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ESC Expert Consensus Document

# Expert Consensus Document on the Use of Antiplatelet Agents

## The Task Force on the Use of Antiplatelet Agents in Patients with Atherosclerotic Cardiovascular Disease of the European Society of Cardiology

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## Preamble

Guidelines and Expert Consensus Documents aim to present all the relevant evidence on a particular issue in order to help physicians to weigh the benefits and risks of a particular diagnostic or therapeutic procedure. They should be helpful in everyday clinical decision-making.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by different organizations, the European Society of Cardiology (ESC) and by other related societies. By means of links to web sites of National Societies several hundred guidelines are available. This profusion can put at stake the authority and validity of guidelines, which can only be guaranteed if they have been developed by an unquestionable decision-making process. This is one of the reasons why the ESC and others have issued recommendations for formulating and issuing Guidelines and Expert Consensus Documents.

In spite of the fact that standards for issuing good quality Guidelines and Expert Consensus Documents are well defined, recent surveys of Guidelines and Expert Consensus Documents published in peer-reviewed journals between 1985 and 1998 have shown that methodological standards were not complied within the vast majority of cases. It is therefore of great importance that guidelines and recommendations are presented in formats that are easily interpreted. Subsequently, their implementation programmes must also be well conducted. Attempts have been made to determine whether guidelines improve the quality of clinical practice and the utilization of health resources.

The *ESC Committee for Practice Guidelines* (*CPG*) supervises and coordinates the preparation of new *Guidelines* and *Expert Consensus Documents* produced by

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Task Forces, expert groups or consensus panels. The Committee is also responsible for the endorsement of these Guidelines and Expert Consensus Documents or statements.

## Introduction

The role of aspirin and other platelet-active drugs in the treatment and prevention of atherothrombosis has been reviewed recently by the Sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy[1] (available online at www.chestnet.org). Moreover, updated information on the efficacy and safety of antiplatelet therapy is provided by the collaborative meta-analysis of 287 secondary prevention trials, prepared by the Antithrombotic Trialists' (ATT) Collaboration[2] (available online at www.bmj.com). The purpose of the present guidelines is to integrate a mechanistic understanding as to why some antiplatelet drugs work and some do not, with an evidence-based definition of categories of patients for whom the benefits of antiplatelet therapy clearly outweigh the risk of bleeding complications. Recommendations concerning the use of individual antiplatelet agents will also be provided and open issues discussed.

Specific treatment recommendations are outside the scope of this document and are adequately covered in disease-oriented guidelines issued by the European Society of Cardiology (available online at www.escardio.org). At variance with earlier guidelines incorporating the use of antiplatelet agents in the therapeutic management of a single disease entity (e.g. acute myocardial infarction), the present document intends to provide the practising cardiologist with a novel instrument to guide his/her choice of the most suitable antiplatelet strategy for the individual patient with different clinical manifestations of ischaemic heart disease.

## Platelet pathophysiology

Platelets are vital components of normal haemostasis and key participants in pathologic thrombosis by virtue of their capacity to adhere to injured blood vessels and to accumulate at sites of injury.[3] Although platelet adhesion and activation should be viewed as a 'physiological' response to the sudden 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, vascular occlusion and transient ischaemia or infarction. Currently available antiplatelet drugs interfere with some steps in the activation process, including adhesion, release, and/or aggregation,[3] and have a measurable impact on the risk of arterial thrombosis that cannot be dissociated from an increased risk of bleeding.[4]

In discussing antiplatelet strategies, it is important to recognise that approximately $10^{11}$ platelets are produced each day under physiological circumstances, a level of production that can increase up to tenfold at times of increased need.[5] Platelets form by fragmentation of megakaryocyte cytoplasm and have a maximum circulating life span of about 10 days in man.[5] Thus, platelets are anucleate blood cells that provide a circulating source of chemokines, cytokines and growth factors that are preformed and packaged in storage granules. Moreover, activated platelets can synthesize prostanoids [primarily, thromboxane (TX)$A_2$] from arachidonic acid released from membrane phospholipids, through rapid coordinated activation of phospholipase(s), cyclo-oxygenase (COX)-1 and TX-synthase[3] (Fig. 1). Newly formed platelets also express the inducible isoforms of COX (COX-2) and PGE-synthase, and this phenomenon is markedly amplified in association with accelerated platelet regeneration.[6] Although activated platelets are not thought to synthesize proteins de novo, they can translate constitutive mRNAs into proteins, including interleukin-1β over several hours.[7] Thus, platelets may have previously unrecognized roles in inflammation and vascular injury, and antiplatelet strategies may be expected to impact on platelet-derived protein signals for inflammatory and/or proliferative responses.[7,8]

Negative modulation of platelet adhesion and aggregation is exerted by a variety of mechanisms, including endothelium-derived prostacyclin ($PGI_2$), nitric oxide, CD39/ecto-ADPase and platelet endothelial cell adhesion molecule-1 (PECAM-1).[9–11] Some drugs may interfere with these regulatory pathways, as exemplified by the dose-dependent inhibition of $PGI_2$ production by aspirin and other COX-inhibitors.[1,9] The apparent redundancy of mechanisms of endothelial thromboresistance is likely to limit the clinical consequences of $PGI_2$ inhibition by COX-inhibitors.

## Mechanism of action and clinical efficacy of antiplatelet drugs

### Drugs inducing a permanent modification in platelet function

An ideal antiplatelet agent is one that would exploit the unique metabolic features of platelets noted above through a 'hit-and-run' mechanism of action, i.e. by permanently inactivating a platelet protein (an enzyme or receptor) that cannot be resynthesized during a 24-h dosing interval, through a short-lived active moiety, thus limiting the extent and duration of any potential extraplatelet effect(s). Two currently available antiplatelet drugs, i.e. acetylsalicylic acid (aspirin) and clopidogrel, meet these requirements (Table 1).

#### Aspirin

Aspirin induces a long-lasting functional defect in platelets, which can be detectable clinically as a prolonged bleeding time. This appears to be primarily, if not exclusively, due to permanent inactivation by aspirin of a key enzyme in platelet arachidonate metabolism (Fig. 1). This enzyme, prostaglandin (PG) H-synthase, is responsible for the formation of $PGH_2$, the precursor of $TXA_2$. In human platelets, $TXA_2$ provides a mechanism for amplifying the activation signal through its being synthesized and released in response to various platelet agonists

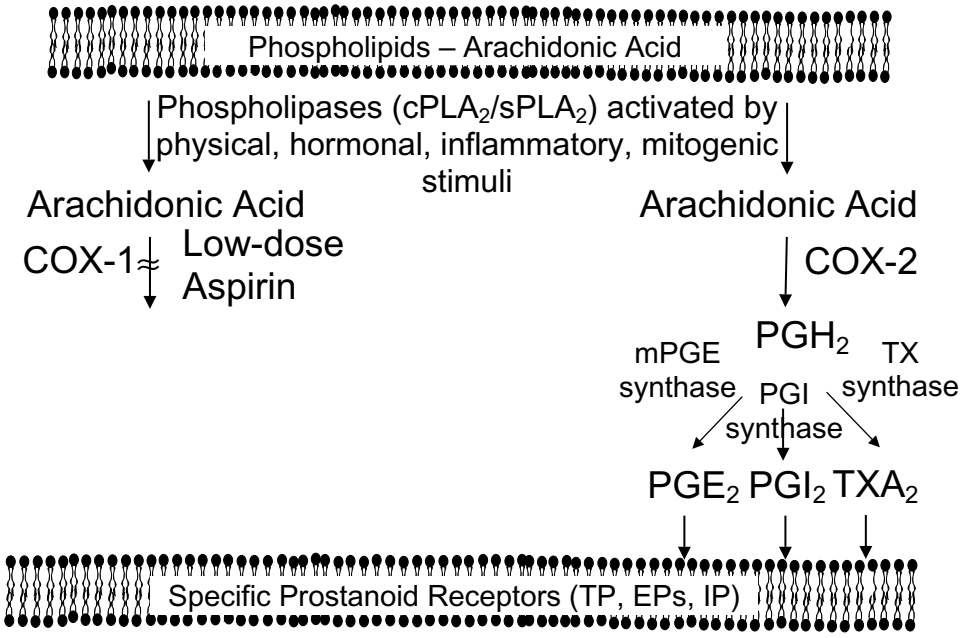


**Fig. 1** Arachidonic acid metabolism via the cyclo-oxygenase (COX) pathways. Low-dose aspirin is shown inhibiting the COX-1 pathway. This results in suppression of thromboxane (TX) $A_2$ and prostaglandin (PG) $E_2$ synthesis in platelets. However, the same products can be formed through the COX-2 pathway in an aspirin-insensitive fashion. $PLA_2$, phospholipase $A_2$; EP, $PGE_2$ receptor; IP, prostacyclin receptor; TP, thromboxane receptor.

**Table 1** Main features of aspirin, clopidogrel and GPIIb/IIIa antagonists[a]

| Feature | Aspirin | Clopidogrel | GPIIb/IIIa antagonists |
|---|---|---|---|
| Targeted platelet protein | COX-1 | $P2Y_{12}$ | $\alpha_{IIb}\beta_3$ |
| Reversibility of the effect | no | no | yes |
| Half-life of the drug or active metabolite | min | min | hours |
| Need for monitoring | no | no | ? |
| Need for dose-titration | no | no | yes |

[a]Modified from Patrono *et al.*[1]

(e.g., collagen, adenosine diphosphate [ADP], platelet-activating factor, thrombin) and, in turn, inducing irreversible aggregation.[12]

Aspirin selectively acetylates the hydroxyl group of a single serine residue at position 529 ($Ser^{529}$) within the polypeptide chain of platelet PGH-synthase. This enzyme exhibits two distinct catalytic activities: a bis-oxygenase (cyclo-oxygenase [COX]) involved in formation of $PGG_2$, and a hydroperoxidase allowing a net two-electron reduction in the 15-hydroperoxyl group of $PGG_2$, thus yielding $PGH_2$. Through O-acetylation of $Ser^{529}$ by aspirin, the cyclo-oxygenase activity is lost permanently, whereas the hydroperoxidase activity is not affected. An inducible form of PGH-synthase has been identified and termed PGH-synthase 2 or COX-2.[13] Aspirin inhibits the cyclo-oxygenase activity of PGH-synthase 2, but at higher concentrations than those required to inhibit PGH-synthase 1 or COX-1 (i.e. the constitutive enzyme).[14] This may account, at least in part, for the different dose requirements of analgesic and anti-inflammatory versus antiplatelet effects of the drug.

A very large database of randomized clinical trials (reviewed recently in refs.[1,2]) now offers the most compelling evidence that prevention of myocardial infarction and ischaemic stroke by aspirin is largely due to permanent inactivation of platelet COX-1. These studies, which tested the efficacy and safety of the drug when given at daily doses ranging from as low as 30 mg to as high as 1500 mg,[1] have established two important facts. First, the anti-thrombotic effect of aspirin is saturable at doses in the range of 75 to 100 mg, as would be expected from human studies of platelet COX-1 inactivation.[12] Second, despite a half-life of approximately 20 min in the human circulation, the anti-thrombotic effect of aspirin is observed with dosing intervals of 24 to 48 h, reflecting the permanent nature of platelet COX-1 inactivation and the duration of $TXA_2$ suppression following oral dosing in man.[12] Other mechanisms of action that have been suggested to contribute to the anti-thrombotic effect of aspirin, such as an anti-inflammatory effect of the drug, are simply incompatible with these unique properties.

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

| Clinical setting | Benefit[a] (Number of patients in whom a major vascular event is avoided per 1000/year) | Risk[b] (Number of patients in whom a major GI bleeding event is caused per 1000/year) | |
|---|---|---|---|
| Men at low to high cardiovascular risk | 1–2 | 1–2 | Benefits and hazards are similar |
| Essential hypertension | 1–2 | 1–2 | |
| Chronic stable angina | 10 | 1–2 | Benefits greatly outweigh hazards |
| Prior myocardial infarction | 20 | 1–2 | |
| Unstable angina | 50 | 1–2 | |

[a]Benefits are calculated from randomized trial data reviewed in refs.[1,2]

[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 to 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 bleeding complications in the 'primary' prevention trials reviewed in ref.[1] ranged between 0.3 and 1.7 per 1000 patient years. Modified from Patrono et al., Chest 2001 (ref.[1]).

Although the search for the lowest effective dose of aspirin for platelet inhibition was largely driven by the explicit concern of concomitant inhibition of vascular $PGI_2$ production,[12] it is still uncertain whether dose-dependent suppression of the latter attenuates the anti-thrombotic effect of aspirin in clinical syndromes of vascular occlusion. The biochemical selectivity of low-dose aspirin arises from both pharmacokinetic determinants, such as the acetylation of platelet COX-1 that occurs in portal blood (prior to first-pass metabolism), and pharmacodynamic determinants, such as the limited sensitivity of endothelial COX-2 to the drug.[14] Aspirin is an effective anti-thrombotic agent in a wide range of daily doses. Whether dose-dependent inhibition by aspirin of a mediator of thromboresistance, such as $PGI_2$, may be responsible for a somewhat attenuated efficacy at high daily doses[15] remains to be demonstrated convincingly.

Aspirin's unique feature in inhibiting platelet COX-1 (i.e. its ability to inactivate the enzyme permanently through a short-lived active moiety) is ideally suited to its role as an antiplatelet drug, because they severely limit the extent and duration of extraplatelet effects of the drug, including the inhibition of $PGI_2$. Moreover, the cumulative nature of platelet COX-1 acetylation by repeated low doses of aspirin[16] explains the clinical efficacy of doses as low as 30 to 50 mg daily, the predictable high-grade inhibition of platelet $TXA_2$ biosynthesis, and the persistence of the drug's effect. These features, in turn, may limit the consequences of less-than-ideal compliance in a real world setting.

Permanent inactivation of platelet COX-1 by aspirin may lead to the prevention of thrombosis as well as to excess bleeding. At least two distinct COX-1-dependent mechanisms contribute to the increased risk of upper GI bleeding associated with aspirin exposure: inhibition of $TXA_2$-mediated platelet function and impairment of $PGE_2$-mediated cytoprotection in the gastrointestinal (GI) mucosa.[1] Whereas the former effect is dose-independent, at least for daily doses >30 mg, the latter effect is clearly dose-dependent. Inhibition of platelet function is largely responsible for the 2-fold increase in the risk of upper GI bleeding associated with daily doses of aspirin in the range of 75 to 100 mg, in as much as a similar relative risk is associated with other antiplatelet agents that do not act on COX and therefore do not affect $PGE_2$-mediated cytoprotection.[17] Inhibition of COX-1-dependent cytoprotection amplifies risk of bleeding/perforation by causing new mucosal lesions or aggravating existing ones, and is associated with a relative risk of four to six at the higher, analgesic or anti-inflammatory doses of aspirin. Assessing the net effect of aspirin requires an estimation of the absolute risk of the individual patient for thrombotic or haemorrhagic complications (Table 2). In individuals at very low risk for vascular occlusion (i.e. less than 1% per year), a very small absolute benefit may be offset by exposure of very large numbers of healthy subjects to undue serious bleeding complications (see below). As the risk of experiencing a major vascular event increases, so does the absolute benefit of antiplatelet prophylaxis with aspirin and, above a certain threshold, benefit clearly outweighs risk of bleeding (Fig. 2).[1]

### Ticlopidine and clopidogrel

Ticlopidine and clopidogrel are structurally related thienopyridines with platelet inhibitory properties. Both drugs selectively inhibit ADP-induced platelet aggregation, with no direct effects on the metabolism of arachidonic acid.[4] Ticlopidine and clopidogrel also can inhibit platelet aggregation induced by collagen and thrombin, but these inhibitory effects are abolished by increasing the agonist concentration and, therefore, likely reflect blockade of ADP-mediated amplification of the response to other agonists.

Neither ticlopidine nor clopidogrel affect ADP-induced platelet aggregation when added in vitro up to 500 μM, thus suggesting that in vivo hepatic transformation to an active metabolite, or metabolites, is necessary for their antiplatelet effects. A short-lived, active metabolite of clopidogrel has been characterized.[18] Recent evidence suggests that clopidogrel and, probably, ticlopidine

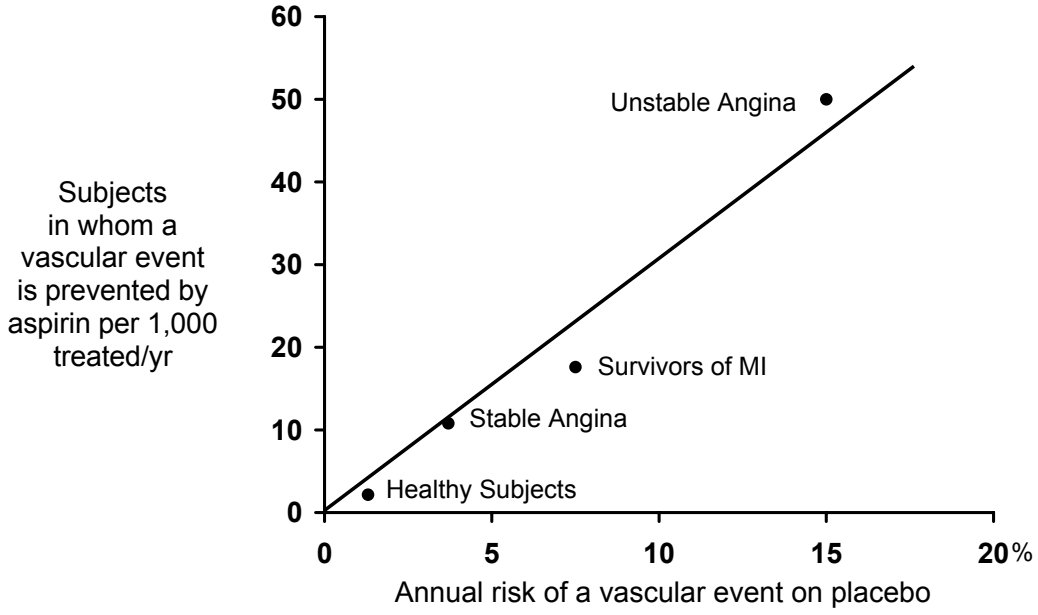


**Fig. 2** The absolute risk of vascular complications is the major determinant of the absolute benefit of antiplatelet prophylaxis. Data are plotted from placebo-controlled aspirin trials in different clinical settings. For each category of patients, the abscissa denotes the absolute risk of experiencing a major vascular event as recorded in the placebo arm of the trial(s). The absolute benefit of antiplatelet treatment is reported on the ordinate as the number of subjects in whom an important vascular event (non-fatal myocardial infarction, nonfatal stroke, or vascular death) is actually prevented by treating 1000 subjects with aspirin for 1 year. Reproduced from ref.[1] with permission from the American College of Chest Physicians.

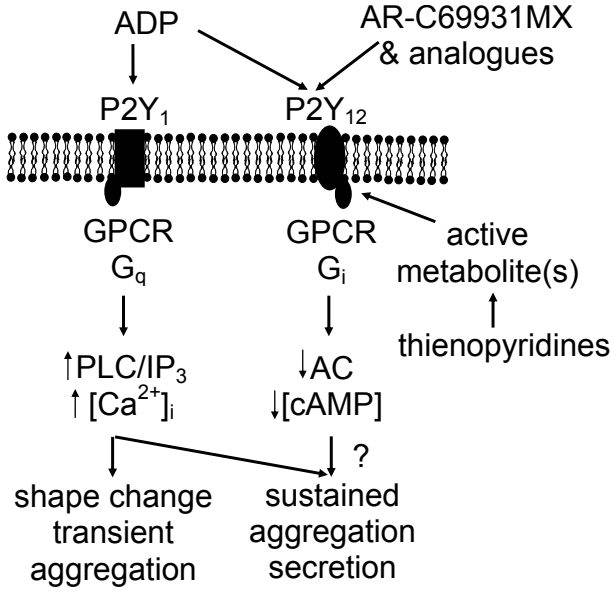


**Fig. 3** The two receptor model of ADP-induced platelet activation. The thienopyridines, ticlopidine and clopidogrel, inhibit ADP-induced platelet aggregation through active metabolites irreversibly inactivating the $P2Y_{12}$ receptor. Other antiplatelet agents, such as AR-C69931MX, compete with ADP for binding reversibly to the same receptor. GPCR, G-protein coupled receptor; PLC, phospholipase C; AC, adenylate cyclase.

induce irreversible alterations of the platelet ADP receptor $P2Y_{12}$ mediating inhibition of stimulated adenylyl cyclase activity by ADP[19] (Fig. 3). Inhibition of platelet function by clopidogrel is associated with a selective reduction in ADP-binding sites, with no consistent change in the binding affinity. Permanent modification of an ADP receptor by thienopyridines is consistent with time-dependent, cumulative inhibition of ADP-induced platelet aggregation on repeated daily dosing and with slow recovery of platelet function on drug withdrawal.[4]

After single oral doses of clopidogrel, ADP-induced platelet aggregation was inhibited in a dose-dependent

fashion in healthy volunteers, with an apparent ceiling effect (i.e. 40% inhibition) at 400 mg. Inhibited platelet aggregation was detectable 2 h after oral dosing of 400 mg, and it remained relatively stable up to 48 h.[4] With repeated daily dosing of 50 to 100 mg in healthy volunteers, ADP-induced platelet aggregation was inhibited from the second day of treatment (25–30% inhibition) and reached a steady state (50–60% inhibition) after 4 to 7 days. Such maximal inhibition is comparable to that achieved with ticlopidine (500 mg daily). Ticlopidine, however, has shown a slower onset of antiplatelet effect compared with clopidogrel.

The best available interpretation of these findings is that the active metabolite of clopidogrel has a pharmacodynamic pattern quite similar to that of aspirin in causing cumulative platelet inhibition on repeated daily low-dose administration.[1] As with aspirin, platelet function returned to normal 7 days after the last dose. Both the cumulative nature of the inhibitory effects and the slow recovery rate of platelet function are consistent with the active moieties of aspirin (i.e. acetylsalicylic acid) and clopidogrel (i.e. active metabolite) causing a permanent defect in a platelet protein that cannot be repaired during the 24-h dosing interval and can be replaced only through platelet turnover.[1] This also justifies the once-daily regimen of both drugs despite their short half-life in the circulation. Bleeding times measured in the same multiple-dose study of clopidogrel described earlier showed a comparable prolongation (by 1.5–2.0-fold over controls) at 50 to 100 mg daily or ticlopidine at 500 mg daily.[4]

Clopidogrel has undergone an unusual clinical development, with limited phase II studies and a single large phase III trial (i.e. CAPRIE) to test its efficacy and safety at 75 mg daily compared with aspirin at 325 mg daily.[20] Clopidogrel was slightly more effective than aspirin, and there was some suggestion from a marginally significant heterogeneity test that clopidogrel may be particularly effective at preventing vascular events in patients with symptomatic peripheral arterial disease. This interesting and, perhaps, unexpected finding suggests that the pathophysiologic importance of $TXA_2$ and ADP varies in different clinical settings. In the CAPRIE trial, the frequency of severe rash was higher with clopidogrel than with aspirin (absolute excess approximately 1–2 per 1000), as was the frequency of diarrhoea, thus reproducing the characteristic side effects of ticlopidine. No excess neutropenia, however, was associated with clopidogrel, but the frequency of this serious complication was extremely low (0.05%) in this trial.[20] The CURE trial[21] has demonstrated the efficacy and safety of adding clopidogrel (a loading dose of 300 mg, followed by 75 mg daily) to aspirin in the long-term management of patients with acute coronary syndromes without ST-segment elevation. Moreover, the combination of aspirin and clopidogrel has become standard treatment for 1 month after coronary stent implantation.[22] The recently reported CREDO trial[23] has demonstrated that following percutaneous coronary interventions, long-term (1-year) clopidogrel therapy significantly reduces the risk of adverse ischaemic events.

## Drugs inducing a reversible inhibition of platelet function

At least four distinct platelet proteins represent the target of reversible inhibitors with variable antiplatelet effects, i.e. COX-1, glycoprotein (GP)IIb/IIIa, the $PGH_2$/$TXA_2$ (TP) receptor and the ADP receptor $P2Y_{12}$.[4] Whether incomplete, reversible inhibition of platelet COX-1 by traditional non-steroidal anti-inflammatory drugs (NSAIDs) is associated with clinical benefits has not been tested adequately in randomized trials. Two population-based observational studies failed to demonstrate an association between non-aspirin NSAID prescription and reduced risk of developing cardiovascular events.[24,25] The incomplete and reversible inhibition of platelet GPIIb/IIIa by oral blockers is not associated with clinically detectable benefits, despite a dose-dependent increase in bleeding complications.[1] This apparent paradox may be reconciled by considering that persistent high-grade blockade of these platelet proteins may be required to prevent thrombosis in response to sudden fissuring of an atherosclerotic plaque as opposed to transient inhibition of the same target potentially causing bleeding from a pre-existing GI lesion.[8] The successful utilization of intravenous, high-grade blockade of GPIIb/IIIa by commercially available antagonists of this receptor (abciximab, tirofiban, eptifibatide)[1] is consistent with these mechanistic considerations and will not be discussed here.

### Reversible COX-1 inhibitors

A variety of non-selective NSAIDs can inhibit $TXA_2$-dependent platelet function through competitive, reversible inhibition of COX-1. When used at conventional anti-inflammatory dosage, these drugs generally inhibit platelet COX-1 activity only by 70 to 90%. Such inhibition may be insufficient to block platelet aggregation adequately in vivo, however, because of the substantial biosynthetic capacity of human platelets to produce $TXA_2$.[1] The only reversible COX-1 inhibitors that have been examined for anti-thrombotic efficacy in relatively small randomized clinical trials are sulfinpyrazone, flurbiprofen, indobufen, and triflusal.[1] None of these reversible COX-1 inhibitors is approved as an antiplatelet drug in the United States, though they are available in a few European countries. Moreover, the randomized clinical trials comparing indobufen to aspirin and triflusal to aspirin largely lack adequate statistical power to test biologically plausible differences in efficacy, nor were they designed to establish therapeutic equivalence.[1,2]

The concomitant administration of ibuprofen, but not rofecoxib, a selective COX-2 inhibitor,[26] acetaminophen, or diclofenac antagonizes the irreversible platelet inhibition induced by low-dose aspirin.[27]

### Oral GPIIb/IIIa blockers

The success of short-term, high-grade blockade of platelet GPIIb/IIIa with intravenous agents has led to the development of an array of oral GPIIb/IIIa antagonists in the hope of extending this benefit to the long-term management of patients with acute coronary syndromes.

To date, five large-scale clinical trials have been completed (EXCITE, OPUS, SYMPHONY 1 and 2, BRAVO) and a meta-analysis of four of these has been published.[28] The consistent finding of these large-scale trials involving over 40 000 patients is that oral GPIIb/IIIa antagonists (xemilofiban, orbofiban, sibrafiban and lotrafiban) are not more effective than aspirin or, when combined with aspirin, are not superior to placebo and may in fact increase mortality.[1,28] Several mechanisms have been put forward to explain these results. One is that the poor oral bioavailability of these compounds and the target of approximately 50% inhibition of platelet aggregation resulted in poor antiplatelet activity in many patients. This would explain a lack of clinical response, but not an increase in mortality. Indeed, overall there was an increase in the frequency of bleeding and a reduced requirement of urgent revascularization, suggesting some degree of clinical efficacy.[28]

An alternative explanation is that GPIIb/IIIa antagonists can activate platelets, at least in some individuals.[29,30] GPIIb/IIIa is not a passive receptor, rather like all integrins it responds to ligand binding by activating the cell. Thus, fibrinogen binding leads to signals that further activate platelets and are essential for platelet aggregation. Several studies suggest that ligands designed to bind to the receptor and prevent platelet aggregation may trigger some of these activating signals.[29,30] Moreover, the partial agonist activity may not be confined to oral drugs, as abciximab has been reported to activate platelets and promote procoagulant activity by promoting the shedding of CD40L.

### TP antagonists

The $TXA_2/PGH_2$ (TP) receptor is a G protein-coupled receptor, which on ligand stimulation results in activation of phospholipase C and subsequent increase in inositol 1,4,5-triphosphate, diacylglycerol, and intracellular $Ca^{2+}$ concentrations.[4]

Potent ($K_d$ in the low nanomolar range) and long-lasting (half-life >20 h) TP antagonists have been developed, including GR 32191, BMS-180291 (ifetroban), and BM 13.177 (sulotroban). Despite the anti-thrombotic activity demonstrated in various animal species and the interesting 'cardioprotective' activity demonstrated in dogs and ferrets, these compounds have yielded disappointing results in phase II/III clinical trials.[4] Before drawing definitive conclusions on the apparent failure of this approach, however, it should be mentioned that these studies suffer from severe limitations, including: (1) unrealistic hypotheses of risk reduction being tested (e.g., a 50% reduction in the late clinical failure rate after successful coronary angioplasty); (2) heterogeneous end-points being pooled together, including 'clinically important restenosis', for which no evidence of $TXA_2$-dependence was obtained during earlier aspirin trials; and (3) an anti-ischaemic effect being tested in individuals with unstable coronary syndromes treated using standard therapy, including aspirin and heparin.[4]

Clinical development of GR 32191 and sulotroban has been discontinued because of these disappointing — though largely predictable — results. It would be interesting to see at least one such compound developed through phase III clinical trials with adequate end-points and realistic sample sizes. The potential advantages of potent TP antagonists compared with low-dose aspirin relate to the recent discovery of aspirin-insensitive agonists of the platelet receptor, such as $TXA_2$ derived from the COX-2 pathway[31] and the $F_2$-isoprostane, 8-iso-$PGF_{2\alpha}$, which is a product of free radical-catalyzed peroxidation of arachidonic acid.[32] The latter can synergize with sub-threshold concentrations of other platelet agonists to evoke a full aggregatory response, thus amplifying platelet activation in those clinical settings associated with enhanced lipid peroxidation.[33] The TP antagonist, S-18886, has recently completed phase II clinical development with promising results.

### Other $P2Y_{12}$ antagonists

A new class of direct $P2Y_{12}$ antagonists (e.g. AR-C69931MX) is currently being developed that appears to block this ADP receptor more effectively than clopidogrel.[34]

## Patients that may benefit from antiplatelet therapy

In the most recent meta-analysis of the ATT collaboration,[2] allocation of high-risk patients to a prolonged course of antiplatelet therapy reduced the combined outcome of nonfatal myocardial infarction, non-fatal stroke or vascular death ('serious vascular events') by about 25%. Non fatal myocardial infarction 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 were 36 per 1000 treated for 2 years, among patients with previous myocardial infarction; 38 per 1000 patients treated for 1 month among patients with acute myocardial infarction; 36 per 1000 treated for 2 years among those with previous stroke or transient ischaemic attack (TIA); nine per 1000 treated for 1 month among those with acute ischaemic stroke; and 22 per 1000 treated for 2 years among other high-risk patients, including those with stable angina, peripheral arterial disease and atrial fibrillation.[2] In each of these high-risk categories, the absolute benefits substantially outweighed the absolute risks of major bleeding complications.[2]

Two thirds of the information came from aspirin trials, with thienopyridines contributing an important component of the other third. Efficacy of antiplatelet therapy in each of these high-risk settings (eg, acute myocardial infarction, acute ischaemic stroke, unstable angina, stable angina, atrial fibrillation, previous stroke or TIA) is provided by individual placebo-controlled trials with statistically significant differences in the primary end-point and/or meta-analyses of relatively small, inconclusive trials (eg, peripheral arterial disease).

Both ticlopidine and clopidogrel have been tested against aspirin in patients with recent myocardial infarction, and both trials showed non-significantly lower rates of major vascular events in the aspirin-treated arms,

**Table 3** Planned/ongoing trials of clopidogrel plus aspirin

| Trial | Clinical setting | Number of patients |
|---|---|---|
| CHARISMA | High-risk atherothrombosis | 15 000 |
| CCS-2/COMMIT | Acute myocardial infarction | 40 000 |
| CLARITY/TIMI28 | Acute myocardial infarction+thrombolysis | 2200 |
| CASPAR | Bypass surgery for peripheral arterial disease | 1460 |
| CAMPER | Angioplasty for peripheral arterial disease | 2000 |
| ACTIVE | Atrial fibrillation | 14 000 |

including a smaller number of vascular deaths.[20,35] In patients with chronic stable angina, aspirin (75 mg daily) significantly reduced the occurrence of the primary end-point (myocardial infarction or sudden death) by 34% after a median duration of follow-up of 50 months, with no evidence of attenuation of the benefit over such an extended period of observation.[36] Both aspirin and ticlopidine have been shown to reduce by approximately 50% the rate of myocardial infarction and death in controlled studies of patients with unstable angina, and the benefit of aspirin has been demonstrated in a wide range of daily doses, i.e. 75 to 1300 mg in four different placebo-controlled trials.[1,2] Blockade of platelet COX-1 with aspirin and of the platelet ADP receptor $P2Y_{12}$ with clopidogrel produced additive effects in patients with acute coronary syndromes without ST-segment elevation, by reducing the rate of the first primary outcome (a composite of cardiovascular death, non fatal myocardial infarction, or stroke) by 20% as compared to aspirin alone, with no evidence of attenuation of the additional benefit over 12 months of follow-up.[21] 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). The efficacy and safety of this combined antiplatelet strategy is currently being tested in patients with acute myocardial infarction, a clinical setting where aspirin alone (162.5 mg started within 24 h of the onset of symptoms) reduced the primary end-point of vascular death by 23% and non-fatal vascular events by 50%.[37] At least six studies of clopidogrel and aspirin in approximately 75 000 high-risk patients are currently ongoing (Table 3).

## Balance of benefits and risks of antiplatelet therapy

The absolute benefits of aspirin therapy substantially outweigh the absolute risks of major bleeding (particularly, gastrointestinal) complications in a variety of clinical settings characterized by moderate to high risk of occlusive vascular events (Table 2). However, in low-risk individuals the benefit/risk profile of such a preventive strategy is uncertain. Thus, a very small absolute benefit may be offset by exposure of very large numbers of healthy subjects to undue bleeding complications. The risk of upper gastrointestinal bleeding (UGIB) associated with medium-to-high doses of aspirin can be reduced to a relative risk of 2.0 vs non-users[38] by using the lowest effective dose of the drug (i.e. 75 to 160 mg daily). However, this risk can not be further reduced by other strategies (eg enteric-coated or buffered formulations) since it is most likely related to the antiplatelet effect of aspirin, which is largely dose-independent for daily doses in excess of 30 mg.[12] Thus, recent studies have attempted to determine which groups of patients may derive particular benefit or experience harm from the use of low-dose aspirin for the primary prevention of ischaemic heart disease.[39–41] It has been claimed, on the basis of subgroup analysis of the Thrombosis Prevention Trial that the benefit of low-dose aspirin may occur mainly in those with lower systolic blood pressures, although it is not clear even in these men that the benefit outweighs the potential hazards.[39] A recently discontinued trial of low-dose aspirin in general practice failed to demonstrate a clearly favourable benefit/risk profile of this preventive strategy in men and women aged 50 years or older with one or more major cardiovascular risk factors.[40]

A meta-analysis of four primary prevention trials suggests that aspirin treatment is safe and worthwhile at coronary event risk equal to or greater than 1.5% per year.[42] However, as depicted in Fig. 4, we substantially lack clinical trial data in this critically important area of cardiovascular risk that is intermediate between the observed risk in the placebo arm of the Thrombosis Prevention Trial[39] and that of the Swedish trial in patients with chronic stable angina (SAPAT)[36] i.e. in the range of 1 to 3% per annum. The exact relationship between the underlying cardiovascular risk (i.e. the observed rate of major vascular events in the placebo arm) and the absolute benefit of aspirin prophylaxis in the six 'primary' prevention studies represented in the figure may be influenced by the composite nature of the main outcome used for these analyses, ie non-fatal myocardial infarction, non-fatal stroke or vascular death. It should be emphasized that while aspirin has a substantial effect on each of these components of the composite outcome in 'high-risk' clinical settings (including chronic stable angina),[1,2] the measurable impact of long-term antiplatelet prophylaxis in 'low-risk' individuals is largely restricted to non-fatal myocardial infarction.[1]

Another important lesson that can be derived from the analysis of 'primary' prevention trials is that the actual rate of major vascular events recorded in trials that recruited individuals considered to be at 'high'

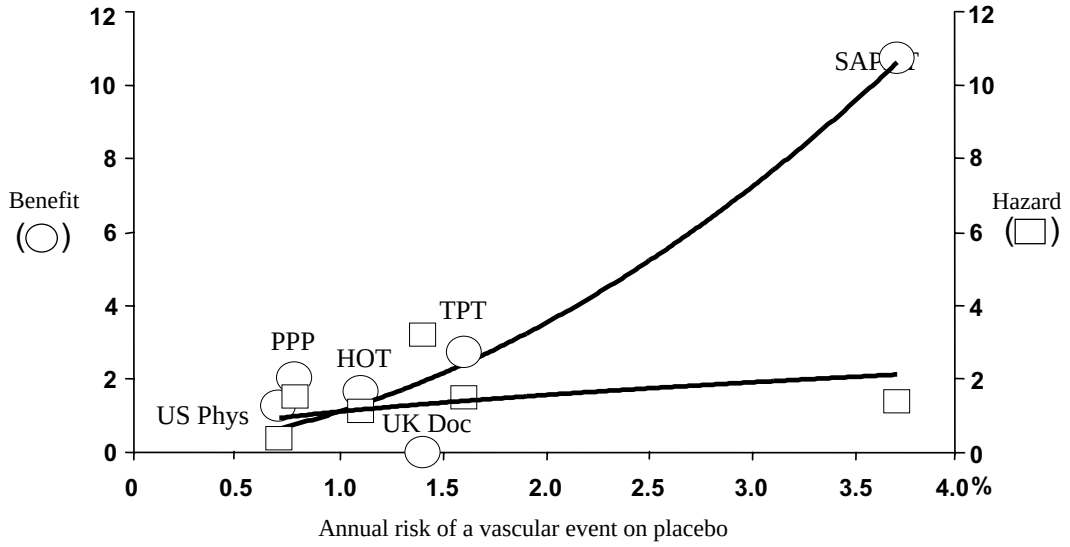


**Fig. 4** Absolute benefit and bleeding risk of aspirin in primary prevention. Data are plotted from placebo-controlled aspirin trials in different settings characterized by variable cardiovascular risk, as noted on the abscissa. The benefit (○) is reported on the left ordinate axis as the number of subjects in whom an important vascular event (i.e. non-fatal myocardial infarction, non-fatal stroke or vascular death) is prevented by treating 1000 subjects with low-dose aspirin for 1 year. The bleeding risk (□) is reported on the right ordinate axis as the number of subjects in whom a major bleeding complication is caused by treating 1000 subjects with low-dose aspirin for 1 year. For each of the six trials, a couple of symbols denote benefit (○) and bleeding risk (□) associated with long-term aspirin prophylaxis. US Phys, US Physicians' Health Study; PPP, Primary Prevention Project; HOT Hypertension Optimal Treatment; UK Doc, British Doctors Trial; TPT, Thrombosis Prevention Trial; SAPAT, Swedish Angina Pectoris Aspirin Trial.

cardiovascular risk was lower than expected and quite comparable to that recorded in earlier trials of American and British doctors (e.g. compare the event rate of PPP to PHS and TPT to UK-Doctors in Fig. 4). Aggressive treatment of modifiable risk factors within the context of the most recent randomized trials (e.g. PPP)[40] is likely to substantially reduce the rate of $TXA_2$ biosynthesis related to complex metabolic disorders and to cigarette smoking[43–45] and therefore the rate of aspirin-sensitive thrombotic complications and the need for long-term aspirin prophylaxis.

## Recommendations concerning individual antiplatelet agents

### Aspirin

Aspirin once daily is recommended in all clinical conditions in which antiplatelet prophylaxis has a favourable benefit/risk profile. In consideration of dose-dependent GI toxicity and its potential impact on compliance, physicians are encouraged to use the lowest dose of aspirin that was shown to be effective in each clinical setting.[1] 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 (i.e. ≥3% per annum). In clinical situations where an immediate antithrombotic effect is required (such as in acute coronary syndromes or in acute ischaemic stroke), a loading dose of 160–300 mg should be given at diagnosis in order to ensure rapid and complete inhibition of $TXA_2$-dependent platelet aggregation.[2] No test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient.

The routine use of proton pump inhibitors or cytoprotective agents is not recommended in patients taking daily doses of aspirin in the range of 75–100 mg, because of lack of randomized trials demonstrating the efficacy of such GI protective strategies in this setting.

Non-aspirin NSAIDs have been investigated inadequately in terms of their potential cardiovascular effects. Thus, physicians prescribing these drugs to arthritic patients with prior vascular complications should not discontinue treatment with low-dose aspirin, even though concomitant administration of the two may amplify the risk of upper GI bleeding.[1] In patients treated with low-dose aspirin requiring NSAID therapy, selective COX-2 inhibitors (coxibs) may offer a GI safety advantage vis-à-vis conventional NSAIDs.[26]

The substantial heterogeneity of approved cardiovascular indications for aspirin among different European countries requires regulatory harmonization.

### Ticlopidine

The role of ticlopidine in the present therapeutic armamentarium is uncertain. Now that ticlopidine is available as a generic drug in many countries, its lower cost as compared to clopidogrel is being emphasized within a broad cost-containment strategy. Although there are no sufficiently large head-to-head comparisons between the two thienopyridines,[22] indirect comparisons are highly suggestive of a lower burden of serious bone-marrow toxicity with clopidogrel as compared to ticlopidine.[1] Moreover, in contrast to clopidogrel, ticlopidine does not have an approved indication for patients with a recent myocardial infarction.

### Clopidogrel

Although clopidogrel may be slightly more effective than aspirin, the size of any additional benefit is statistically uncertain[2] and the drug has not been granted a claim of superiority vs aspirin by regulatory authorities. Clopidogrel, 75 mg daily, is an appropriate alternative for high-risk patients with coronary, cerebrovascular or peripheral arterial disease who have a contraindication to low-dose aspirin.

The recent publication of the CURE trial[21] has led to FDA approval of a new indication for clopidogrel in patients with acute coronary syndromes without ST-segment elevation. A loading dose of 300 mg clopidogrel should be used in this setting followed by 75 mg daily. Revision of the existing guidelines will need a consensus agreement by the experts with respect to timing of percutaneous coronary intervention, length of clopidogrel treatment, and combination with GPIIb/IIIa antagonists.[46,47]

### Dipyridamole

The addition of dypyridamole to aspirin has not been shown clearly to produce additional reductions in serious vascular events in a recent overview of 25 trials among approximately 10 000 high-risk patients,[2] although one trial suggested that there may be a worthwhile further reduction in stroke.[48] Reasons for this apparent effect on stroke in the ESPS-2 Study include the possibility that the newer formulation of dipyridamole with improved oral bioavailability as well as the 2-fold higher daily dose (400 mg vs 225 mg in previous studies) resulted in a clinically detectable antiplatelet effect of the drug. It is also plausible that these findings arose largely or wholly by the play of chance, or were due to a vasodilatory effect of dipyridamole resulting in lower blood pressure. Although the combination of low-dose aspirin and extended-release dipyridamole (200 mg bid) is considered an acceptable option for initial therapy of patients with non-cardioembolic cerebral ischaemic events,[49] there is no basis to recommend this combination in patients with ischaemic heart disease.

### Abciximab, eptifibatide and tirofiban

The pharmacokinetics and pharmacodynamics of commercially available GPIIb/IIIa antagonists have been reviewed together with a detailed account of randomized trial data that led to their regulatory approval[1] (available online at www.chestnet.org). Although abciximab currently has no place outside of the catheterization laboratory, the disappointing results of GUSTO IV ACS[50] are also causing reassessment of the role of eptifibatide and tirofiban in patients managed conservatively.[46] A recent meta-analysis of all major randomized clinical trials of GPIIb/IIIa antagonists in 31 402 patients with acute coronary syndromes who were not routinely scheduled to undergo early coronary revascularization suggests a 9% reduction in the odds of death or myocardial infarction at 30 days.[51] However, the true size of the additional benefit resulting from short-term, high-grade blockade of GPIIb/IIIa combined with standard anti-thrombotic therapy is somewhat uncertain, since the 95% confidence interval ranged from 2% to 16% further reduction in serious vascular events. Moreover, the 1% absolute difference in death or myocardial infarction was balanced by an absolute excess of 1% in major bleeding complications associated with GPIIb/IIIa antagonists vs control.[51] The PARAGON-B Investigators[52] have recently reported that dose-titrated lamifiban had no significant effects on clinical outcomes in patients with non-ST-elevation acute coronary syndromes and yet caused excess bleeding, thus reinforcing the uncertainty noted above.

Thus, we believe that the benefit/risk profile of currently available GPIIb/IIIa antagonists is substantially uncertain for patients with acute coronary syndromes who are not routinely scheduled for early revascularization. In contrast, for patients undergoing percutaneous coronary intervention, intensification of antiplatelet therapy by adding an intravenous GPIIb/IIIa blocker is an appropriate strategy to reduce the risk of procedure-related thrombotic complications.

### Other antiplatelet drugs

As noted above, indobufen, triflusal and picotamide are commercially available in a few European countries, based on relatively limited evidence for efficacy and safety.[1,2] There is substantial statistical uncertainty surrounding the direct randomized comparisons of these antiplatelet agents vs aspirin and inadequate statistical power of the studies to assess reliably any difference in serious bleeding complications. Therefore, the use of indobufen, triflusal or picotamide instead of aspirin is not recommended.

## Areas where we need new trials

When considering strategies for the prevention of serious vascular events among patients with occlusive arterial disease, a key principle is that, in general, the proportional differences between active anti-thrombotic agents tend to be smaller than those between an active agent and no treatment. Hence, much larger benefits at the population level will accrue by the identification and treatment of those who do not currently receive any anti-thrombotic therapy, than by switching from one agent to another in those who are already being treated. It is also clear from randomized trials that large benefits can accrue when anti-thrombotic efficacy is intensified through the addition of a second antiplatelet agent to aspirin, provided that the risks of bleeding are acceptable. When considering the design of randomized trials of new agents, therefore, it is worth bearing in mind that a trial demonstrating that a new agent adds substantially to the effects of aspirin will be of greater public health relevance than a trial showing that the agent is 'equivalent' to aspirin. Hence, the main emphasis should be on two questions: First, are there any types of patients who might benefit from aspirin, but for whom the trial evidence is incomplete? Secondly, what is the evidence that

the addition to aspirin of another anti-thrombotic drug might be beneficial, and what further trials would be useful?

Whilst aspirin is clearly beneficial among high-risk patients with a prior myocardial infarction or stroke, or some other definite evidence of occlusive arterial disease, many patients at 'intermediate' annual risk (i.e. about 1–3%) of serious vascular events might also benefit from aspirin. In the absence of a history of myocardial infarction or stroke there are two specific conditions that appear to be associated with an 'intermediate' risk of a serious vascular event and in which trial evidence supporting aspirin use is currently deficient: diabetes mellitus and chronic renal failure.

(a)Diabetes mellitus: It has already been established that antiplatelet therapy is effective in diabetic patients with a history of occlusive arterial disease, but the effects of antiplatelet therapy among lower-risk diabetic patients without any history of vascular disease are unclear, and several surveys have reported that less than a quarter of such patients take aspirin regularly[53,54] despite ad-hoc recommendations from the American Diabetes Association.[55] The ongoing Prevention of Progression of Asymptomatic Diabetic Arterial Disease (POPADAD) trial is currently comparing aspirin versus placebo among 1200 diabetic patients without CHD (but with reduced ankle-brachial pressure index), but this study may be too small to provide definite evidence of efficacy and safety, and so similar trials are a key priority since the prevalence of diabetes is predicted to increase substantially in the coming decades.[56]

(b)Chronic renal failure: Among patients with end-stage renal failure, cardiac mortality is around 20 times higher than in the general population, and even mild renal impairment (e.g. serum creatinine > 150 μmol/l or 1.7 mg/dl) in the absence of established vascular disease is associated with a 2- to 3-fold increased risk of vascular events.[57] However, although the results from mainly short-term studies suggest that antiplatelet therapy may prevent serious vascular events in patients with renal failure,[2] renal disease increases the risks of bleeding,[58] so any benefits of aspirin could well be counter-balanced by a large absolute excess risk of bleeding. Whilst end-stage renal failure is relatively rare, less severe degrees of renal impairment are common, particularly among older patients. Hence a trial comparing aspirin versus placebo among patients with varying degrees of renal impairment would be of interest.

Among low-risk individuals without a clear history of vascular disease, in whom the annual risk of a vascular event is generally about 1% or less, any small absolute reduction in the risk of serious vascular events (e.g. a few less per 1000) produced by aspirin could be substantially offset by a small increase in major bleeds (e.g. a few more per 1000). In order to help ensure that aspirin is used appropriately in the primary prevention of vascular events among previously healthy individuals, it is important to determine reliably which (if any) such patients are likely to gain benefits that clearly outweigh the risks. In practical terms, this means that we need to identify apparently healthy individuals with multiple risk factors for arterial disease who are at 'intermediate' (i.e. 1%–3%) annual risk of a serious vascular event. An ongoing meta-analysis of individual patient data from completed trials of aspirin versus control in low-risk populations may help to clarify this area, and several trials in progress are also addressing this question among women [the Womens' Health Study[59]] and among people with reduced ankle-brachial pressure index [the Aspirin in Asymptomatic Atherosclerosis [AAA] Study]. There is, however, a dearth of information about the effects of aspirin in healthy individuals aged 80 or more, and further trials comparing aspirin vs placebo in this group would perhaps be helpful.

Dipyridamole, the thienopyridines ticlopidine and clopidogrel, and glycoprotein IIb/IIIa-antagonists have all been tested in trials comparing aspirin plus another antiplatelet agent versus the same dose of aspirin. In the updated ATT meta-analysis the addition of dipyridamole to aspirin was associated with only a non-significant further reduction in serious vascular events,[2] , but there did appear to be a reduction in the risk of recurrent stroke. The ongoing European and Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) will help to clarify whether the addition to aspirin of dipyridamole is of particular value for stroke prevention.[60]

The large Clopidogrel in Unstable angina to prevent Recurrent Events (CURE]) study has demonstrated that the addition of clopidogrel to aspirin reduced the risk of a serious vascular event among patients with unstable angina by about a fifth,[21] and a similar study, the Chinese Cardiac Study [CCS-2],[61] is currently assessing the effects of adding clopidogrel to aspirin among patients with ST-elevation acute myocardial infarction. Several ongoing trials involve a comparison of the combination of clopidogrel and aspirin with another active antiplatelet regimen, but none is specifically designed to establish whether adding clopidogrel to aspirin produces further benefit. Hence, further long-term trials comparing clopidogrel (or perhaps some other antiplatelet agent inhibiting ADP-dependent platelet aggregation) plus aspirin versus *the same* aspirin regimen would be useful among high-risk patients with a prior myocardial infarction, stroke or transient ischaemic attack, and most particularly among those who experienced such an event whilst taking aspirin (so-called 'aspirin failures').

## Conclusion

There are several potential strategies for improving the prevention of myocardial infarction, stroke and vascular death with anti-thrombotic therapy. One important task is to ensure that aspirin is used appropriately widely among those who are known to benefit (Table 4). Recent surveys have shown that many patients who may benefit do not receive aspirin, and considerable efforts are needed to remedy this. In some patients, however, low rates of aspirin use arise mainly because the randomized evidence supporting such use is inadequate, and there is a need for further trials in those areas, an important example of which is in diabetic patients with no history of occlusive arterial disease. In those high-risk patients who

**Table 4** Recommendations on the use of antiplatelet agents in different clinical presentations of vascular disease

| Clinical setting | | Recommendation | Specifications | Grade[a] | Reference |
|---|---|---|---|---|---|
| Ischaemic heart disease | | | | | |
| Chronic stable angina | | aspirin | | 1A | 2,36 |
| | | clopidogrel | as an alternative to aspirin | 1C+ | 20 |
| Acute coronary syndromes | with PCI | aspirin | | 1A | 2 |
| without persistent | | clopidogrel+aspirin | more effective than aspirin alone | 1A | 21 |
| ST-segment elevation[b] | | i.v. GPIIb/IIIa inhibitors | peri-procedural use | 1A | 62 |
| | without PCI | aspirin | | 1A | 2 |
| | | clopidogrel+aspirin | more effective than aspirin alone | 1A | 21 |
| | | i.v. GPIIb/IIIa inhibitors | tirofiban or eptifibatide | 2A | 50,63,64 |
| ST elevation AMI[b] | | aspirin | | 1A | 2 |
| | with primary PCI | i.v. GPIIb/IIIa inhibitors | abciximab | 1A | 65–68 |
| Prior MI | | aspirin | | 1A | 2 |
| | | clopidogrel | as an alternative to aspirin | 1A | 20 |
| After coronary bypass surgery | | aspirin | | 1A | 69 |
| Elective PCI | | aspirin | | 1A | 62 |
| | | clopidogrel | in case of stent application | 1A | 62 |
| | | ticlopidine | in case of stent application | 1A | 62 |
| | | i.v. GPIIb/IIIa inhibitors | grade 2 in stable patients | 2A | 62 |
| Acute ischaemic stroke/TIA | | aspirin | | 1A | 2,49 |
| Prior stroke/TIA | | aspirin | | 1A | 2,49 |
| | | clopidogrel | as an alternative to aspirin | 1A | 20 |
| Peripheral vascular disease | | aspirin | | 1C+ | 2,70 |
| | | clopidogrel | as an alternative to aspirin | 1A | 20 |
| Primary prevention in high-risk groups | | | | | |
| Diabetes mellitus | | aspirin | | 2B | 71 |
| Hypertension | | aspirin | | 2A | 72 |
| Atrial fibrillation | | aspirin | in intermediate-risk subjects or in high-risk patients not candidate to warfarin | 1A | 2 |
| Valve disease | | aspirin | rheumatic mitral valve disease in patients not candidate to warfarin | 1B | 2,73 |
| Valve surgery | | aspirin | in combination with warfarin in patients with mechanical valves[c] | 2B | 2,74 |

[a]Grades of recommendation for antithrombotic agents, as defined by Guyatt *et al.*[75] Grade 1 indicates that benefits clearly outweigh risks, burden and costs. Grade 2 indicates that the tradeoff between benefits and risks is substantially uncertain. The methodological quality of the underlying evidence is summarized as A, B, or C to denote decreasing confidence in the recommendation because of methodological weaknesses, inconsistent results, generalization of the results or observational studies. A somewhat different grading system has been adopted in ESC guidelines.

[b]The ESC guidelines are available on the ESC Website: www.escardio.org

[c]Dipyridamole has also been approved in some European countries for patients with mechanical heart valves.

do already take aspirin, however, the largest gains are likely to result from adding a second anti-thrombotic agent-either an antiplatelet or an anticoagulant, depending on circumstances- and although there is already some randomized evidence in support of this strategy, more is needed. By contrast, replacing one anti-thrombotic drug with another of the same (or similar) type offers little scope for major improvements in cardiovascular prevention, since the true difference between such drugs is likely to be modest (and in any case trials that are large enough to demonstrate this are hugely expensive).

## Summary

### Antiplatelet drugs that may prevent atherothrombosis

- Approximately 20 different agents have been shown to inhibit platelet aggregation through different mechanisms of action.
- However, inhibition of platelet aggregation as measured ex vivo does not necessarily translate into prevention of atherothrombosis.
- Antiplatelet drugs that have been successfully tested against placebo in adequately large randomized clinical trials include aspirin, ticlopidine and clopidogrel for chronic oral dosing, and abciximab, tirofiban and eptifibatide for short-term intravenous administration.

### Patients that may benefit from antiplatelet therapy

- Allocation of high-risk patients to a prolonged course of antiplatelet therapy reduced the combined outcome of nonfatal myocardial infarction, nonfatal stroke or vascular death ('serious vascular events') by about 25%.
- Absolute reductions in the risk of having a serious vascular event were 36 per 1000 treated for 2 years, among patients with previous myocardial infarction; 38 per 1000 patients treated for 1 month among patients with acute myocardial infarction; 36 per 1000 treated for 2 years among those with previous stroke or transient ischaemic attack (TIA); nine per 1000 treated for 1 month among those with acute ischaemic stroke; and 22 per 1000 treated for 2 years among other high-risk patients, including those with stable angina, peripheral arterial disease and atrial fibrillation.
- In each of these high-risk categories, the absolute benefits substantially outweighed the absolute risks of major bleeding complications.

### Clinical trial evidence in patients with ischaemic heart disease

- Both ticlopidine and clopidogrel have been tested against aspirin in patients with recent myocardial infarction, and both trials showed non-significantly lower rates of serious vascular events in the aspirin-treated arm, including a smaller number of vascular deaths.
- In patients with chronic stable angina, aspirin (75 mg daily) significantly reduced the occurrence of the primary end-point (myocardial infarction or sudden death) by 34% after a median duration of follow-up of 50 months, with no evidence of attenuation of the benefit over such an extended period of observation.
- Both aspirin and ticlopidine have been shown to reduce by approximately 50% the rate of myocardial infarction and death in randomized trials of patients with unstable angina, and the benefit of aspirin has been demonstrated in a wide range of daily doses, i.e. 75 to 1300 mg, in four different placebo-controlled trials.
- Blockade of platelet COX-1 with aspirin and of the platelet ADP receptor $P2Y_{12}$ with clopidogrel produced additive effects in patients with acute coronary syndromes without ST-segment elevation, by reducing the rate of the first primary outcome (a composite of cardiovascular death, non fatal myocardial infarction, or stroke) by 20% as compared to aspirin alone, with no evidence of attenuation of the additional benefit over 12 months of follow-up.
- The efficacy and safety of this combined antiplatelet strategy is currently being tested in patients with acute myocardial infarction, a clinical setting where aspirin alone (162.5 mg started within 24 h of the onset of symptoms) reduced the primary end-point of vascular death by 23% and non-fatal vascular events by 50%.

### Balance of benefits and risks of antiplatelet therapy

- The absolute benefits of aspirin therapy substantially outweigh the absolute risks of major bleeding [particularly, gastrointestinal (GI)] complications in a variety of clinical settings characterized by moderate to high risk of occlusive vascular events (Table 2). However, in low-risk individuals the benefit/risk profile of such a preventive strategy is uncertain.
- A meta-analysis of four primary prevention trials suggests that aspirin treatment is safe and worthwhile at coronary event risk equal to or greater than 1.5% per year.

### Recommendations concerning individual antiplatelet agents

#### Aspirin

- Aspirin once daily is recommended in all clinical conditions in which antiplatelet prophylaxis has a favourable benefit/risk profile.
- Because of GI toxicity and its potential impact on compliance, physicians are encouraged to use the lowest dose of aspirin that was shown to be effective in each clinical setting.
- 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 (i.e. ≥3% per annum).
- In clinical situations where an immediate anti-thrombotic effect is required (such as in acute coronary syndromes or in acute ischaemic stroke), a loading dose of 160 mg should be given at diagnosis in order to ensure rapid and complete inhibition of $TXA_2$-dependent platelet aggregation.
- No test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient.
- The routine use of proton pump inhibitors or cytoprotective agents is not recommended in patients taking daily doses of aspirin in the range of 75–100 mg, because of lack of randomized trials demonstrating the efficacy of such protective strategies in this setting.
- Non-steroidal anti-inflammatory drugs (NSAIDs) have been investigated inadequately in terms of their potential cardiovascular effects. Thus, physicians prescribing these drugs to arthritic patients with prior vascular complications should not discontinue treatment with low-dose aspirin.
- Because of potential pharmacodynamic interactions between traditional NSAIDs (e.g. ibuprofen) and aspirin, patients treated with low-dose aspirin requiring NSAID therapy may benefit from the use of selective COX-2 inhibitors.

### Ticlopidine

- The role of ticlopidine in the present therapeutic armamentarium is uncertain. Now that ticlopidine is available as a generic drug in many countries, its lower cost as compared to clopidogrel is being emphasized within a broad cost-containment strategy.
- Although there are no large head-to-head comparisons between the two thienopyridines, indirect comparisons are highly suggestive of a lower burden of serious bone-marrow toxicity with clopidogrel as compared to ticlopidine.
- In contrast to clopidogrel, ticlopidine does not have an approved indication for patients with a recent myocardial infarction.

### Clopidogrel

- Although clopidogrel may be slightly more effective than aspirin, the size of any additional benefit is statistically uncertain and the drug has not been granted a claim of superiority vs aspirin by regulatory authorities.
- Clopidogrel, 75 mg daily, is an appropriate alternative for high-risk patients with coronary, cerebrovascular or peripheral arterial disease who have a contraindication to low-dose aspirin.
- The results of the CURE trial have led to approval of a new indication for clopidogrel in patients with acute coronary syndromes without ST-segment elevation. A loading dose of 300 mg clopidogrel should be used in this setting followed by 75 mg daily. Revision of the existing guidelines will need a consensus agreement by the experts with respect to timing of percutaneous coronary intervention, length of clopidogrel treatment, and combination with GPIIb/IIIa antagonists.

### Dipyridamole

- Although the combination of low-dose aspirin and extended-release dipyridamole (200 mg bid) is considered an acceptable option for initial therapy of patients with non-cardioembolic cerebral ischaemic events, there is no basis to recommend this combination in patients with ischaemic heart disease.

### Abciximab, eptifibatide and tirofiban

- The benefit/risk profile of currently available GPIIb/IIIa antagonists is substantially uncertain for patients with acute coronary syndromes who are not routinely scheduled for early revascularization.
- In contrast, for patients undergoing percutaneous coronary intervention, intensification of antiplatelet therapy by adding an intravenous GPIIb/IIIa blocker is an appropriate strategy to reduce the risk of procedure-related thrombotic complications.

### Other antiplatelet drugs

- Indobufen, triflusal and picotamide are commercially available in a few European countries, based on relatively limited evidence for efficacy and safety.
- Because of substantial statistical uncertainty surrounding the direct randomized comparisons of these antiplatelet agents vs aspirin and inadequate statistical power of the studies to assess reliably any difference in serious vascular events, the use of indobufen, triflusal or picotamide instead of aspirin is not recommended.

## Conclusions

- There are several potential strategies for improving the prevention of myocardial infarction, stroke and vascular death with anti-thrombotic therapy. One important task is to ensure that aspirin is used appropriately widely among those who are known to benefit (Table 4). Recent surveys have shown that many patients who may benefit do not receive aspirin, and considerable efforts are needed to remedy this.
- In some patients, however, low rates of aspirin use arise mainly because the randomized evidence supporting such use is inadequate, and there is a need for further trials in those areas, an important example of which is in diabetic patients with no history of occlusive arterial disease.
- In those high-risk patients who do already take aspirin, however, the largest gains are likely to result from adding a second anti-thrombotic agent-either an antiplatelet or an anticoagulant, depending on circumstances- and although there is already some randomized evidence in support of this strategy, more is needed.
- By contrast, replacing one anti-thrombotic drug with another of the same (or similar) type offers little scope

for major improvements in cardiovascular prevention, since the true difference between such drugs is likely to be modest.

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