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REVIEW

Frontiers in cardiovascular medicine

Antiplatelet agents for the treatment and prevention of atherothrombosis

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The clinical pharmacology of antiplatelet drugs has been reviewed previously by the European Society of Cardiology (ESC) Task force and by the 8th American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines. Moreover, information on the efficacy and safety of antiplatelet drugs in the treatment and prevention of atherothrombosis is provided by collaborative meta-analyses of 287 secondary prevention trials and 6 primary prevention trials. The present document intends to provide practicing physicians with an updated instrument to guide their choice of the most suitable antiplatelet strategy for the individual patient at risk, or with different clinical manifestations, of atherothrombosis.

Keywords Atherothrombosis • Antiplatelet drugs • Aspirin • Clopidogrel • Dipyridamole • Prasugrel • Ticagrelor • Ticlopidine

Introduction

The clinical pharmacology of antiplatelet drugs has been reviewed previously by a European Society of Cardiology (ESC) task force[1] and by the 8th American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines.[2] Moreover, information on the efficacy and safety of antiplatelet drugs in the treatment and prevention of atherothrombosis is provided by collaborative meta-analyses of 287 secondary prevention trials and 6 primary prevention trials.[3,4] The present document intends to provide practicing physicians with an updated instrument to guide their choice of the most suitable antiplatelet strategy for the individual patient at risk, or with different clinical manifestations, of atherothrombosis.

Platelet pathophysiology

Platelets are vital components of normal haemostasis and key participants in atherothrombosis by virtue of their capacity to adhere

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to injured blood vessels and to accumulate at sites of injury.[5] Although platelet adhesion and activation should be viewed as a physiological response to the fissuring or rupture of an atherosclerotic plaque, eventually contributing to its repair, uncontrolled progression of such a process through a series of self-sustaining amplification loops may lead to intraluminal thrombus formation, and vascular occlusion with transient or permanent ischaemia or necrosis. The major agonists, receptors, and effector systems participating in platelet activation are discussed and illustrated in the Supplementary material online, *Figure S1*. Currently available antiplatelet drugs (*Table 1*) interfere with some of the steps leading to platelet aggregation (*Figure 1*),[1,2] and have a measurable impact on the risk of arterial thrombosis that cannot be dissociated from an increased risk of bleeding.[1,2]

Mechanism of action of antiplatelet drugs

Aspirin

Aspirin induces a permanent functional defect in platelets, which can be detected clinically as a prolonged bleeding time. This appears to be primarily, if not exclusively, due to irreversible inactivation of a key enzyme in platelet arachidonate metabolism through acetylation of a critical serine residue near its catalytic site (Supplementary material online, *Figure S2*). This enzyme, cyclooxygenase (COX)-1, is responsible for the formation of prostaglandin (PG)H_2, the precursor of thromboxane (TX)A_2. The non-linear relationship between inactivation of platelet COX-1 and inhibition of TXA_2-dependent platelet function by low-dose aspirin[6] (Supplementary material online, *Figure S3*) has important implications: (i) a substantial reduction in platelet inhibition is associated with less than maximal inactivation of COX-1; (ii) recovery of platelet function is disproportionately rapid, occurring within 3–4 days upon drug withdrawal,[6] (iii) the requirement for virtually complete and persistent inhibition of platelet COX-1 cannot be met by most traditional non-steroidal anti-inflammatory drugs (NSAIDs), allowing their COX-2-dependent cardiotoxicity to be unmasked.[7] Moreover, inhibition of TXA_2-dependent platelet function by aspirin leaves other platelet pathways [adenosine diphosphate (ADP)-$P2Y_{12}$, thrombin-protease-activated receptor (PAR)-1] largely unaffected, thus providing a rationale for dual or triple antiplatelet therapy in high-risk settings.

Table 1 Currently available antiplatelet drugs and investigational agents

COX-1 inhibitors
Irreversible: aspirin
Reversible: indobufen, triflusal
$P2Y_{12}$ inhibitors
Irreversible: ticlopidine, clopidogrel, prasugrel
Reversible: ticagrelor, cangrelor[a], elinogrel[a]
Phosphodiesterase inhibitors
Dipyridamole
Cilostazol
GPIIb/IIIa blockers
Abciximab
Eptifibatide
Tirofiban
Thromboxane receptor (TP) antagonists
Terutroban[a]
Thrombin receptor (PAR-1) antagonists
Vorapaxar[a]
Atopaxar[a]

[a]Investigational agent.

Thienopyridines

Thienopyridines inhibit adenosine diphosphate (ADP)-dependent platelet function by irreversible modification of the platelet $P2Y_{12}$ receptor[8] through short-lived active metabolites, generated by liver cytochrome P-450 (CYP) isozymes, that form covalent bonds with critical cysteine residues within the receptor.[9] The inhibition of ADP-dependent platelet function by clopidogrel is less predictable than the inhibition of TXA_2-dependent platelet function by aspirin. Insufficient availability of the active metabolite of clopidogrel at conventional therapeutic doses results in incomplete inactivation of platelet $P2Y_{12}$.[10] Because of the linear relationship between $P2Y_{12}$ inactivation and inhibition of ADP-dependent platelet aggregation, recovery of platelet function after drug withdrawal occurs linearly over 7–8 days as a function of platelet turnover.[1] Genetic variation of the liver enzymes responsible for the metabolism of clopidogrel as well as drug–drug interactions [e.g. with proton pump inhibitors (PPIs)] are important determinants of the variable circulating levels of its active metabolite.[11,12,13] These, in turn, are associated with variable inhibition of ADP-induced platelet aggregation and variable clinical response to clopidogrel treatment.[11,12]

Like ticlopidine and clopidogrel, prasugrel is a prodrug that is inactive *in vitro*.[14] While equimolar concentrations of the active metabolites of clopidogrel and prasugrel result in similar levels of platelet inhibition *in vitro*, the markedly different amounts of each metabolite generated *in vivo* following a loading dose of clopidogrel (300 mg) or prasugrel (60 mg) result in ~10-fold higher platelet exposure to the latter when compared with the former.[14] This observation provides a pharmacokinetic basis for the faster, more profound and less variable inhibition of platelet function observed with prasugrel when compared with clopidogrel in healthy subjects[14] as well as in patients with ischaemic heart disease.[10,15,16] In contrast to clopidogrel, the lack of drug interaction potential and the apparent independence of CYP2C19 genetic variance result in a predictable antiplatelet response to prasugrel.[15–17]

Glycoprotein (GP)IIb/IIIa blockers

GPIIb/IIIa antagonists prevent fibrinogen binding to activated GPIIb/IIIa receptors and, thus, formation of fibrinogen bridges between platelets (reviewed in detail in ref. [2]). Activation of GPIIb/IIIa

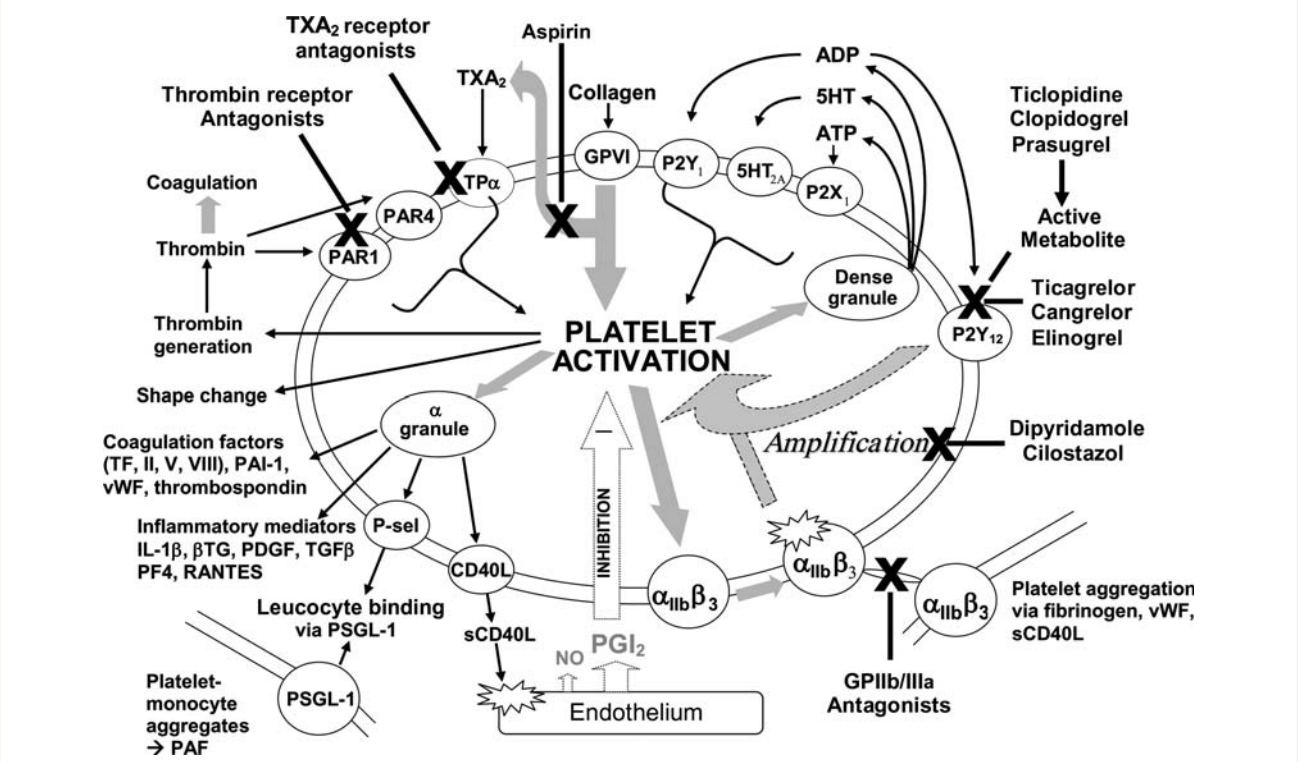

Figure 1 Platelet activation and inhibition mechanisms and the sites of action of antiplatelet drugs. Platelet activation via multiple pathways leads to numerous responses including: shape change; dense granule secretion of ATP, 5HT, and ADP (which binds to $P2Y_1$ and $P2Y_{12}$ receptors, the latter playing a powerful role in amplification of platelet activation); α granule secretion of chemokines—which lead to leucocyte and endothelial cell activation—and coagulation factors; procoagulant changes in the platelet surface membrane supporting thrombin generation and activation of $\alpha_{IIb}\beta_3$ (GPIIb/IIIa) leading to platelet aggregation and outside-in signalling that further amplifies platelet activation. Release of NO and PGI_2 from the endothelium reduces platelet reactivity. Adapted with permission from Storey RF. Biology and pharmacology of the platelet $P2Y_{12}$ receptor. *Current Pharmaceutical Design*. 2006;**12**:1255–1259.

constitutes the final common pathway of platelet aggregation. Currently, three GPIIb/IIIa blockers are available for intravenous administration: abciximab, eptifibatide, and tirofiban (reviewed in detail in ref.[2]).

Abciximab, a non-competitive inhibitor of GPIIb/IIIa, is the humanized chimeric Fab-fragment of the monoclonal mouse antibody 7E3. Abciximab cross-reacts with the $\alpha_v\beta_3$ integrin on endothelial cells and smooth muscle cells and with the $\alpha_M\beta_2$ integrin (CD11b/CD18) on granulocytes and monocytes.

Two small-molecule GPIIb/IIIa blockers act specifically on the α_{IIb}-chain of GPIIb/IIIa: eptifibatide, a cyclic heptapeptide, and tirofiban, a non-peptide ('peptidomimetic') antagonist. Eptifibatide and tirofiban are competitive inhibitors. Their effect on platelet aggregation is closely linked to plasma concentrations.[1] Owing to their short plasma half-lives, continuous infusion is needed for sustained platelet inhibition.[1]

Thromboxane receptor antagonists

Potent thromboxane receptor (TP) antagonists have been developed, including GR 32191, BMS-180291 (ifetroban), BM 13.177 (sulotroban), and S-18886 (terutroban). Despite the anti-thrombotic activity demonstrated in various animal species and the cardioprotective and antiatherogenic activities demonstrated in experimental models, these compounds have yielded disappointing results in phase 2 and 3 clinical trials.[2] The clinical development of terutroban has been discontinued recently after an interim futility analysis revealed that superiority vs. low-dose aspirin on major vascular events in over 19 000 patients with recent cerebrovascular ischaemia was unlikely to be demonstrated.[18]

Reversible $P2Y_{12}$ antagonists

Three direct-acting and reversible $P2Y_{12}$ antagonists, ticagrelor (an oral agent), cangrelor (an intravenous agent), and elinogrel (available both as an intravenous and oral agent) are associated with rapid onset and offset of platelet inhibition.[11,19,20] Unlike the thienopyridines, they do not require metabolic activation by the liver. Detailed molecular studies of ticagrelor have demonstrated that this selective $P2Y_{12}$ inhibitor displays a non-competitive antagonism towards ADP-induced receptor activation, suggesting the existence of more than one ligand-binding site on $P2Y_{12}$.[21] Ticagrelor is rapidly absorbed and undergoes enzymatic transformation to at least one active metabolite.[19] Peak plasma concentrations of ticagrelor and maximum platelet inhibition are achieved within 1–3 h after dosing. The plasma half-life of

ticagrelor is 6–13 h, which dictates a twice daily regimen of administration.[19]

Thrombin receptor antagonists

Thrombin interacts with two platelet receptors, called PAR-1 and -4, that are activated through proteolytic cleavage (*Figure 1*).[22] Protease-activated receptor-1 is the major human platelet receptor, exhibiting 10–100 times higher affinity for thrombin when compared with PAR-4.[22] Two thrombin receptor antagonists (TRA) with PAR-1 selectivity are currently under clinical evaluation. Vorapaxar (SCH530348), a synthetic analogue of himbacine, is a potent oral TRA[23,24] with half-life of 126–269 h, that inhibits platelet function for up to 4 weeks after its withdrawal.[23,24] Two ongoing placebo-controlled phase 3 trials in high-risk acute coronary syndrome (ACS) patients[25] and in stable patients at high cardiovascular risk[26] have undergone recent changes recommended by their data and safety monitoring board. Another oral TRA, atopaxar (E5555), has recently completed phase 2 evaluation.[27] This compound has a shorter half-life and faster recovery of platelet function after its withdrawal than vorapaxar.[28] However, a dose-dependent increase in liver function abnormalities and QTc prolongation were noted in the dose-finding study of atopaxar.[27]

Phosphodiesterase inhibitors

Dipyridamole is a pyrimidopyrimidine derivative with vasodilator and antiplatelet properties. Its mechanism of action as an antiplatelet agent has been a subject of controversy (reviewed in ref.[2]). The absorption of dipyridamole from conventional formulations is quite variable and may result in low systemic bioavailability of the drug. A modified-release formulation of dipyridamole with improved bioavailability has been developed and tested in association with low-dose aspirin. Dipyridamole is eliminated primarily by biliary excretion as a glucuronide conjugate and is subject to enterohepatic recirculation. A terminal half-life of 10 h has been reported. This is consistent with the b.i.d. regimen used in recent clinical studies.[29,30]

Cilostazol is a reversible type III phosphodiesterase inhibitor, with vasodilator and antiplatelet effects. It increases intraplatelet cAMP, reduces cellular adenosine uptake, and inhibits vascular smooth muscle cell proliferation.[31] Added to a standard combination of aspirin plus clopidogrel, cilostazol 100 mg b.i.d. has been found to potentiate inhibition of ADP-induced platelet aggregation when compared with aspirin and clopidogrel.[32]

Patients who may benefit from different antiplatelet regimens

Single antiplatelet therapy

In the meta-analysis of the antithrombotic trialists'(ATT) collaboration,[3] allocation of high-risk patients to a prolonged course of antiplatelet therapy reduced the combined outcome of non-fatal myocardial infarction (MI), non-fatal stroke or vascular death ('serious vascular events') by ~25% compared with placebo. Non-fatal MI was reduced by one-third, non-fatal stroke by one-quarter, and vascular mortality by one-sixth. Absolute reductions in the risk of having a serious vascular event in different groups of high-risk patients are illustrated in Supplementary material online, *Figure S4*. In each of these high-risk categories, the absolute benefits substantially outweighed the absolute risks of major bleeding complications (*Table 2*).

It is interesting to compare the effects of low-dose aspirin in primary prevention with the well-known benefits in secondary prevention (*Table 3*).[4] In the six primary prevention trials among 95 000 low-risk individuals, with mean follow-up 6.9 years, aspirin allocation yielded a 12% relative risk reduction in serious vascular events, from an annual rate of 0.57 to 0.51%.[4] This effect was mainly due to a reduction in non-fatal MI, from 0.23 to 0.18% per year. The net effect on stroke was not significant, reflecting a small reduction in presumed ischaemic stroke and counterbalancing effects on haemorrhagic stroke and other stroke.[4] There was no significant reduction in vascular mortality.

Table 2 Benefit/risk ratio of antiplatelet prophylaxis with aspirin in different settings

Clinical setting	Benefit[a]	Risk[b]	Benefit/risk ratio
	Number of patients in whom a major vascular event is avoided per 1000/year	Number of patients in whom a major GI bleeding event is caused per 1000/year	
Men and women at low-cardiovascular risk	1–2	1–2	1
Essential hypertension	1–2	1–2	1
Chronic stable angina	10	1–2	5–10
Prior stroke or TIA	10	1–2	5–10
Prior myocardial infarction	15	1–2	7.5–15
Unstable angina	50	1–2	25–50

[a]Benefits are calculated from randomized trial data reviewed in refs[2,4] and depicted in Supplementary Figure 4.
[b]Risks of upper GI bleeding are estimated from a background rate of 1 event per 1000 per year in the general population of non-users and a relative risk of 2.0–3.0 associated with aspirin prophylaxis. Such an estimate assumes comparability of other risk factors for upper GI bleeding, such as age and concomitant use of NSAIDs, and may actually underestimate the absolute risk in an elderly population exposed to 'primary' prevention. The absolute excess of major extra-cranial bleeding complications in the 'primary' prevention trials reviewed in ref.[4] ranged between 0.2 and 2.0 per 1000 patient-years. Modified from Patrono *et al., Chest 2008*[2].

Table 3 Comparison of proportional and absolute effects of aspirin in primary and secondary prevention trials

	Rate ratio (aspirin vs. control)		Absolute differences (per 1000/year)	
	Primary prevention	Secondary prevention	Primary prevention	Secondary prevention
(a) Major coronary event	0.82	0.80	−0.6	−10.0
Non-fatal MI	0.77	0.69	−0.5	−6.6
CHD mortality	0.95	0.87	−0.1	−3.4
(b) Stroke	0.95	0.81	−0.1	−4.6
Haemorrhagic	1.32	1.67	+0.1	NA[a]
Ischaemic	0.86	0.78	−0.2	NA[a]
Unknown cause	0.97	0.77	−0.01	NA[a]
(c) Vascular death	0.97	0.91	−0.1	−2.9
(a,b,c) Any serious vascular event	0.88	0.81	−0.6	−14.9

MI, myocardial infarction; CHD, coronary heart disease.
[a]Stroke causes very incompletely reported. Modified from antithrombotic trialists' (ATT) collaboration. *Lancet 2009*[4].

Table 4 Rate ratios (95% CI) associated with risk factors for selected outcomes in people with no known vascular disease in primary prevention trials

	Major coronary event	Probably ischaemic stroke	Haemorrhagic stroke	Major extracranial bleed
Age (per decade)	1.84 (1.74–1.95)	2.46 (2.27–2.65)	1.59 (1.33–1.90)	2.15 (1.93–2.39)
Male sex[a]	2.43 (1.94–3.04)	1.44 (1.14–1.82)	1.11 (0.52–2.34)	1.99 (1.45–2.73)
Diabetes mellitus	2.66 (2.28–3.12)	2.06 (1.67–2.54)	1.74 (0.95–3.17)	1.55 (1.13–2.14)
Current smoker	2.05 (1.85–2.28)	2.00 (1.72–2.31)	2.18 (1.57–3.02)	1.56 (1.25–1.94)
Mean blood pressure (per 20 mmHg)[b]	1.73 (1.59–1.89)	2.00 (1.77–2.26)	2.18 (1.65–2.87)	1.32 (1.09–1.58)
Cholesterol (per 1 mmol/L)	1.18 (1.12–1.24)	1.02 (0.95–1.09)	0.90 (0.77–1.07)	0.99 (0.90–1.08)
Body mass index (per 5 kg/m^2)	1.09 (1.03–1.15)	1.06 (0.98–1.14)	0.85 (0.71–1.02)	1.24 (1.13–1.35)

[a]Analyses are stratified by trial. The relevance of male sex can therefore be assessed only in the two trials that included both men and women, so the 95% CIs for it are wide, particularly for stroke.
[b]Mean of systolic and diastolic blood pressure. Associations with measured values are not corrected for the effects of regression dilution. Reproduced from antithrombotic trialists' (ATT) Collaboration. *Lancet 2009*[4].

Aspirin allocation increased gastrointestinal (GI) (or other extracranial) bleeds from 0.07 to 0.1% per year.[4] The risks of serious vascular events and of major extra-cranial bleeds were predicted by the same independent risk factors (age, male gender, diabetes mellitus, current smoking, blood pressure, and body mass index) (*Table 4*), so individuals at higher risk of vascular complications also had a high risk of bleeding.[4]

While for secondary prevention the net benefits of adding aspirin to other, safer, preventive measures (e.g. statin therapy, antihypertensive therapy) would substantially exceed the bleeding hazards, irrespective of age and gender, in people without pre-existing vascular disease the benefits of adding long-term aspirin to other, safer, forms of primary prevention (e.g. statins and antihypertensive drugs) would be of similar magnitude as the hazards.[4] Hence, the currently available trial results do not seem to justify general guidelines advocating the routine use of aspirin in all apparently healthy individuals above a moderate level of coronary risk, unless additional long-term benefits of antiplatelet therapy[33] become established.

Ticlopidine and clopidogrel have been tested for superiority vs. aspirin in patients with a recent MI, and both drugs failed to demonstrate superiority in this setting.[34,35] Both aspirin[36–39] and ticlopidine[40] have been shown to reduce by ~50% the rate of MI or death in randomized controlled trials (RCTs) of patients with unstable angina.

Dual antiplatelet therapy

In the CURE study, blockade of both platelet COX-1 with aspirin and the platelet $P2Y_{12}$ receptor with clopidogrel produced additive effects in patients with non-ST-elevation (NSTE)-ACS, by reducing the rate of the first primary outcome (a composite of cardiovascular death, non-fatal MI, or stroke) from 11.4 to 9.3% (RR, 0.80; 95%

CI, 0.72–0.90, $P < 0.001$) when compared with aspirin alone, with no evidence of attenuation of the additional benefit over 12 months of treatment.[41] As would be expected from more aggressive antiplatelet therapy, there were significantly more patients with major bleeding complications in the aspirin plus clopidogrel group than in the aspirin alone group (3.7 vs. 2.7%; $P = 0.001$), an effect in part related to the variable aspirin dose (75–325 mg daily) used in this trial[41] (Supplementary material online, *Table S1*).

The clinical benefit of dual antiplatelet therapy vs. aspirin alone has been confirmed in patients undergoing PCI,[42] in the short-term treatment of those presenting with an acute STEMI treated with fibrinolysis,[43,44] and in patients with non-valvular atrial fibrillation.[45] Although long-term treatment with aspirin and clopidogrel for 1 year after a STEMI is recommended by the ESC guidelines, irrespective of the acute reperfusion treatment, no studies have been performed in this regard.[46]

At present there is no sound evidence for defining the optimal duration of dual antiplatelet therapy after elective drug-eluting stent (DES) placement with current recommendations ranging between 3 and 12 months, depending on DES type.[47] However, convincing data exist only for continuation up to 6 months. In the combined analysis of two trials performed by Park *et al.*,[48] the use of dual antiplatelet therapy for a period longer than 12 months in patients who had received DES was not significantly more effective than aspirin monotherapy in reducing the rate of MI or cardiac death. Preliminary data from the PRODIGY trial, in which 6 months of clopidogrel was compared with 24 months of clopidogrel following coronary stent implantation, have shown a statistically significant two-fold increase in the bleeding rates without evidence of significant efficacy with the longer duration of clopidogrel and so do not support the use of long-term dual antiplatelet therapy following percutaneous coronary intervention (Valgimigli M, presented at ESC annual scientific congress, Paris, France, 30 August 2011). Several randomized studies, such as EXCELLENT, OPTIDUAL, ISAR-SAFE, and DAPT, are currently investigating this controversial issue. Until the results of these studies are available, the potential benefit of extended dual antiplatelet therapy needs to be weighed against the excess risk of major bleeding.

In contrast to the consistent finding of a favourable benefit/risk profile of dual antiplatelet therapy in ACS patients[41,43,44] and those undergoing PCI,[42] the same strategy has not proven advantageous when compared with clopidogrel alone in patients after a recent ischaemic stroke or TIA,[49] or when compared with aspirin alone in patients at high risk for atherothrombotic events.[50] Major bleeding was increased by dual antiplatelet therapy in both MATCH[49] and CHARISMA.[50]

The potential of dual antiplatelet therapy with low-dose aspirin and new $P2Y_{12}$ inhibitors in ACS has been shown by two large trials: the TRITON-TIMI 38 trial comparing prasugrel to clopidogrel in ACS patients undergoing PCI[51] and the PLATO trial comparing ticagrelor to clopidogrel in high-risk ACS[52] (Supplementary material online, *Table S1*). Both trials met their primary endpoint by demonstrating that the 12-month (ticagrelor) or 15-month (prasugrel) rate of major vascular events can be further reduced by 16% (ticagrelor) to 19% (prasugrel) over clopidogrel with a $P2Y_{12}$ blocker that achieves faster, more profound and less variable inhibition of ADP-dependent platelet function than clopidogrel.[51,52] Differences between the two trials are worth noting (Supplementary material online, *Table S1*). While the benefit of prasugrel vs. clopidogrel was largely confined to a reduction in non-fatal MI,[51] the incremental benefit of ticagrelor translated into a significant reduction in vascular as well as total mortality.[52] It is unknown whether the mortality reduction was entirely due to greater $P2Y_{12}$ inhibition in a high-risk population, or whether reversibility of receptor binding and/or off-target effects of ticagrelor also contributed. It should be emphasized that this finding derives from a single trial, in which mortality was not the primary endpoint. $P2Y_{12}$ blockade with prasugrel was associated with significant increases in both fatal and non-fatal major bleeds.[51] Ticagrelor did not increase the total number of major bleeds but did increase non-fatal spontaneous [i.e. non-coronary artery bypass grafting (CABG)-related] bleeds and fatal intracranial haemorrhages.[52] Coronary artery bypass grafting-related bleeds were not significantly different in PLATO, but increased in TRITON-TIMI 38. Three patient subsets appeared to be particularly prone to major bleeding with prasugrel: the elderly and the underweight (who derived no net benefit), and patients with prior cerebrovascular ischaemia (who derived net harm).[51] Regardless of the mechanism(s), the increase in fatal haemorrhagic complications of prasugrel treatment may have masked any benefit of the drug on vascular mortality. Additional side effects of the novel agents include non-platelet related effects, with prasugrel associated with a higher rate of diagnosis of colonic neoplasms (13 vs. 4, $P = 0.03$), a finding which remains to be confirmed and may be a chance finding,[51] and ticagrelor associated with more frequent episodes of dyspnoea and ventricular pauses than clopidogrel.[52] No head-to-head comparison of prasugrel and ticagrelor has been performed yet.

Based on the TRITON-TIMI 38 results, prasugrel has been approved by both the FDA and EMA for the reduction in thrombotic cardiovascular events in ACS patients who undergo PCI. A black-boxed warning underscores the increased bleeding risk for patients 75 years of age or older and for patients undergoing urgent CABG. Prasugrel is contraindicated in patients with prior stroke or TIA. Because of the high probability of a false positive finding, the imbalance in newly diagnosed cancers is described in the adverse-reactions section of prasugrel's label but is not emphasized as a warning.[53] However, the sponsors have a post-marketing requirement by the FDA to collect baseline and subsequent data on cancer in a large, ongoing clinical trial.[53]

Based on the PLATO results, ticagrelor has been approved by the EMA and FDA for the reduction in thrombotic cardiovascular events in ACS patients regardless of planned management strategy and including patients older than 75 years or with prior history of ischaemic stroke or TIA but excluding those with a history of intracranial haemorrhage. In the FDA label, a boxed warning indicates that maintenance doses of aspirin >100 mg reduce the effectiveness of ticagrelor and should be avoided.

Antiplatelet therapy in patients on oral anticoagulation is discussed in the Supplementary material online.

GPIIb/IIIa receptor blockade

Whereas the efficacy of GPIIb/IIIa receptor blockade in the setting of conservative treatment of ACS is marginal,[54] this class of drugs substantially improved the safety of PCI in the 1990s. By preventing

peri-procedural thrombotic events, GPIIb/IIIa blockade reduced the 30-day rate of major adverse cardiac events after PCI by up to 55%.[55] Pooled analysis of five randomized trials including 11 612 patients yielded a relative risk reduction by GPIIb/IIIa blockade of 31% (95% CI, 23–39%) for the 30-day event rate.[56] This early benefit was maintained for 3 years.[57]

These early studies have been recently challenged, because PCI was then performed without pre-treatment with thienopyridines (see Supplementary material online). Currently, the place of systematic GPIIb/IIIa blockade for primary PCI is uncertain within the context of concomitant antithrombotic treatment. There appears to be a role for provisional GPIIb/IIIa blockade in this setting, but efficacy and indications of this approach need further study. There is no sound evidence that upstream vs. in-cath-lab administration of GPIIb/IIIa blockers affords a beneficial effect that is clinically relevant.

Perioperative management of antiplatelet therapy

The practice of withdrawing antiplatelet therapy 7–10 days before surgery/endoscopy/biopsy is undergoing critical reappraisal. Patients with a clear indication for antiplatelet therapy have a three-fold, or greater, incidence of thrombotic events associated with discontinuation of antiplatelet drugs,[58] overwhelming the estimated 1.5-fold bleeding hazard associated with perioperative drug continuation.[59] Indeed, up to 10% of acute vascular events may be linked to antiplatelet therapy withdrawal.[59] Moreover, the post-operative acute phase is thrombogenic, involving platelet hyperreactivity, increased synthesis of coagulation factors, and hypofibrinolysis. Perioperative interruption of antiplatelet therapy should therefore be considered carefully and, if deemed necessary, carried out for the shortest possible time.[60]

Data from RCTs in patients undergoing 'on pump' cardiac surgery indicate that aspirin continuation increases reoperation rates ~2.5-fold, without affecting transfusion rates.[61] Post-operative blood loss increases as well, by ~100 mL, but not for daily aspirin doses <325 mg.[61] A comprehensive meta-analysis of non-cardiac surgery indicates that length of operation, length of hospitalization, severity of bleeding (with the exception of intracranial surgery), and need for transfusions are not increased by aspirin.[59] Similarly, a randomized trial comparing 150 mg daily aspirin to placebo in patients undergoing transurethral prostatectomy showed increased post-operative blood loss (~140 mL) with aspirin, but no significant differences in intra-operative bleeding, transfusion rates, or length of hospitalization.[62]

A risk-benefit assessment should be performed, based on the patient's thrombotic risk of stopping therapy against the haemorrhagic risk of continuing single or dual antiplatelet therapy (*Table 5*),[63] particularly in patients with stents or with ACSs. Antiplatelet therapy may be withdrawn before surgery when it is prescribed for primary prevention (given the relatively low-

Table 5 Proposal for perioperative antiplatelet management based on patient's risk of thrombosis vs. surgical bleeding risk

Surgical bleeding risk	Patient's thrombotic risk		
	Low: >9–12 months after uncomplicated ACS, DES, POBA, BMS, CABG	**Medium: 7 weeks to 9–12 months after uncomplicated ACS, POBA, BMS, CABG; 7–12 months after DES, or high-risk stent**	**High: ≤6 weeks after ACS, POBA, BMS, CABG, or <9–12 months after their complications; ≤6 months after DES or high-risk stent**
Low (transfusion usually not needed): general biopsies. skin, dental, anterior eye, minor general, minor orthopaedic, minor ENT surgery, endoscopy	Maintain low-dose aspirin	Maintain low-dose aspirin and $P2Y_{12}$ blocker (if prescribed)	Maintain low-dose aspirin and $P2Y_{12}$ blocker (if prescribed)
Medium (transfusion often required): cardiovascular, visceral, ENT, reconstructive, major orthopaedic, endoscopic urological surgery	Maintain low-dose aspirin	Maintain low-dose aspirin and $P2Y_{12}$ blocker (if prescribed)	Maintain low-dose aspirin and $P2Y_{12}$ blocker (if prescribed)
High: intracranial, spinal canal, posterior eye surgery. Possible bleed in closed space. Large expected blood loss	Withdraw aspirin for 3–5 days	Postpone elective surgery. If urgent, maintain low-dose aspirin for all but intracranial surgery. Withdraw $P2Y_{12}$ blocker (if prescribed) for 5 days[a]	Postpone non-vital surgery. If vital, maintain low-dose aspirin. Withdraw $P2Y_{12}$ blocker (if prescribed) for 5 days.[a] Consider bridging with small molecule i.v. GPI

Individual characteristics that enhance bleeding risk (e.g. age, renal failure) are not considered here but are discussed elsewhere. Withdrawal of aspirin is recommended for only one, and or $P2Y_{12}$ blockers for two, of the nine combinations. Because stroke patients may receive aspirin alone, aspirin + dipyridamole, or clopidogrel alone, their management is not discussed, nor are there sufficient data to make specific recommendations.

ACS, acute coronary syndrome; BMS, bare metal stent; CABG, coronary artery bypass graft; DES, drug-eluting stent; ENT, ear nose and throat; GPI, glycoprotein IIb/IIIa inhibitor. POBA, plain old balloon angioplasty.

[a]The duration of $P2Y_{12}$ blocker withdrawal may vary according to the individual agent; however, comparative data among the three available $P2Y_{12}$ blockers are lacking.

thrombotic risk) or when bleeding in a closed space may be life-threatening or irreversible (e.g. intracranial, posterior eye).[60,63] At the other extreme, patients receiving BMS within 6 weeks or DES within 6 months should not routinely discontinue dual antiplatelet therapy prior to surgery.[63] When aspirin is maintained, a daily dose of 75–100 mg should be given. Resuming antiplatelet therapy is considered safe 12–24 h after adequate haemostasis has been achieved.

Management of bleeding

In ACS patients, therapy-related major bleeding is associated with an increase in early and late morbidity and mortality[64,65] and there is emerging evidence that this association may be in part causal.[66,67] There is also solid data to indicate that bleeding is not unpredictable: there are well-characterized risk factors for bleeding, such as age, renal disease, female gender, low body weight (factors potentially associated with overdosing of antithrombotic drugs) which have led to the design of bleeding risk scores for stable[68] and unstable coronary artery disease.[69,70] Therefore, proper quantification of bleeding by use of appropriate standardized consensus definitions[71] and identification of patients at risk through the use of bleeding risk scores are important to improve assessment and prevention. The design of algorithms to integrate the stratification of risk on the ischaemic/thrombotic side with that on the bleeding side[72] is a key topic for future research.

When bleeding occurs, physicians are tempted to interrupt antiplatelet therapy. The withdrawal of platelet and coagulation inhibition may, however, re-exacerbate pro-thrombotic mechanisms with the consequence of precipitating additional ischaemic events.[64,65] Withdrawal of only one antiplatelet agent in case of dual anti-platelet therapy may be more appropriate, although this suggestion is not based on randomized trial evidence.

Various effects, including the release of epinephrine and norepinephrine, angiotensin, endothelin-1, and vasopressin as well as the depletion in 2,3-diphosphoglyceric acid and nitric oxide, may explain why the transfusion of packed red blood cells is not as beneficial as expected. In fact, a restrictive transfusion strategy is associated with lesser ischaemic events, pulmonary oedema, and even mortality.[73–75] Therefore, an aggressive transfusion strategy cannot be recommended and blood transfusions should be restricted to patients with a haematocrit value $<25\%$ or a Hb <80 g/L.[76]

Bleeding is sufficiently controlled by local measures in most cases, when it is attributable to a single local source. Few bleeding events require surgical interventions, and most of these interventions can safely be performed despite residual platelet inhibition. Antiplatelet therapy may be continued or reinstituted early after surgery. Platelet transfusions, FVIIa, aprotinin, or tranexamic acid are required only in rare cases. Such treatments, however, may carry a risk of thromboembolic events.

Recommendations concerning individual antiplatelet agents

Aspirin

Aspirin once daily is recommended in clinical conditions in which antiplatelet prophylaxis has a favourable benefit/risk profile. The available evidence supports daily doses of aspirin in the range of 75–100 mg for the long-term prevention of serious vascular events in high-risk patients, including those with ACS and those undergoing PCI.[77] In situations where an immediate antithrombotic effect is required (such as in ACS or in acute ischaemic stroke), a loading dose of 160–300 mg should be given in order to ensure complete inhibition of TXA_2-dependent platelet aggregation.[1,78] The use of intravenous formulations of aspirin is considered unnecessary, unless dictated by the inability of the patient to swallow or chew an oral formulation. It should be emphasized that the commonly used intravenous administration of 500 mg of aspirin would achieve systemic drug levels equivalent to ~1000 mg of plain aspirin given orally, thereby producing substantial inhibition of PGI_2 biosynthesis.[79] These considerations should limit the use of intravenous aspirin to 80–150 mg and encourage drug companies to develop an appropriate intravenous formulation of low-dose aspirin.

No test of platelet function is routinely recommended to assess the antiplatelet effect of aspirin in the individual patient. Measurement of serum TXB_2 may help detect non-compliance or less than complete inactivation of platelet COX-1 due to an interaction with other NSAIDs (see Supplementary material online).

The routine use of PPIs or cytoprotective agents is not recommended in patients taking daily doses of aspirin in the range of 75–100 mg, because of lack of large randomized trials demonstrating the efficacy of such protective strategies in reducing the risk of upper GI bleeding complications. Two randomized studies[80,81] suggest that the combination of esomeprazole and low-dose aspirin is superior to clopidogrel in preventing recurrent ulcer bleeding in patients with a history of aspirin-induced ulcer bleeding.

Arthritic patients on low-dose aspirin therapy should be instructed to avoid the use of ibuprofen or naproxen because even over-the-counter doses of these NSAIDs may interfere with the antiplatelet effect of aspirin.[82,83] Alternative options are represented by paracetamol or diclofenac, because they do not interfere with the platelet pharmacodynamics of low-dose aspirin.[84]

Clopidogrel

Clopidogrel, 75 mg daily, is an appropriate alternative for patients with coronary, cerebrovascular or peripheral arterial disease who cannot tolerate low-dose aspirin.

The publication of the CURE,[41] COMMIT,[44] and CLARITY-TIMI 28[43] trials and the need for dual antiplatelet therapy after stenting has led to the guideline recommendation of aspirin and clopidogrel for both patients with NSTE-ACS and STEMI. While not overcoming the problem of variability in response, higher loading and maintenance doses of clopidogrel (600 vs. 300 mg loading and 150 vs. 75 mg daily for 7 days) achieve greater mean levels of platelet inhibition.[85] However, when evaluated in a wide population of ACS patients intended to undergo PCI, high-dose clopidogrel was not found to reduce significantly the 30-day outcome when compared with standard dose, except in the subgroup actually undergoing PCI,[86] but major bleeding was significantly increased in high- vs. low-dose clopidogrel.

Table 6 Antiplatelet treatment options in different settings of myocardial ischaemia and in the primary prevention of CV disease

Setting	Antiplatelet treatment	Comment
ACS patients		
All ACS patients	ASA 160–300 mg oral LD (80–150 mg i.v.) plus ASA 75–100 mg p.o. o.d. long-term plus $P2Y_{12}$ receptor blocker for 12 months[a]	Dual antiplatelet therapy (i.e. ASA plus a $P2Y_{12}$ blocker) is recommended for 12 months in all ACS patients, whether or not PCI is performed (I A)
All ACS patients	Clopidogrel as $P2Y_{12}$ blocker, 300 mg oral LD plus 75 mg p.o. o.d. for 12 months[b]	Clopidogrel on top of ASA is recommended when ticagrelor or prasugrel (in case of PCI) are unavailable or contraindicated (I B)
All ACS patients	Ticagrelor as $P2Y_{12}$ blocker, 180 mg oral LD plus 90 mg p.o. b.i.d. for 12 months	Ticagrelor (instead of clopidogrel) is recommended if available and not contraindicated (I B)
ACS patients undergoing PCI	Prasugrel as $P2Y_{12}$ blocker, 60 mg oral LD plus 10 mg p.o. o.d. for 12 months	For ACS patients undergoing PCI, prasugrel is recommended, if available and not contraindicated, instead of clopidogrel but not instead of ticagrelor (I B)[c]
Primary PCI	Bail-out i.v. GPI + routine bivalirudin	Routine bivalirudin + bail-out i.v. GPI is recommended instead of routine i.v. GPI + heparin (I B)
[b]STEMI with fibrinolysis	300 mg LD of clopidogrel	Tested—and therefore safely recommendable—only in patients ≤75 years (I B)
	75 mg p.o. o.d.	Tested only up to 4 weeks (I A)[a]
[b]Primary PCI	Clopidogrel 600 mg oral LD	A LD of 600 instead of 300 mg is recommended based on *post hoc* analyses and non-randomized clinical studies (I C)
[b]ACS undergoing PCI	Clopidogrel 600 mg oral LD + 150 mg p.o. o.d. for 6 days post-PCI	This regimen (instead of 300 mg LD + 75 mg o.d.) should be considered during the first week post PCI, based on a large prespecified subgroup analysis (IIa B)
PCI in NSTEMI	i.v. Abciximab	i.v. Abciximab (on top of ASA, clopidogrel and heparin) should be considered in NSTEACS patients with troponin elevation undergoing PCI (IIa B)
NSTEACS undergoing PCI	Bail-out i.v. GPI + routine bivalirudin	Bivalirudin + bail-out i.v. GPI should be considered instead of routine i.v. GPI + heparin (IIa B)
Elective PCI patients	ASA 160–300 mg oral LD (80–150 mg i.v.) plus ASA 75–100 mg p.o. o.d. long-term plus clopidogrel 75 mg p.o. o.d.	Dual antiplatelet therapy is recommended initially for all patients undergoing elective PCI (I A); the duration of $P2Y_{12}$ blocker administration varies according to type of coronary stent: at least 1 month after BMS (I B); at least 3 months (I B), 6 months (IIa B), or 1 year (IIb C) after DES
	Clopidogrel 300 mg oral LD >12 h before PCI	An upstream LD of clopidogrel 300 mg (instead of delayed or no LD) is recommended (I B)
Chronic IHD patients	ASA 75–100 mg p.o. o.d. long term	Low-dose ASA is recommended in the absence of contraindications in all patients with diagnosed IHD (I A)
E.g. stable angina, elective CABG, >12 months post-ACS	Clopidogrel 75 mg p.o. o.d. long term	Long-term clopidogrel instead of ASA is recommended in case of ASA intolerance (I B)
Asymptomatic individuals at high risk (>2% pa) of CV disease	ASA 75–100 mg p.o. o.d. long term	Low-dose ASA may be considered on an individual basis, if risk remains high after optimal blood pressure control and statin therapy (IIa C)

ACS, acute coronary syndrome; ASA, aspirin; b.i.d., bis in die; BMS, bare metal stent; CABG, coronary artery bypass graft; CV, cardiovascular, DES, drug-eluting stent; GPI, glycoprotein IIbIIIa inhibitor, IHD, ischaemic heart disease; i.v., intravenous, LD, loading dose, o.d., once a day, MI, myocardial infarction, NSTE, non-ST-elevation, o.d. , once a day, pa, per annum, PCI, percutaneous coronary intervention, p.o., per os, STE, ST-elevation.

[a]Although $P2Y_{12}$ blockers (namely clopidogrel) have been tested against placebo only in patients with NSTEACS with or without PCI for up to 12 months and in patients with STEMI (treated with fibrinolysis) for up to 4 weeks, a $P2Y_{12}$ blocker should be considered on top of ASA in all STEMI patients for up to 12 months (IIa C).

[b]Indicates general statement reported for all ACS patients would apply to three separate sub-settings.

[c]A head to head comparison of prasugrel vs. ticagrelor is lacking.

Based on international recommendations,[87,88] PPIs are recommended to reduce GI bleeding among patients with a history of upper GI bleeding. Proton pump inhibitors are appropriate in patients with multiple risk factors for GI bleeding who require antiplatelet therapy.[88] However, PPIs might also interact with the antithrombotic effect of clopidogrel because of a pharmacokinetic interaction reducing formation of its active metabolite.[11] The FDA and EMA have issued warnings concerning all or specific PPIs in

terms of the potential clinical impact of this pharmacokinetic interaction. A recently published meta-analysis of observational studies and *post hoc* analyses of RCTs[12] has reported that PPI users displayed a 41% increased risk of MACE and an 18% increased risk of death compared with non-users. The majority of patients included in the meta-analysis was treated with omeprazole, the most potent CYP2C19 inhibitor.[12] The COGENT trial represents the first, randomized assessment of a fixed combination of clopidogrel (75 mg) and omeprazole (20 mg), compared with clopidogrel in 3873 ACS patients with a median follow-up of 133 days.[89] One hundred and nine patients had a cardiovascular event and there was no evidence of an adverse interaction between omeprazole and clopidogrel (HR = 0.99; 95% CI, 0.68–1.44). However, due to premature termination of the trial, COGENT had limited statistical power to detect a clinically relevant interaction. These recent findings suggest the need for reconsidering the appropriateness of PPI co-administration in CHD patients treated with clopidogrel, carefully balancing the potential benefits and risks of this adjuvant therapy in the individual patient.

Tailoring antiplatelet therapy according to platelet function and genotype is discussed in the Supplementary material online.

Prasugrel

The main advantage of prasugrel over clopidogrel appears to be the prevention of non-fatal MI and stent thrombosis in ACS patients who undergo PCI.[51] The cost of this prevention is excess bleeding. The improved efficacy of prasugrel may be exploited in the setting of STEMI referred for primary PCI or after coronary angiography in patients with NSTE-ACS undergoing PCI.[47] The use of prasugrel should also be considered in patients who develop stent thrombosis despite aspirin and clopidogrel therapy. The place of prasugrel in the initial medical management of ACS remains uncertain until further ongoing studies are completed.[90]

A lower maintenance dose of 5 mg in the elderly (>75 years) and the underweight (<60 kg) would seem logical, but formal testing of this hypothesis is necessary before such a strategy can be recommended.[90] The ongoing TRILOGY trial and other studies are designed to answer this question.

Dipyridamole

The addition of dipyridamole to aspirin has not been shown clearly to produce additional reductions in serious vascular events in an overview of 25 trials among ~10 000 high-risk patients,[3] although two trials suggested that there may be a worthwhile further reduction in stroke.[29,30] The combination of low-dose aspirin and extended-release dipyridamole (200 mg, b.i.d.) is considered an acceptable option for patients with non-cardioembolic cerebral ischaemic events;[91] however, there is no basis to recommend this combination in patients with ischaemic heart disease.

Ticagrelor

Ticagrelor provides superior prevention of death and recurrent MI compared with clopidogrel when used in patients with STEMI planned for primary PCI or moderate-to-high-risk NSTE-ACS and is therefore recommended in these patients other than those with prior history of intracranial haemorrhage or active pathological bleeding that cannot be controlled by local measures. There is no requirement to modify the dose of ticagrelor according to age or body weight but the concomitant use of strong CYP3A inhibitors such as ketoconazole is contraindicated since these will markedly increase the plasma levels of ticagrelor and increase the risk of bleeding and other side effects. The PEGASUS-TIMI 54 study will address the question of whether ticagrelor compared with placebo provides ongoing benefit in moderate-to-high-risk patients >1 year after MI (Clinicaltrials.gov identifier NCT01225562).

Ticagrelor can be commenced prior to obtaining the results of coronary angiography and may be administered to patients who have already received clopidogrel. If it is not tolerated as a result of adverse effects other than bleeding, maintenance therapy with either clopidogrel or prasugrel, as appropriate, may be commenced in its place. Despite the observation of greater creatinine increases in ticagrelor-treated vs. clopidogrel-treated patients in the PLATO study,[52] ticagrelor showed a greater absolute risk reduction compared with clopidogrel in patients with evidence of chronic kidney disease and is therefore recommended in these patients, other than those requiring renal replacement therapy.[92]

The main treatment recommendations of antiplatelet drugs are summarized in *Table 6*.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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