 patients. At follow-up (between 3.6 and 10.1 years), acetylsalicylic acid use was associated with a reduction in the rate of nonfatal MI compared with that in controls (1.2% versus 1.4%; relative reduction 22%) but only a modest reduction in mortality (4.2% versus 4.3%; relative reduction 6%)[25]. In addition, acetylsalicylic acid was associated with increased rates of gastrointestinal bleeding (0.6% versus 0.4%; relative increase 59%) and haemorrhagic stroke (0.3% versus 0.2%; relative increase 33%)[26].

Cardioembolic stroke prevention

In a meta-analysis of seven trials that compared acetylsalicylic acid with either placebo (five trials) or no treatment (two trials) in patients with atrial fibrillation (AF), acetylsalicylic acid was associated with a nonsignificant 19% relative reduction in stroke[27]. This result was driven by the SPAF trial[28], published in 1991, which showed

Table 1 | **Current recommendations for acetylsalicylic acid use in secondary prevention**

Clinical setting	ESC recommendations	ACC and AHA recommendations	Refs
NSTE-ACSs	• Acetylsalicylic acid is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (in acetylsalicylic acid-naive patients) and a long-term maintenance dose of 75–100 mg daily regardless of treatment strategy (class I, level of evidence A)	• Non-enteric-coated, chewable acetylsalicylic acid (162–325 mg) should be given to all patients with NSTE-ACSs without contraindications as soon as possible after presentation, and a maintenance dose of acetylsalicylic acid (81–325 mg daily) should be continued indefinitely (class I, level of evidence A)	8,9
STEMI	• Antiplatelet therapy with low-dose acetylsalicylic acid (75–100 mg) is indicated (class I, level of evidence A)	• Acetylsalicylic acid 162–325 mg should be given before primary PCI (class I, level of evidence B) • Acetylsalicylic acid 162–325 mg should be given to patients with STEMI who receive fibrinolytic therapy (class I, level of evidence A) • After PCI, acetylsalicylic acid should be continued indefinitely (class I, level of evidence A) • It is reasonable to use 81 mg acetylsalicylic acid daily in preference to higher maintenance doses after primary PCI (class IIa, level of evidence B)	10,11
Stable CAD	• Low-dose acetylsalicylic acid daily is recommended in all patients with stable CAD (class I, level of evidence A)	• Treatment with acetylsalicylic acid 75–162 mg daily should be continued indefinitely in the absence of contraindications in patients with stable ischaemic heart disease (class I, level of evidence A) • Treatment with acetylsalicylic acid 75–162 mg and clopidogrel 75 mg daily might be reasonable in selected high-risk patients with stable ischaemic heart disease (class IIb, level of evidence B)	12,13
PCI	• Acetylsalicylic acid is indicated before elective stenting (class I, level of evidence B) • An acetylsalicylic acid loading dose of 150–300 mg (oral) or 80–150 mg (intravenous) is recommended in patients who are not pretreated (class I, level of evidence C) • Lifelong antiplatelet monotherapy, usually acetylsalicylic acid, is recommended (class I, level of evidence A)	• Patients already receiving daily acetylsalicylic acid therapy should take 81–325 mg acetylsalicylic acid before PCI (class I, level of evidence B) • Patients not receiving acetylsalicylic acid therapy should be given non-enteric-coated acetylsalicylic acid 325 mg before PCI (class I, level of evidence B)	14,15
Secondary prevention	• In ACS, a $P2Y_{12}$ inhibitor for 12 months is recommended in addition to acetylsalicylic acid, unless there are contraindications such as excessive risk of bleeding (class I, level of evidence A) • In the chronic phase (>12 months) after MI, acetylsalicylic acid is recommended (class I, level of evidence A) • In patients with non-cardioembolic ischaemic stroke or TIA, acetylsalicylic acid only, dipyridamole plus acetylsalicylic acid, or clopidogrel alone is recommended (class I, level of evidence A)	• Acetylsalicylic acid 75–162 mg daily is recommended in all patients with CAD unless contraindicated (class I, level of evidence A) • In patients with extracranial carotid or vertebral atherosclerosis who have had an ischaemic stroke or TIA, treatment with acetylsalicylic acid alone (75–325 mg daily), clopidogrel alone (75 mg daily), or the combination of acetylsalicylic acid plus extended-release dipyridamole (25 mg and 200 mg twice daily, respectively) should be started and continued (class I, level of evidence B) • For patients with symptomatic atherosclerotic peripheral artery disease of the lower extremities, antiplatelet therapy with acetylsalicylic acid (75–325 mg daily) or clopidogrel (75 mg daily) should be started and continued (class I, level of evidence A)	16,17

ACS, acute coronary syndrome; CAD, coronary artery disease; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; $P2Y_{12}$, P2Y purinoceptor 12; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischaemic attack.

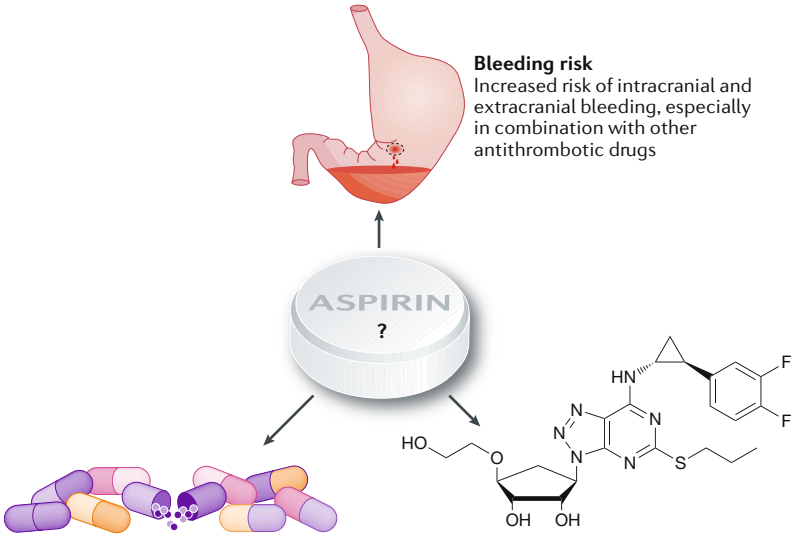

Fig. 1 | **Uncertainties surrounding the use of acetylsalicylic acid for secondary prevention.** Three major arguments challenge the use of acetylsalicylic acid for secondary prevention in combination therapy with other antithrombotic drugs. Firstly, acetylsalicylic acid is associated with an increased risk of intracranial and extracranial (for example, gastrointestinal) bleeding, especially when administered in combination with other antithrombotic drugs. Secondly, contemporary antithrombotic drugs favourably alter an individual's baseline risk of cardiovascular events, which translates the relative benefits of acetylsalicylic acid into smaller absolute effects. Finally, the availability of new compounds with potent antithrombotic efficacy could make the use of acetylsalicylic acid no longer necessary.

a treatment effect of 44% compared with placebo, with no apparent increase in clinically relevant bleeding events. However, in a post hoc analysis of the trial data, acetylsalicylic acid reduced the occurrence of strokes categorized as non-cardioembolic significantly more than it did those categorized as cardioembolic (risk reduction 100% versus 31%; $P=0.01$)[29]. The recognition of the specific nature of thrombi in patients with AF (that is, less platelet-dependent than arterial thrombi generated in conditions of high shear stress) shifted the research focus towards studying alternative strategies for cardioembolic stroke prevention. As discussed below, this effort culminated in the introduction of oral anticoagulation therapy for secondary prevention in patients with AF.

Off-target noncardiac effects

Acetylsalicylic acid use can be associated with favourable and unfavourable noncardiac (off-target) effects. In particular, permanent COX1 inactivation might increase the risk of upper gastrointestinal bleeding through inhibition of thromboxane A_2-mediated platelet aggregation and dose-dependent impairment of prostaglandin-mediated cytoprotection in the gastrointestinal mucosa. Also, concomitant use of reversible COX1 inhibitors (NSAIDs such as ibuprofen and naproxen) exerts a competitive effect on the irreversible acetylation of platelets by acetylsalicylic acid, with uncertain clinical consequences[30]. By contrast, other mechanisms of action (such as acetylation of proteins in blood coagulation, inhibition of cyclooxygenase 2 (COX2; also known as prostaglandin G/H synthase 2) activity, and COX-independent mechanisms) have been invoked to explain some favourable effects of acetylsalicylic acid beyond suppression of thromboxane A_2-mediated platelet activation and aggregation[24]. These effects include the prevention of venous thromboembolism, a reduced risk of neurocognitive impairment (which might result from platelet-related reduced brain inflammation), and the chemoprevention of colorectal cancer resulting from interference with neoplastic transformation of the intestinal mucosa and tumour progression[31]. Several prospective trials are ongoing to confirm or disprove these chemopreventive effects of acetylsalicylic acid, which seem to begin about 10 years after the initiation of chronic use for cardiovascular prevention[31,32]. These chemopreventive effects were initially attributed to earlier diagnosis, particularly in relation to mild gastrointestinal bleeding in patients receiving long-term acetylsalicylic acid therapy; this factor might operate in isolation or in combination with the other protective effects of acetylsalicylic acid.

The relevance of these noncardiac effects of acetylsalicylic acid is endorsed by the latest US Preventive Services Task Force recommendations, in which low-dose acetylsalicylic acid is indicated for the primary prevention of both cardiovascular disease and colorectal cancer in adults aged 50–59 years who have a 10-year cardiovascular risk of ≥10%, are not at increased risk of bleeding, have a life expectancy of ≥10 years, and are willing to take low-dose acetylsalicylic acid daily for ≥10 years[33]. Because renouncing the downregulation of platelets by low-dose acetylsalicylic acid can lead to the loss of these potential noncardiac long-term benefits, this loss should be accounted for in the design of studies investigating acetylsalicylic acid-free strategies by the inclusion of outcomes measures that capture the full spectrum of benefits and risks associated with acetylsalicylic acid therapy.

Adjunctive antithrombotic therapy

The persistence of a residual risk of recurrent cardiovascular events despite acetylsalicylic acid therapy led to the initiation of multiple trials to explore the effects of adjunctive antithrombotic therapies on a background of acetylsalicylic acid for a variety of disease presentations (FIG. 2; TABLE 2).

Cardiovascular disease

Acute coronary syndromes. The most notable adjunctive strategy consists of adding a $P2Y_{12}$ inhibitor to acetylsalicylic acid, a strategy known as dual antiplatelet therapy (DAPT). The benefit of DAPT (specifically the combination of acetylsalicylic acid and clopidogrel) was demonstrated in patients with an acute coronary syndrome (ACS) from the CURE trial[34], which showed a 20% relative reduction in ischaemic events at 1 year (9.3% versus 11.4%; $P<0.001$), albeit at the expense of a 38% relative increase in major bleeding (3.7% versus 2.7%; $P=0.001$). In current guidelines, 1 year of DAPT has a class Ia recommendation in patients after an ACS[8–11,35]. The benefits

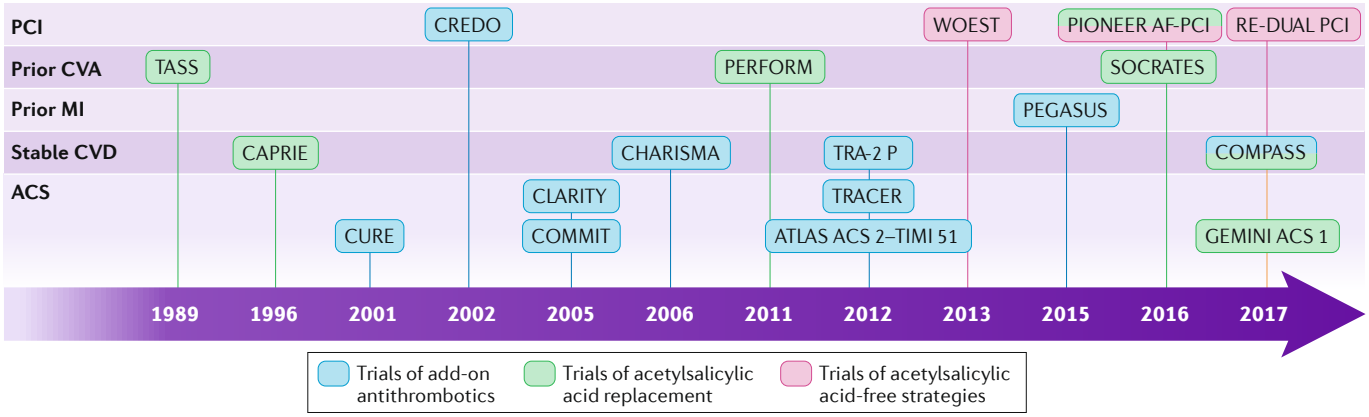

Fig. 2 | **Trials of antithrombotic approaches in cardiovascular diseases.** A timeline of studies investigating antithrombotic therapies across different presentations of cardiovascular disease. Studies are categorized on the basis of their therapeutic strategies with respect to acetylsalicylic acid: trials of add-on antithrombotic therapy; trials of acetylsalicylic acid replacement; and trials of acetylsalicylic acid withdrawal. ACS, acute coronary syndromes; CVA, cerebrovascular accident; CVD, cardiovascular disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

of DAPT (acetylsalicylic acid and clopidogrel) were subsequently confirmed in patients with acute MI[36,37] and those undergoing percutaneous coronary intervention (PCI)[38], in whom DAPT also has a class Ia recommendation[35,39]. In patients with an invasively managed ACS, doubling the maintenance dose of clopidogrel increased the risk of major bleeding and did not result in any improvement in efficacy over the standard (75 mg) clopidogrel dose, although the increased dose did benefit those who ultimately underwent PCI after randomization[40,41].

Despite the benefits associated with adjunctive clopidogrel, numerous pharmacodynamic investigations showed that some treated individuals had persistently high on-treatment platelet reactivity (also characterized as a poor clopidogrel response) and increased rates of atherothrombotic complications, particularly in-stent thrombosis[42]. This observation, along with pharmacokinetic issues, led to the development of more-potent oral $P2Y_{12}$ inhibitors, such as prasugrel and ticagrelor, which are characterized by predictable, potent, and rapid pharmacodynamic effects. In patients with ACSs, DAPT with prasugrel or ticagrelor proved better than DAPT with clopidogrel in reducing ischaemic recurrences, including in-stent thrombosis, but this effect was accompanied by increased rates of spontaneous (that is, nonprocedural) major bleeding in the TRITON[43] and PLATO trials[44]. In a subsequent trial, conducted in patients with a medically managed ACS, prasugrel was not superior to clopidogrel in the whole trial cohort, although the subgroup of patients who had undergone angiography did seem to benefit[45,46].

Some studies have assessed the effect of adding a third antithrombotic agent to standard DAPT (mainly acetylsalicylic acid and clopidogrel) in patients with an ACS. The addition of vorapaxar (an antiplatelet drug that targets PAR1) to DAPT did not significantly reduce the risk of ischaemic events in the TRACER trial[47], and the risk of bleeding, including intracranial haemorrhage, was unacceptably high. Notably, the subgroup of patients who underwent bare-metal stent implantation at the time of PCI and subsequently received a truncated course of DAPT showed greater benefit and less bleeding liability from the addition of vorapaxar to the standard of care[48].

Adding a very low dose of the NOAC rivaroxaban to DAPT in patients with an ACS but no formal indication for oral anticoagulation therapy (such as those with AF, for example) resulted in a significant reduction in ischaemic events — but again, at the price of an increase in major bleeding, particularly gastrointestinal bleeding — in the ATLAS ACS-2 trial[49]. Conversely, full-dose anticoagulation with apixaban (in most patients, added to DAPT) in high-risk patients with an ACS did not reduce ischaemic events but did increase major bleeding in the APPRAISE-2 trial[50]. Collectively, the results of these studies underscore the importance of avoiding testing new antithrombotic drugs solely on a background of existing combination therapies, as this approach is very likely to increase the risk of bleeding and to hamper the opportunity to observe the benefit of blocking new targets.

If the studies investigating blockade of an adjunctive pathway (that is, targeting thrombin on the platelet membrane using vorapaxar or targeting circulating thrombin using a NOAC) had been conducted in the absence of acetylsalicylic acid, we might reasonably argue that the clinical benefit associated with the blockade of this thrombotic pathway might more easily have been unravelled. Understanding how monotherapy with some of these novel antithrombotic approaches would perform compared with standard DAPT and other approaches would also be of interest.

Secondary prevention in other high-risk groups. In individuals at high risk of atherothrombotic events despite the absence of a recent ACS, DAPT with clopidogrel was not significantly more effective than acetylsalicylic acid monotherapy in the CHARISMA trial[51], but some benefit was discernible in those with established atherothrombosis. In the TRA-2 P trial[52], vorapaxar added to

either single-agent antiplatelet therapy or DAPT reduced the risk of ischaemic events in patients with a history of MI, ischaemic stroke, or peripheral artery disease (PAD); however, this treatment increased the relative risk of moderate or severe bleeding by 66%. In the PEGASUS trial[53], DAPT with ticagrelor was superior to acetylsalicylic acid monotherapy in patients with prior MI, but increased the risk of major bleeding. Long-term DAPT, preferably with ticagrelor 60 mg twice daily, is a strategy currently recommended by European and US guidelines for high-risk patients with prior MI, in whom this approach has a class IIb recommendation[35,39]. In aggregate, these data suggest that adding antiplatelet drugs to acetylsalicylic acid increases the risk of major bleeding but also has beneficial effects for some patients with atherothrombotic conditions[54]. Interestingly, a clear benefit of adding acetylsalicylic acid to other antiplatelet drugs has never been proved. In the MATCH trial[55], conducted in patients with prior stroke, DAPT with acetylsalicylic acid and clopidogrel was not superior to clopidogrel monotherapy and was associated with an increased risk of major and life-threatening bleeding. This study unfortunately did not include a control group who received acetylsalicylic acid only, which makes the net benefit of acetylsalicylic acid difficult to discern in this context.

Dual-pathway antithrombotic therapy (in which an antiplatelet agent is combined with an anticoagulant rather than another antiplatelet drug) is undergoing investigation in secondary prevention trials. In the

Table 2 | **Trials of add-on antithrombotic therapies on a background of acetylsalicylic acid**

Study	*n*	Population	Treatment groups	Outcomes (intervention versus control)	Refs
CURE	12,562	ACS	Clopidogrel versus placebo	• Cardiovascular death, nonfatal MI, or stroke at 12 months: 9.3% versus 11.4%; $P<0.001$ • Major bleeding at 12 months: 3.7% versus 2.7%; $P=0.001$	34
CLARITY	3,491	ACS undergoing fibrinolysis	Clopidogrel versus placebo	• Death, nonfatal MI, or occluded infarct-related artery on angiography at 3–8 days: 15.0% versus 21.7%; $P<0.001$ • Major bleeding at 3–8 days: 1.3% versus 1.1%; NS	36
COMMIT	45,852	ACS invasively managed	Clopidogrel versus placebo	• Death, nonfatal MI, or stroke at 28 days: 9.2% versus 10.1%; $P=0.002$ • Major bleeding in-hospital: 0.6% versus 0.6%; NS	37
CREDO	2,116	PCI	Clopidogrel versus placebo	• Death, nonfatal MI, or stroke at 28 days: 6.8% versus 8.3%; NS • Death, nonfatal MI, or stroke at 12 months: 26.9% reduction with clopidogrel; $P=0.02$ • Major bleeding at 12 months: 8.8% versus 6.7%; NS	38
CURRENT	25,086	ACS	High-dose clopidogrel versus standard dose	• Death, nonfatal MI, or stroke at 30 days: 4.2% versus 4.4%; NS • Major bleeding at 30 days: 2.5% versus 2.0%; $P=0.01$	40
TRITON	13,608	ACS undergoing PCI	Prasugrel versus clopidogrel	• Cardiovascular death, nonfatal MI, or stroke at 15 months: 9.9% versus 12.1%; $P<0.001$ • Major bleeding at 15 months: 2.4% versus 1.8%; $P=0.03$	43
TRILOGY	7,243	ACS without revascularization	Prasugrel versus clopidogrel	• Cardiovascular death, nonfatal MI, or stroke at 17 months: 13.9% versus 16.0%; NS	45
PLATO	18,624	ACS	Ticagrelor versus clopidogrel	• Cardiovascular death, nonfatal MI, or stroke at 12 months: 9.8% versus 11.7%; $P<0.001$ • Major bleeding at 12 months: 4.5% versus 3.8%; $P=0.03$	44
TRACER	12,944	ACS	Vorapaxar versus placebo	• Cardiovascular death, nonfatal MI, or stroke at 24 months: 14.7% versus 16.4%; $P=0.02$ • Moderate or severe bleeding at 24 months: 7.2% versus 5.2%; $P<0.001$	47
ATLAS ACS-2	15,526	ACS	Rivaroxaban versus placebo	• Cardiovascular death, nonfatal MI, or stroke at 24 months: 8.9% versus 10.7%; $P=0.008$ • Major bleeding at 24 months: 2.1% versus 0.6%; $P<0.001$	49
CHARISMA	15,603	CVD or multiple risk factors	Clopidogrel versus placebo	• Cardiovascular death, nonfatal MI, or stroke at 28 months: 6.8% versus 7.3%; NS • Severe bleeding at 28 months: 1.7% versus 1.3%; NS	51
PEGASUS	21,162	Prior MI	Ticagrelor 60 mg twice daily or 90 mg twice daily versus placebo	• Cardiovascular death, nonfatal MI, or stroke at 36 months (ticagrelor 90 mg): 7.9% versus 9.0%; $P=0.008$ • Major bleeding at 36 months (ticagrelor 90 mg): 2.6% versus 1.1%; $P<0.001$ • Cardiovascular death, nonfatal MI, or stroke at 36 months (ticagrelor 60 mg): 7.8% versus 9.0%; $P=0.004$ • Major bleeding at 36 months (ticagrelor 60 mg): 2.3% versus 1.1%; $P<0.001$	53
TRA-2 P	26,449	Prior MI, prior stroke, or PAD	Vorapaxar versus placebo	• Cardiovascular death, nonfatal MI, or stroke at 36 months: 9.3% versus 10.5%; $P<0.001$ • Moderate or severe bleeding at 36 months: 4.2% versus 2.5%; $P<0.001$	52
COMPASS	27,395	Prior MI or PAD	Rivaroxaban versus placebo	• Cardiovascular death, nonfatal MI, or stroke at 23 months: 4.1% versus 5.4%; $P<0.0001$ • Major bleeding at 23 months: 3.1% versus 1.9%; $P<0.0001$	56

ACS, acute coronary syndrome; CVD, cardiovascular disease; MI, myocardial infarction; NS, not significant; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

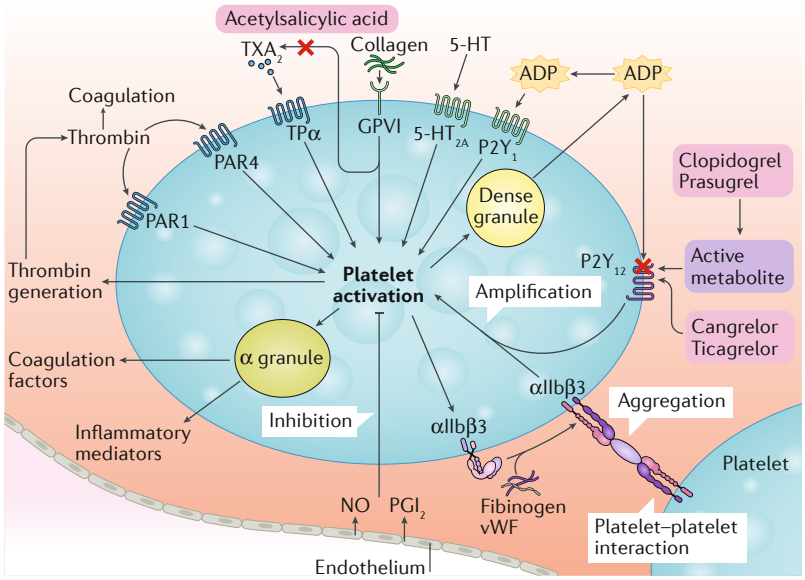

Fig. 3 | **Platelet activation mechanisms.** Platelet activation is initiated by soluble agonists, such as thrombin, thromboxane A_2 (TXA_2), 5-hydroxytryptamine (5-HT), ADP (via P2Y purinoceptor 1 ($P2Y_1$)), and ATP, and by adhesive ligands, such as collagen and von Willebrand factor (vWF). Consequently, dense granule secretion of platelet agonists and secretion of TXA_2, as a result of phospholipase A_2 activation, lead to amplification of platelet activation and the associated responses. The P2Y purinoceptor 12 ($P2Y_{12}$) receptor has a major role in the amplification of platelet activation, which is also supported by outside-in signalling via integrin αIIbβ3 (the glycoprotein IIb/IIIa receptor). Combined inhibition of TXA_2 release and $P2Y_{12}$ activation has additive effects on collagen-induced platelet activation and the associated platelet responses. 5-HT_{2A}, 5-HT receptor 2A; GPVI, platelet glycoprotein VI; NO, nitric oxide; PAR, proteinase-activated receptor; PGI_2, prostacyclin receptor; TPα, TXA_2 receptor isoform α. Adapted from REF.[71], Macmillan Publishers Limited.

COMPASS trial[56], a total of 27,395 patients with stable coronary artery disease or PAD and no indication for oral anticoagulation were randomly assigned to rivaroxaban alone or in combination with acetylsalicylic acid or to acetylsalicylic acid monotherapy. This study was stopped early (after a mean follow-up of 23 months) owing to evidence of a significant reduction in ischaemic outcomes, including a significant reduction in cardiovascular mortality, in the group receiving rivaroxaban 2.5 mg twice daily plus acetylsalicylic acid (relative reduction 24%; 4.1% versus 5.4%; $P < 0.001$), albeit at the price of a significant increase in major bleeding (but no significant increase in fatal and intracranial bleeding) compared with placebo (relative increase 70%; 3.1% versus 1.9%; $P < 0.001$).

Cardioembolic stroke

In patients with AF who are unsuitable for oral anticoagulation therapy, DAPT reduces the risk of major vascular events, especially stroke, by 11% compared with acetylsalicylic acid monotherapy[57]. However, in patients amenable to oral anticoagulation, DAPT was associated with a 44% relative increase in thrombotic events[58], rendering it clearly inferior to vitamin K antagonists. In these patients, moreover, NOACs are also preferable to vitamin K antagonists owing to the increased risk of intracranial haemorrhage, stroke, and death associated with the latter, despite some hints of increased gastrointestinal bleeding in patients receiving NOACs[59]. In a randomized trial of apixaban compared with acetylsalicylic acid monotherapy for patients with AF for whom vitamin K antagonist therapy was unsuitable, apixaban reduced the risk of stroke or systemic embolism by 55% without increasing the risk of bleeding[60]. In aggregate, these data suggest that acetylsalicylic acid monotherapy has no role in cardioembolic stroke prevention at present.

Importantly, patients receiving both oral anticoagulation and antiplatelet therapy (such as patients with AF who develop an ACS and/or undergo PCI) experience an increased risk of nonfatal and fatal bleeding compared with patients receiving acetylsalicylic acid monotherapy. The extent of the increase in risk depends on the number and type of antithrombotic agents: 1.84-fold for acetylsalicylic acid and vitamin K antagonists, 3.50-fold for clopidogrel and vitamin K antagonists, and 4.00-fold for triple antithrombotic therapy with acetylsalicylic acid, clopidogrel, and vitamin K antagonists[61]. Not surprisingly, as noted below, the initial attempts to investigate the effect of dropping acetylsalicylic acid as an approach to reduce bleeding complications while preserving antithrombotic efficacy were made in this particular category of patients at high bleeding risk[35,62,63].

Patients undergoing transcatheter aortic valve implantation (TAVI) can experience cardioembolic stroke, either as a consequence of the procedure (typically within 48 h) or later (owing to patient-related factors such as AF and/or valve-related factors such as exposure of the stent surface and leaflet thrombosis)[64]. In patients who are not receiving oral anticoagulation, DAPT seems to be associated with an increased risk of major or life-threatening events compared with acetylsalicylic acid and does not decrease the risk of ischaemic events, but more evidence from large studies is needed[65,66].

Pharmacodynamics of drug withdrawal

When tests that specifically assess COX1 activity are used, acetylsalicylic acid resistance is infrequently observed, and when such resistance is present, it is typically attributed to poor treatment adherence[18]. Commercially available regimens of 75–100 mg acetylsalicylic acid daily clearly exceed the minimal dose required for a full pharmacodynamic effect (that is, complete platelet COX1 blockade)[4]. However, the pharmacodynamic profiles of different oral $P2Y_{12}$ inhibitors can lead to variable degrees of blockade of the $P2Y_{12}$ signalling pathway. In particular, clopidogrel is associated with a broader range of interindividual response profiles, and high on-treatment platelet reactivity is observed in a sizeable proportion of treated patients[42]. This variable platelet response is diminished but not abolished by prasugrel and ticagrelor[67].

The DAPT approach reflects the evidence that acetylsalicylic acid and $P2Y_{12}$ antagonists independently inhibit the thromboxane A_2-dependent and $P2Y_{12}$-dependent pathways of platelet activation and consequently have additive or synergistic inhibitory effects on platelet activation[68]. Activation of platelet $P2Y_{12}$ by ADP causes a series of intracellular events that ultimately lead to amplification of platelet activation and stabilization of the platelet aggregate[69–71] (FIG. 3). In doing so, the

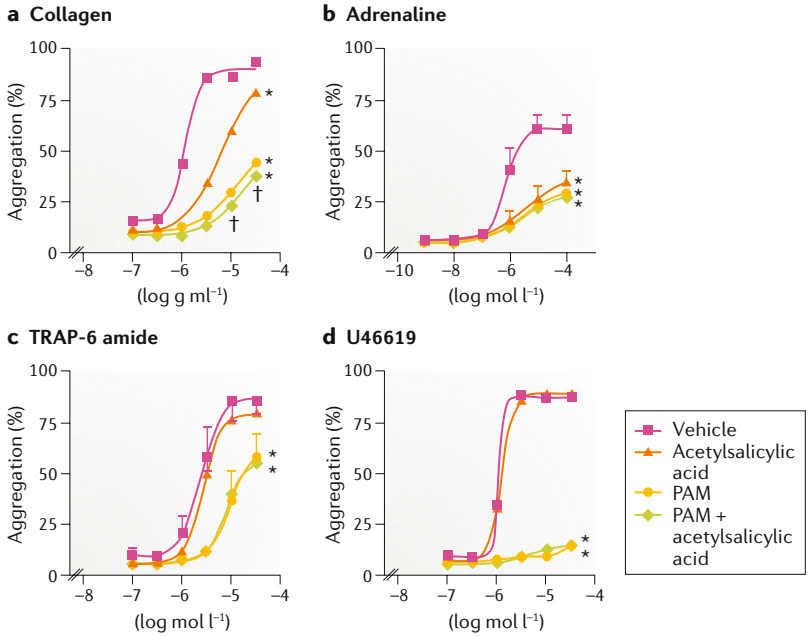

Fig. 4 | **In the presence of strong $P2Y_{12}$ receptor blockade, acetylsalicylic acid provides little additional inhibition of platelet aggregation.** In these studies, platelet aggregation was induced by four different platelet agonists: collagen 0.1–30.0 µg/ml (part **a**), adrenaline 0.001–100.0 µmol/l (part **b**), the synthetic proteinase-activated receptor 1 (PAR1) antagonist TRAP-6 amide (H-Ser–Phe–Leu–Leu–Arg–Asn–NH_2) 0.1–30.0 µmol/l (part **c**), and the thromboxane A_2 mimetic U46619 0.1–30.0 µmol/l (part **d**) in the presence of acetylsalicylic acid 30.0 µmol/l and/or prasugrel active metabolite (PAM) 3.0 µmol/l. The data shown are mean ± SEM responses measured by 96-well plate aggregometry in citrated platelet-rich plasma prepared from four different individuals. *$P < 0.05$ for difference from vehicle by two-way analysis of variance (ANOVA) plus a Bonferroni post hoc test. †$P < 0.05$ for difference between PAM and PAM plus acetylsalicylic acid. Symbols at the end of lines signify the difference in sets; symbols at individual points signify particular differences. Adapted with permission from REF.[81], John Wiley and Sons.

$P2Y_{12}$ signalling pathway also interacts with other non-purinergic platelet signalling pathways. In particular, the blockade of platelet $P2Y_{12}$ inhibits thromboxane A_2-dependent pathways of platelet activation independently of acetylsalicylic acid through inhibiting the effects of thromboxane A_2-induced ADP release[72–75]. Blockade of platelet $P2Y_{12}$ also interferes with thromboxane A_2-independent processes, such as thrombin generation and thrombin receptor activation[74,76]. Of note, however, acetylsalicylic acid suppresses thromboxane A_2 generation (which contributes to platelet procoagulant activity) to a much larger extent than $P2Y_{12}$ does, whereas activation of $P2Y_{12}$ has little or no effect on thromboxane A_2 generation under physiological conditions[77–79].

Moreover, some data suggest that off-target effects (those that are not secondary to platelet COX1 blockade) of acetylsalicylic acid are more apparent with high-dose regimens[80]. However, the potential clinical benefits of these pharmacodynamic findings are unknown, and high-dose acetylsalicylic acid therapy carries a well-established increase in the risk of bleeding complications[4]. Some data show little additional platelet inhibition following stimuli with several agonists in the presence of potent $P2Y_{12}$ receptor blockade[81] (FIG. 4). Although these findings have been shown with collagen-induced platelet aggregation (a sensitive marker of acetylsalicylic acid-induced effects), this observation has been attributed to lack of sufficient shear stress in these experiments because a much greater additive effect of aspirin is seen when using conventional aggregometry[77,78]. However, thromboxane A_2 has little influence on the response to platelet agonists other than collagen, in contrast to the wide-reaching effects of ADP mediated by $P2Y_{12}$ activation. These considerations raise the hypothesis that potent platelet $P2Y_{12}$ inhibition alone might provide sufficient reduction in platelet reactivity to prevent arterial thrombotic events[77,81,82].

Notably, in the PLATO trial[44], the use of high acetylsalicylic acid doses (>100 mg) appeared to blunt the benefits of ticagrelor[83]. Although the reasons for this treatment interaction have not been clearly elucidated[84,85], this finding suggests that such high maintenance doses of acetylsalicylic acid interfere with the efficacy of at least ticagrelor, if not other $P2Y_{12}$ antagonists. Unlike prasugrel, for instance, ticagrelor might also have off-target effects that contribute to drug-specific adverse effects (such as dyspnoea) and might also make this agent a potential treatment option when considering a strategy of antiplatelet monotherapy[86]. These effects are mediated by inhibition of equilibrative nucleoside transporter 1 (ENT1), which mediates influx and efflux of nucleosides across cell membranes. ENT1 has particular affinity for adenosine, so ENT1 inhibition reduces cellular uptake of adenosine, which increases its circulating levels and biological activity, particularly at sites of ischaemia and tissue injury[86]. In the PLATO trial[87], ticagrelor reduced the risk of death compared with clopidogrel, a finding that has been attributed not only to atherothrombotic protection and prevention of sudden death but also possibly to differential effects on the immune system, as indicated by reductions in episodes of sepsis and pulmonary adverse events[88]. In aggregate, these notions offer justification for comparative studies of potent $P2Y_{12}$ blockade versus conventional DAPT, as the same benefit on atherothrombotic complications could be obtained with reduced bleeding risk with $P2Y_{12}$ blockade alone.

Targeting thrombin-mediated platelet activation by treatment with direct factor Xa inhibitors (such as rivaroxaban) and/or by removing acetylsalicylic acid from the antithrombotic combination also represents an interesting line of research supported by a sound pharmacodynamic rationale. Indeed, rivaroxaban exerts indirect antiplatelet effects by reducing levels of thrombin, a PAR agonist[89]. In humans, four PARs (PAR1–PAR4) have been identified and are expressed on the membranes of platelets and several cell types, including endothelial cells, leukocytes, and smooth muscle cells[90]. PAR1, PAR3, and PAR4 are activated rapidly by thrombin, and PAR1 can also be activated by tissue factor–factor VIIa complexes and factor Xa. PAR2 can be activated by factor Xa or tissue factor–factor VIIa complexes, but not by thrombin[91]. In a pig model, rivaroxaban reduced the weight of experimentally induced stent thrombus by 66% versus that in controls, and the effect size was dose-dependent, which suggests some degree of thrombin-mediated antithrombotic efficacy[92].

However, adding rivaroxaban to acetylsalicylic acid yielded thrombus reduction of 86%, and rivaroxaban in combination with DAPT almost completely suppressed in-stent thrombus formation (thrombus reduction of 98%). By contrast, the reduction in thrombus formation with DAPT alone was 79%[92]. In vitro investigations have confirmed that rivaroxaban inhibits thrombin generation in a concentration-dependent manner; this effect is enhanced with the addition of ticagrelor or ticagrelor plus acetylsalicylic acid[93]. Moreover, rivaroxaban and ticagrelor inhibit tissue factor-induced platelet aggregation in a concentration-dependent manner, and their combination synergistically increases this inhibition (FIG. 5). These data support the hypothesis of an antiplatelet effect of rivaroxaban. In particular, the synergistic effects on platelet inhibition achieved with rivaroxaban and ticagrelor support the potential use of this combination for preventing thrombosis after stent deployment. However, suboptimal protection against cardiovascular events was afforded by low-dose rivaroxaban monotherapy in the COMPASS trial[56], in comparison with that provided by combinations including at least one antiplatelet agent. The early cessation of this trial (owing to detection of a significant benefit in the combination treatment group compared with the acetylsalicylic acid-only group) might have hampered a definitive comparison between the two strategies.

Overall, the results of pharmacodynamic investigations indicate that no other commercially available antithrombotic agent can replace the selective inhibitory effects of acetylsalicylic acid on platelet COX1. Indeed, the synergism shown between acetylsalicylic acid and other antithrombotic agents, as described above, might be the reason that combinations that include another agent plus acetylsalicylic acid can be more effective than either treatment alone. However, many antithrombotic agents have wider-reaching properties than acetylsalicylic acid, enabling an increased magnitude of antithrombotic effects. As a consequence, adjunctive treatment with acetylsalicylic acid might not be required to achieve an appropriate balance of efficacy and safety. This hypothesis is the subject of ongoing clinical investigations, discussed below.

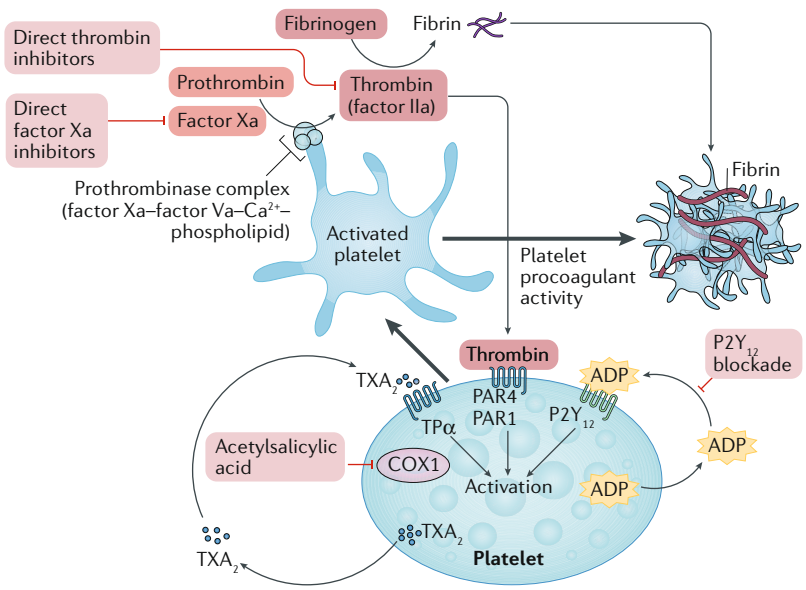

Fig. 5 | **Synergy of oral anticoagulant and antiplatelet therapy.** Oral anticoagulant therapy, including direct inhibitors of factor IIa or factor Xa, and antiplatelet agents, such as acetylsalicylic acid and $P2Y_{12}$ inhibitors, synergistically target two essential components of thrombosis: coagulation and platelet activation. COX1, cyclooxygenase 1; PAR, proteinase-activated receptor; $P2Y_{12}$, P2Y purinoceptor 12; TXA_2, thromboxane A_2; TPα, TXA_2 receptor isoform α.

Acetylsalicylic acid-free strategies

Acetylsalicylic acid replacement

Comparisons of acetylsalicylic acid with other antiplatelet monotherapies have yielded mixed results (TABLE 3). In the CAPRIE trial[94], clopidogrel provoked less gastrointestinal bleeding and proved more effective than acetylsalicylic acid in patients with various presentations of atherothrombosis, namely, prior MI, stroke, and PAD. These findings were consistent across all disease subgroups, although the greatest benefit was observed in patients with PAD. Event rates with clopidogrel were numerically lower than with acetylsalicylic acid in patients with prior stroke, although the opposite pattern was evident in patients with MI. However, the benefits of clopidogrel over acetylsalicylic acid were amplified in patients at high vascular risk (that is, with prior MI or stroke) or with concomitant diabetes[95,96]. An observational study of 3,243 patients who received drug-eluting stents further corroborated these findings by showing that clopidogrel monotherapy achieved a reduction in recurrent ischaemic events compared with acetylsalicylic acid monotherapy after 12 months of DAPT[97].

In the EUCLID trial[98], ticagrelor was not more beneficial than clopidogrel in patients with PAD. The use of acetylsalicylic acid versus other antiplatelet monotherapies for secondary prevention in the setting of prior stroke also remains an area of uncertainty[99]. Ticlopidine was somewhat superior to acetylsalicylic acid in patients with prior stroke from the small TASS trial[100], but this was not the case for terutroban in the PERFORM trial[101] or ticagrelor in the SOCRATES trial[102].

In the GEMINI-ACS-1 trial[103], a phase II study of patients with a stabilized ACS, a dual-pathway antithrombotic approach that combined low-dose rivaroxaban with a $P2Y_{12}$ inhibitor demonstrated a similar risk of clinically significant bleeding compared with DAPT. In an exploratory analysis, the combined frequency of ischaemic events did not differ between the dual-pathway and DAPT strategies, and no significant interaction by treatment assignment was noted in patients treated with ticagrelor versus clopidogrel[103]. Indeed, a large-scale phase III investigation in patients with an ACS is warranted to determine whether a dual-pathway antithrombotic approach combining low-dose rivaroxaban with a $P2Y_{12}$ inhibitor is superior to standard DAPT.

In the above-mentioned COMPASS trial[56], although the early termination of the trial resulted in a missed opportunity to unravel fully the efficacy and safety profile of rivaroxaban 5 mg monotherapy, the patients in this treatment group did not demonstrate any

Table 3 | **Trials of acetylsalicylic acid-free and acetylsalicylic acid replacement strategies**

Study	*n*	Population	Treatment groups	Outcomes (intervention versus control)	Refs
Acetylsalicylic acid-free strategies					
WOEST	573	Oral anticoagulation and undergoing PCI	Clopidogrel versus DAPT	• Any bleeding at 12 months: 19.4% versus 44.4%; $P<0.0001$	104
PIONEER AF-PCI	2,124	AF and undergoing PCI	Rivaroxaban plus clopidogrel versus VKA plus DAPT	• Clinically significant bleeding at 23 months: 16.8% versus 26.7%; $P<0.001$	105
RE-DUAL PCI	2,725	AF and undergoing PCI	Dabigatran 110 mg twice daily or 150 mg twice daily and clopidogrel or ticagrelor versus VKA plus DAPT	• Major or clinically relevant non-major bleeding at 14 months (dabigatran 150 mg): 20.2% versus 25.7%; $P<0.001$ for noninferiority • Major or clinically relevant non-major bleeding at 14 months (dabigatran 110 mg): 15.4% versus 26.9%; $P<0.001$ for noninferiority; $P<0.001$ for superiority • Death, nonfatal MI, stroke, systemic embolism, or unplanned revascularization at 14 months: 13.7% versus 13.4%; $P=0.005$ for noninferiority	107
Acetylsalicylic acid replacement strategies					
CAPRIE	19,185	Prior MI, prior stroke, or PAD	Clopidogrel versus acetylsalicylic acid	• Cardiovascular death, nonfatal MI, or stroke per year: 5.3% versus 5.8%; $P=0.043$ • Severe bleeding: 1.4% versus 1.6%; NS	94
TASS	3,069	Prior stroke or TIA	Ticlopidine versus acetylsalicylic acid	• Death or stroke at 36 months: 17% versus 19%; $P=0.048$ • Any bleeding at 36 months: 9% versus 10%; NS	100
PERFORM	9,562	Prior stroke or TIA	Terutroban versus acetylsalicylic acid	• Cardiovascular death, nonfatal MI, or stroke at 28 months: 11% versus 11%; NS • Minor bleeding at 28 months: 12% versus 11%; $P<0.05$	101
SOCRATES	13,199	Prior stroke or TIA	Ticagrelor versus acetylsalicylic acid	• Death, nonfatal MI, or stroke at 3 months: 6.7% versus 7.5%; NS • Major bleeding: 0.5% versus 0.6%; NS	102
GEMINI ACS 1	3,037	ACS	Rivaroxaban versus acetylsalicylic acid	• Major bleeding at 12 months: 5% versus 5%; NS	103
COMPASS	27,395	Prior MI or PAD	Rivaroxaban versus acetylsalicylic acid	• Cardiovascular death, nonfatal MI, or stroke at 23 months: 4.9% versus 5.4%; NS • Major bleeding at 23 months: 2.8% versus 1.9%; $P<0.0001$	56

ACS, acute coronary syndrome; AF, atrial fibrillation; DAPT, dual antiplatelet therapy; MI, myocardial infarction; NS, not significant; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

improvement in clinical outcomes compared with those receiving placebo and did show a significant increase in bleeding complications. In aggregate, the results of COMPASS support the concept of dual-agent antithrombotic therapy with rivaroxaban 2.5 mg twice daily plus acetylsalicylic acid (which achieved a reduction in ischaemic outcomes versus placebo, including a significant reduction in cardiovascular mortality) but do not support the use of rivaroxaban monotherapy for secondary prevention in patients with stable atherosclerosis. Although the results of the COMPASS trial seem to argue against the need for additional studies to assess acetylsalicylic acid-free strategies, we would underscore that this benefit occurred at the expense of significantly increased rates of major bleeding. Importantly, most studies of acetylsalicylic acid-free approaches are being conducted in a very different clinical context from that of the COMPASS trial, as described in greater detail below.

Acetylsalicylic acid withdrawal

Three randomized trials that included acetylsalicylic acid-free antithrombotic strategies as a comparison group have been conducted in patients undergoing PCI to assess the safety of triple antithrombotic therapy with vitamin K antagonists and DAPT (TABLE 3). The randomized WOEST trial[104] in 573 patients receiving oral anticoagulation (69.0% with AF, 65.0% treated with drug-eluting stents, and 27.5% with ACS) found a significant reduction in bleeding episodes with dual antithrombotic therapy (relative decrease 64%; 19.4% versus 4.4%; $P<0.0001$). The dual-agent group did not show any increase in the risk of thrombotic events, and all-cause mortality was significantly lower than in the triple-therapy group, but the study was underpowered to assess efficacy end points.

The PIONEER AF-PCI trial[105] compared three antithrombotic treatment strategies after PCI in 2,124 patients with AF: reduced-dose rivaroxaban (15 mg once daily) plus a single $P2Y_{12}$ inhibitor (mostly clopidogrel); low-dose rivaroxaban (2.5 mg twice daily) plus DAPT; and standard triple antithrombotic therapy with a vitamin K antagonist plus DAPT. The primary end point of clinically significant bleeding at 12 months was reduced in both groups receiving rivaroxaban-based strategies compared with the group receiving standard triple antithrombotic therapy. This difference was driven by a reduction in the rate of bleeding requiring medical attention. The rate of haemorrhagic stroke was numerically lower in the acetylsalicylic acid-free group than in the triple antithrombotic therapy group (absolute values 0.2% and 0.5%; nonsignificant relative reduction 69%). The rate of major adverse cardiovascular events

(defined as a composite of death from cardiovascular causes, MI, or stroke) did not differ across strategies, nor did the rates of the individual ischaemic end points and stent thrombosis, but the statistical power to detect differences in such low-frequency outcomes was low, as in the WOEST trial[104]. By contrast, the two rivaroxaban strategies significantly reduced the combined end point of all-cause mortality or recurrent hospitalization for adverse events[106].

The RE-DUAL PCI trial[107] involved 2,725 patients with AF who had undergone PCI (half of them in the setting of an ACS). The participants were randomly assigned to one of two dual antithrombotic therapy regimens that included dabigatran and a $P2Y_{12}$ inhibitor (mostly clopidogrel, but ticagrelor in 12%) or to a regimen of triple antithrombotic therapy with vitamin K antagonists. At a mean of 14 months, the 110 mg dabigatran dual therapy was noninferior (and also superior) to triple antithrombotic therapy in terms of the risk of major or clinically relevant non-major bleeding. Dual therapy with 150 mg dabigatran also demonstrated noninferiority but did not show superiority to triple therapy with regard to this safety end point. Intracranial bleeding was reduced in both the 110 mg and 150 mg dabigatran dual-therapy groups compared with the triple antithrombotic therapy group: nonsignificantly by 70% in the 110 mg group and significantly by 88% in the 150 mg group. The risk of thromboembolic events (defined as a composite of MI, stroke, or systemic embolism) in the two dual-therapy groups combined was noninferior to that in the triple antithrombotic therapy group. However, the study was not adequately powered to assess individual ischaemic end points. In this context, dual therapy was associated with a numerical increase in rates of MI: 4.5% in the 110 mg dabigatran dual-therapy group, 3.4% in the 150 mg dual-therapy group, and 3.0% in the triple antithrombotic therapy group. Similarly, dual therapy was associated with a numerical increase in stent thrombosis rates: 1.5% in the 110 mg dabigatran group compared with 0.9% in both the 150 mg dabigatran and triple-therapy groups.

Overall, the results of these trials show reductions in bleeding risk without any apparent trade-off in antithrombotic efficacy, which supports the role of a double-pathway approach (oral anticoagulation plus a $P2Y_{12}$ inhibitor) and for dropping acetylsalicylic acid immediately after hospital discharge for most patients with AF who undergo PCI. This conclusion is also now reflected in a number of meta-analyses[108,109] and endorsed in guideline updates[35,110]. Although the PIONEER AF-PCI[105] and RE-DUAL PCI[107] results showed a reduction in bleeding with a double-therapy regimen lacking acetylsalicylic acid, the comparator treatment was triple therapy with a vitamin K antagonist and DAPT. Therefore, the conclusion cannot be drawn that acetylsalicylic acid alone is responsible for the increase in bleeding events associated with triple therapy. Moreover, these studies do not address how a NOAC compares with a vitamin K antagonist in the absence of acetylsalicylic acid, as studied in the WOEST trial[104]. These aspects are addressed in ongoing investigations, as described below.

Ongoing studies

Strategies for PCI

Several ongoing trials aim to provide novel insights with respect to the potential role of $P2Y_{12}$ monotherapy for long-term platelet inhibition in a broad population of patients undergoing PCI with drug-eluting stents (TABLE 4). The GLOBAL-LEADERS trial[111] is a superiority study in 16,000 patients undergoing PCI with umirolimus-eluting stents designed to assess whether 24 months of ticagrelor plus 1 month of acetylsalicylic acid treatment is superior to conventional DAPT with regard to a composite end point of all-cause mortality or new Q-wave MI. The key safety end point is the rate of class 3 or 5 bleeding according to the Bleeding Academic Research Consortium (BARC) definitions. Enrolment of the GLOBAL-LEADERS study has been completed, and the data and safety monitoring board has reported no concerns requiring premature termination of the trial. The results are expected in the third quarter of 2018. This pragmatic study will not address rates of nonfatal ischaemic recurrences or bleeding events. However, the GLASSY trial[112] (a substudy of GLOBAL-LEADERS) is currently ongoing and will assess the superiority of the experimental treatment strategy over standard of care in >7,000 patients in terms of a composite end point of fatal and nonfatal ischaemic and bleeding events.

The TWILIGHT trial[113] is a double-blind superiority study that will compare the efficacy and safety of antiplatelet therapy with ticagrelor versus that of continued DAPT with acetylsalicylic acid and ticagrelor in ≤9,000 high-risk patients receiving DAPT who are event-free at 3 months after PCI with drug-eluting stents. The double-blind design, which aims to eliminate reporting bias, is a strength of this study. The primary end point is class 2, 3, or 5 bleeding at 12 months according to the BARC definitions. Noninferiority of ticagrelor monotherapy to DAPT in terms of ischaemic events will also be assessed. This trial has also recently completed enrolment, and the primary results are expected in the second quarter of 2019.

The SMART-CHOICE trial[114] is designed to test the noninferiority of $P2Y_{12}$ inhibitor monotherapy compared with acetylsalicylic acid plus a $P2Y_{12}$ inhibitor after 3 months of mandatory DAPT in 3,000 patients undergoing PCI with drug-eluting stents. The primary end point is a composite of all-cause death, MI, and cerebrovascular events at 12 months after the index procedure. Similarly, in the TICO trial[115], 3,056 patients receiving DAPT with acetylsalicylic acid and ticagrelor who are event-free at 3 months after PCI with a biodegradable polymer drug-eluting stent will be randomly assigned to receive either ticagrelor monotherapy or continued DAPT. Primary outcomes of interest are the 1-year rates of major adverse cardiovascular clinical events and major bleeding, in accordance with Thrombolysis in Myocardial Infarction (TIMI) criteria. Finally, in the STOPDAPT-2 trial[116], patients who have undergone PCI with a non-resorbing polymer everolimus-eluting stent will be randomly assigned to one of the following strategies: 1 month of DAPT with acetylsalicylic acid and a $P2Y_{12}$ receptor antagonist followed by 59 months

Table 4 | **Ongoing trials of acetylsalicylic acid-free strategies**

Study	*n*	Population	Treatment groups	Primary outcome measure	Refs
GLOBAL-LEADERS	16,000	PCI	DAPT for 1 month followed by ticagrelor for 23 months versus DAPT for 12 months followed by acetylsalicylic acid for 12 months	Death or nonfatal MI at 24 months	111,137
TWILIGHT	9,000	High-risk PCI on ticagrelor, event-free at 3 months	Placebo for 12 months versus acetylsalicylic acid for 12 months	Bleeding at 12 months	113,138
TICO	3,056	ACS-PCI	DAPT for 3 months followed by ticagrelor for 9 months versus DAPT for 12 months	MACCE at 12 months and major bleeding at 12 months	115
SMART-CHOICE	3,000	PCI	DAPT for 3 months followed by clopidogrel for 9 months versus DAPT for 12 months	Death, MI, or stroke at 12 months and major bleeding at 12 months	114
STOPDAPT-2	3,045	PCI	DAPT for 1 month followed by clopidogrel for 59 months versus DAPT for 12 months followed by acetylsalicylic acid for 48 months	NACE at 12 months	116
AUGUSTUS	4,600	AF, on oral anticoagulation, with ACS and/or undergoing PCI	Acetylsalicylic acid for 6 months versus placebo for 6 months	Major or clinically relevant bleeding at 6 months	117,139
ENTRUST-AF-PCI	1,500	AF, on oral anticoagulation, undergoing PCI	Edoxaban and clopidogrel or ticagrelor for 12 months versus vitamin K antagonist for 12 months plus DAPT for 1–12 months	Major or clinically relevant bleeding at 12 months	118,140
GALILEO	1,520	TAVI without indication for oral anticoagulation	Rivaroxaban and acetylsalicylic acid for 3 months followed by rivaroxaban alone for 9–22 months versus DAPT for 3 months followed by acetylsalicylic acid alone for 9–22 months	MACCE at 25 months and major bleeding at 25 months	119,141
ATLANTIS	1,510	TAVI with and without indication for oral anticoagulation	Apixaban for 12 months versus oral anticoagulant or SAPT or DAPT for 12 months	NACEs at 13 months	121,142
TICTAVI	308	TAVI without indication for oral anticoagulation	Ticagrelor for 30 days versus DAPT for 30 days	VARC-2 composite end point or VARC-2 end points at 30 days	123

ACS, acute coronary syndrome; AF, atrial fibrillation; DAPT, dual antiplatelet therapy; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NACE, net adverse cardiac events; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy; TAVI, transcatheter aortic valve implantation; VARC-2, Valve Academic Research Consortium 2.

of clopidogrel monotherapy or 1 month of DAPT with acetylsalicylic acid and a $P2Y_{12}$ receptor antagonist followed by 11 months of DAPT with acetylsalicylic acid and clopidogrel, followed by 48 months of acetylsalicylic acid monotherapy. The primary end point of the study is the incidence of a composite of cardiovascular death, MI, stroke, or TIMI major or minor bleeding events, which aims to demonstrate noninferiority of the acetylsalicylic acid-free strategy at 12 months and its superiority at 60 months from the procedure.

Strategies for oral anticoagulation

Two trials of the NOACs apixaban and edoxaban, with or without acetylsalicylic acid, are also ongoing in patients with ACS and/or are undergoing PCI (TABLE 4). In the AUGUSTUS trial[117], approximately 4,600 patients will be randomly assigned to apixaban 5 mg twice daily plus a $P2Y_{12}$ inhibitor, with or without acetylsalicylic acid, or to warfarin plus a $P2Y_{12}$ inhibitor, with or without acetylsalicylic acid. Interestingly, a blinded 2×2 factorial design has been selected to investigate the role of acetylsalicylic acid in these high-risk patients with AF and coronary artery disease. The primary outcome of interest is the rate of major or clinically relevant non-major bleeding, defined according to the International Society on Thrombosis and Haemostasis (ISTH) classification, at 6 months.

In the ENTRUST-AF PCI trial[118], edoxaban 60 mg (or 30 mg according to dose-reduction criteria) once daily plus a $P2Y_{12}$ inhibitor will be tested in approximately 1,500 patients against standard triple antithrombotic therapy comprising a vitamin K antagonist, acetylsalicylic acid (for 30 days to 12 months), and a $P2Y_{12}$ inhibitor. As in the AUGUSTUS trial, the primary safety end point is the incidence of ISTH-defined major or clinically relevant non-major bleeding.

Strategies for use after TAVI

Studies of acetylsalicylic acid-free strategies are also ongoing in the setting of TAVI[64], wherein many patients present with or develop new-onset AF (TABLE 4). In this setting, the choice of antithrombotic therapy is complicated by a lack of clarity on precisely which thrombotic mechanisms should be targeted. Multifactorial (that is, patient-related and valve-related) strategies relevant to both platelet-mediated and thrombin-mediated processes might be required.

In 1,520 patients with no indication for oral anticoagulation, the GALILEO trial[119] is investigating whether a strategy of low-dose rivaroxaban (10 mg daily) plus acetylsalicylic acid 81 mg for 3 months followed by low-dose rivaroxaban alone is superior to DAPT with acetylsalicylic acid and clopidogrel for 3 months followed by acetylsalicylic acid alone. The primary outcomes of

this study are a composite of death and thromboembolic events (efficacy) and bleeding according to the BARC classification (safety) up to 25 months. An embedded valve imaging substudy will evaluate aortic valve leaflet thrombosis, which has emerged as an important adverse event in patients after TAVI[120]. Patient enrolment has been completed.

The ATLANTIS trial[121] will include 1,510 patients stratified according to the presence or absence of a mandatory indication for oral anticoagulation (that is, for a reason other than the TAVI procedure itself). The trial aims to demonstrate the superiority of anticoagulation with apixaban 5 mg twice daily with dose adjustment compared with the current standard of care (selection of a vitamin K antagonist, a single antiplatelet agent, or DAPT according to the presence or absence of an indication for oral anticoagulation) with respect to a composite end point of death, thromboembolic events, and bleeding events. Enrolment is ongoing.

Studies comparing different antiplatelet strategies and studies comparing different anticoagulant strategies are also underway. In the POPULAR-TAVI trial[122], 1,000 patients will be randomly assigned to antiplatelet therapy with or without clopidogrel on a background of either acetylsalicylic acid therapy (for those with no indication for oral anticoagulation) or warfarin (for those with an indication for oral anticoagulation). The primary end points of the trial are rates of freedom from any bleeding and nonprocedural BARC bleeding at 1 year. The safety of ticagrelor alone versus standardized therapy (which involves lysine acetylsalicylate and clopidogrel) in the early period after TAVI is the objective of the small randomized TICTAVI trial[123]. Finally, the ongoing ENVISAGE-TAVI-AF trial[124] aims to compare the effect of two anticoagulation strategies (edoxaban or a vitamin K antagonist) on the net adverse clinical event rate (a composite of all-cause death, MI, ischaemic stroke, systemic embolic events, valve thrombosis, and ISTH-defined major bleeding) in patients stratified by background antiplatelet monotherapy.

Reappraisal of acetylsalicylic acid

The role of acetylsalicylic acid could require reappraisal in the near future depending on the results of ongoing investigations aimed at exploring the net benefit of its expanded indications and different drug formulations or doses. The clinical effect of combination therapy with new acetylsalicylic acid formulations that are being developed to have improved pharmacodynamic and safety profiles is currently unknown and could also represent an area of research interest[125,126].

Evidence for the use of acetylsalicylic acid in primary prevention is being sought in four ongoing prospective trials that are expected to be completed in 2018: namely, the ACCEPT-D[127], ARRIVE[128], ASPREE[129], and ASCEND[130] trials. In addition, several trials of various adjuvant low-dose acetylsalicylic acid regimens have been initiated in patients with newly diagnosed cancers[31]. The double-blind, placebo-controlled, randomized ADD-ASPIRIN trial[131], in particular, is investigating whether regular acetylsalicylic acid use after standard anticancer therapy prevents recurrence and prolongs survival in participants with four different common types of nonmetastatic solid cancers (FIG. 6).

Some uncertainties remain regarding the optimal dose of acetylsalicylic acid for secondary prevention, as the studies in this area were fairly small and had disparate results, perhaps because they compared patients taking different acetylsalicylic acid doses. To elucidate this issue, the ongoing ADAPTABLE trial[132] will randomly

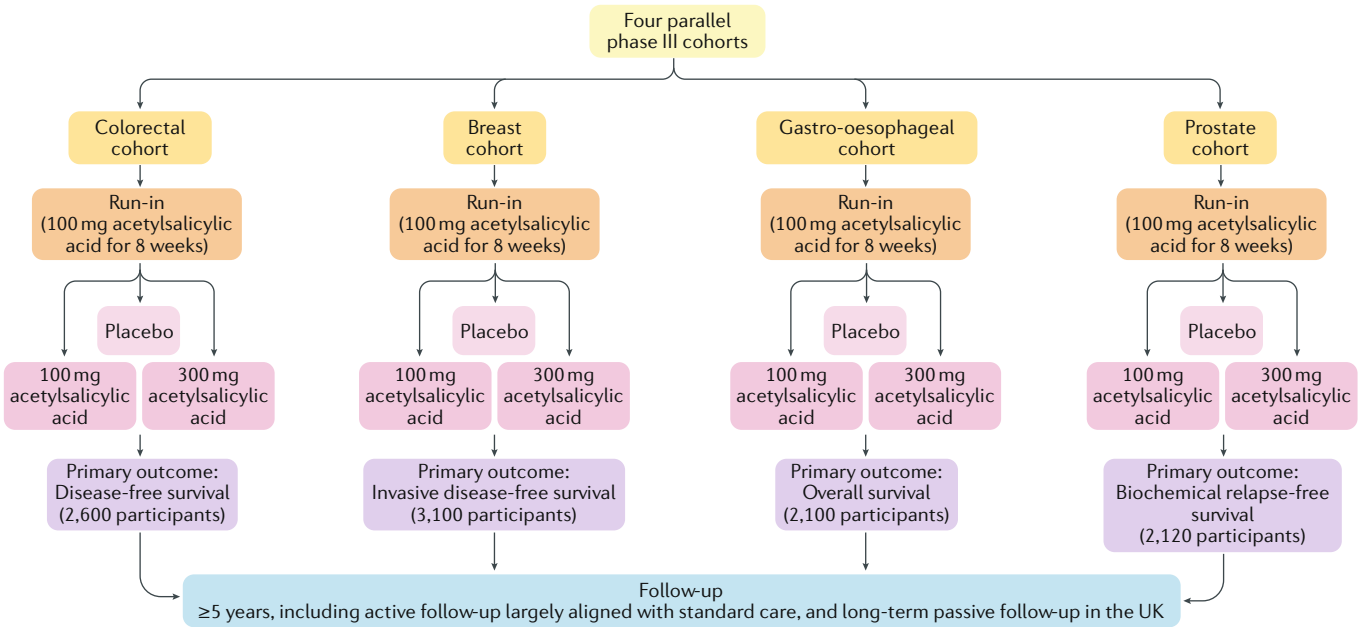

Fig. 6 | **ADD-ASPIRIN trial schema.** The study design of the ADD-ASPIRIN trial, which is investigating whether regular acetylsalicylic acid use after standard anticancer therapy prevents recurrence and prolongs survival in participants with one of four types of common, nonmetastatic, solid tumours. Adapted from REF.[131], CC-BY-4.0.

assign 20,000 patients with established coronary artery disease to either low-dose (81 mg) or high-dose (325 mg) acetylsalicylic acid. Twice daily administration of acetylsalicylic acid has also been suggested in individuals with high platelet turnover rates, such as patients with diabetes mellitus[133]. Ex vivo investigations have indeed shown that twice daily administration of low-dose acetylsalicylic acid is associated with improved pharmacodynamic profiles[134,135]. Whether this pharmacodynamic effect translates into a clinical benefit in patients with diabetes mellitus who present with an ACS is the objective of the ongoing ANDAMAND trial[136].

Conclusions

Both the number of antithrombotic medications and the range of indications for their use have rapidly expanded in the past decade. The dosing regimens of different antithrombotic agents are also important and should be carefully considered when deciding on the combination to be used in each clinical setting. The downside of the improved efficacy of all these agents is bleeding. Prasugrel, ticagrelor, vorapaxar, and rivaroxaban, which all met the primary end point in their respective phase III trials, have been typically tested on a background of acetylsalicylic acid, and the balance of risk and benefit for the use of these drugs as antiplatelet monotherapies is largely unknown.

An interesting array of studies are exploring the possibility of avoiding acetylsalicylic acid therapy altogether in favour of long-term $P2Y_{12}$ inhibitor or NOAC monotherapy. Indeed, the historical role of acetylsalicylic acid for secondary prevention stems from studies that seem largely outdated in comparison with contemporary practice. Lessons from the field of cardioembolic stroke prevention indicate that removing acetylsalicylic acid from the antithrombotic regimen substantially decreases the risk of bleeding in patients who are candidates for oral anticoagulation. The results of a large trial in patients with stable atherosclerosis but without an indication for oral anticoagulation showed that combining acetylsalicylic acid with very low dose (5 mg) rivaroxaban was more effective than acetylsalicylic acid alone for secondary prevention of ischaemic events[56]. Because the trial ended early, the opportunity to fully characterize the comparative efficacy and safety profiles of rivaroxaban 5 mg versus acetylsalicylic acid monotherapy was missed. Other studies are now ongoing in the field of PCI and TAVI to validate acetylsalicylic acid-free approaches. If these studies succeed in proving their hypotheses and cumulatively provide sufficient evidence to reconsider the historical role of acetylsalicylic acid for secondary prevention, uncertainty will nonetheless remain with regard to long-term antithrombotic regimens extending beyond the duration of the antiplatelet monotherapies investigated in clinical trials. Also, although the results of such studies could lead to a paradigm shift in secondary prevention, at least after PCI, the benefits (if any) of dropping acetylsalicylic acid need to be weighed against the loss of the potential noncardiac effects of this agent, including prevention of cancer and cognitive impairment.

Given the indisputable role of acetylsalicylic acid in cardiovascular disease management and prevention, positive results from large-scale clinical trials are warranted before acetylsalicylic acid-free strategies can be recommended for use in routine clinical practice. Moreover, the results of such studies cannot be generalized to all patients in whom acetylsalicylic acid is being considered for secondary prevention but instead should be limited to the context in which that particular agent has been studied. To this extent, some studies have already failed to demonstrate a benefit of ticagrelor monotherapy over standard-of-care approaches in patients with PAD or experiencing a cerebrovascular event[98,102]. Also, current data indicate that a benefit exists for other novel antithrombotic approaches, such as adding low-dose rivaroxaban to acetylsalicylic acid therapy[56], challenging the concept that acetylsalicylic acid-free strategies are always desirable. Ultimately, in addition to demonstrating favourable safety and efficacy profiles, the results of ongoing investigations will also need to support the cost-effectiveness of acetylsalicylic acid-free strategies in light of the considerably higher costs of many novel antithrombotic agents compared with that of acetylsalicylic acid.

Published online: 04 July 2018

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Acknowledgements
D.J.A. is the recipient of funding from the Scott R. MacKenzie Foundation and the US National Institutes of Health (NIH) National Center for Advancing Translational Sciences Clinical and Translational Science Award to the University of Florida UL1 TR000064 and NIH National Human Genome Research Institute U01 HG007269.

Author contributions
D.J.A. and D.C. researched data for the article and wrote the manuscript. All authors contributed substantially to discussions of the article content and undertook reviewing and/or editing of the manuscript before submission.

Competing interests
D.J.A. declares that he has received consulting fees or honoraria from Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Janssen, Merck, PLx Pharma, Pfizer, Sanofi, and The Medicines Company and has received payments for participation in review activities from CeloNova and St Jude Medical. D.J.A. also declares that his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, and Renal Guard Solutions. D.L.B. declares that he has received research funding from Abbott, Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, and The Medicines Company. He also declares that he is an advisory board member for Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences and was on the Board of Directors of the Boston VA Research Institute and the Society of Cardiovascular Patient Care; he was Chair of the American Heart Association Quality Oversight Committee and is on the Data Monitoring Committees of the Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, and Population Health Research Institute; he was a Trustee of the American College of Cardiology (ACC), from whom he receives honoraria for his roles as Senior Associate Editor (Clinical Trials and News) at ACC.org and Vice Chair of the ACC Accreditation Committee. He is a member of the clinical trial steering committees of Duke Clinical Research Institute Population Health Research Institute and Harvard Clinical Research Institute. He was Secretary and Treasurer of the Society of Cardiovascular Patient Care, a member of the Continuing Medical Education steering committee for WebMD, and Chair of the National Cardiovascular Data Registry ACTION Registry Steering Committee and of the VA Clinical Assessment, Reporting, and Tracking Research and Publications Committee. He also acts

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Reviewer information
Nature Reviews Cardiology thanks G. Lip, L. Wallentin, and U. Zeymer for their contribution to the peer review of this work.