ANTIPLATELET TREATMENT FOR CORONARY HEART DISEASE

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Platelets play an essential role in the pathogenesis of acute coronary syndromes (ACS).¹ Therefore an important part of the treatment of ACS, and of primary and secondary preventive measures in coronary heart disease, consists of antiplatelet treatment. Over the years antiplatelet treatment has evolved, and currently several types of antiplatelet drugs are available, each with their specific pharmacological target and with their specific clinical indications. Although antiplatelet treatment is beneficial for vascular patients as a group, some individual patients appear to derive less benefit. In this context the term antiplatelet-drug resistance has been introduced. To date, however, no definite cause, definition, or treatment has been determined for this phenomenon. These issues will be discussed in this article.

▶ PLATELET ACTIVATION

In the case of vascular endothelial damage, the first haemostatic reaction is vasoconstriction. Thereafter, the platelets come into action and the coagulation system is activated. Through disruption of the endothelial layer of the vessel wall, tissue factor is exposed, initiating the coagulation cascade, resulting in thrombin formation. Also subendothelial collagen and Von Willebrand factor are exposed to the flowing blood. Following this event, platelets start to adhere to collagen and Von Willebrand factor through their respective receptors, forming a platelet monolayer covering the damaged part of the vessel wall. This monolayer serves as a base for thrombin generation and platelet aggregation. Adhered platelets undergo shape change, form podocytes, and start to secrete thromboxane A₂ (TXA-2) and their granule contents, such as adenosine diphosphate (ADP). Through their specific receptors on the platelet surface, thrombin, TXA-2, ADP and other substances help recruit and further activate platelets at the site of endothelial damage. Activated platelets express the glycoprotein IIb/IIIa receptor, which is the receptor for fibrinogen. This receptor is essential for irreversible aggregation for which fibrinogen serves as the glue between the platelets (fig 1).

MECHANISM OF ACTION OF ANTIPLATELET DRUGS

Aspirin

Adhering and aggregating platelets secrete TXA-2, which leads to further platelet recruitment and activation. TXA-2 is a product of arachidonic acid metabolism and is formed within the activated platelet. TXA-2 formation is catalysed by the enzyme cyclo-oxygenase (COX)-1. Aspirin inactivates COX-1 for the entire lifespan of the platelet (7–10 days), thereby almost completely abolishing in vitro platelet TXA-2 formation, resulting in reduced platelet function. This anti-aggregatory effect is considered as the main mechanism for the protection against thrombotic events. Additional proposed protective effects of aspirin include anti-inflammatory properties and anti-thrombin actions.

The regular formulation of aspirin has a fast onset of action. It is rapidly absorbed from the stomach and upper small intestine, and peak plasma concentrations are reached after 30–40 minutes. Moreover, aspirin already inhibits platelets in the portal circulation before it enters the systemic circulation.² In contrast, the enteric-coated and microencapsulated preparations only achieve an adequate antiplatelet effect after 2–3 hours. Chewing these tablets accelerates the onset of effect to a degree comparable to regular aspirin.

The optimal dose of aspirin is not completely clear, although daily doses above 325 mg have no additional clinical antithrombotic efficacy but are associated with increased toxicity. Several types of laboratory tests can measure the magnitude of the antiplatelet effect of aspirin. In some studies the results of such tests have been linked to clinical outcome. The first randomised trials studying adjustment of treatment based on laboratory measurement of the effect of aspirin are now on the way. Currently, individualised antiplatelet therapy based on laboratory tests of aspirin effect is not

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Figure 1 Pathways of platelet activation and targets of antiplatelet agents. AA, arachidonic acid; ADP, adenosine diphosphate; COX-1, cyclooxygenase 1; Dense, dense granule; Epi, epinephrine; Gp IIb/IIIa, glycoprotein IIb/IIIa; PgG2, prostaglandin G2; PgH2, prostaglandin H2; Tx A2, thromboxane A2; Tx S, thromboxane synthase; II, coagulation factor II, prothrombin; IIa, activated coagulation factor II, thrombin; α , alpha granule.

yet indicated, and the use of standard doses of aspirin ranging from 75–150 mg per day is still state of the art for long term use. In the acute phase a loading dose of 150–325 mg is recommended.³

Like all antithrombotic drugs, aspirin use is associated with an increased risk of bleeding complications. Gastrointestinal bleeds, the most common bleeding source in aspirin users, are approximately increased by twofold. To reduce the risk of gastrointestinal complications, buffered- and enteric-coated aspirin were introduced. However, in clinical practice these formulations were not shown to reduce upper gastrointestinal tract complications. To prevent gastrointestinal bleeding, high risk patients (previous ulcer, *Helicobacter pylori* positive, >70 years of age) should be treated with a proton pump inhibitor. In case of a gastrointestinal bleed, aspirin treatment should be withheld, and a proton-pump inhibitor should be started. Aspirin can be safely resumed after healing of the bleeding site, provided that the patient continues to use a high dose of proton-pump inhibitor. A much more rare—but also more feared—complication is intracranial haemorrhage which occurs in 0.65% of vascular patients on aspirin compared to 0.54% in patients without aspirin.³ Importantly, despite the increase of haemorrhagic stroke, the overall risk of stroke is reduced by aspirin.

The risk of bleeding appears to be related to the dose of aspirin used, both with or without concomitant clopidogrel use.⁴ Doses between 75–150 mg seem both safe and efficacious.

In case of bleeding, the antiplatelet effect of aspirin can not be directly antagonised. During severe bleeding the only possible corrective treatment is platelet transfusion.

Thienopyridines

After initial activation of platelets, the pro-aggregatory substances of the granules are secreted. One of these substances is ADP, and through activating its specific receptors on the

platelet surface, it triggers the machinery inside the platelet, eventually leading to aggregation. At present three types of ADP receptors on the platelet surface have been discovered: the P2Y1 receptor, the P2X1 receptor, and the P2Y12 receptor. Activation of the first two of these lead to calcium influx into the platelet, resulting in shape change and weak, reversible aggregation. These two receptors are insensitive to thienopyridines. Binding of ADP to the P2Y12 receptor initiates a cascade of events leading to activation of the glycoprotein IIb/IIIa receptor which is necessary for strong, irreversible platelet aggregation. Thienopyridines irreversibly block the P2Y12 receptor.

The first thienopyridine used in clinical practice was ticlopidine. It has been shown to effectively prevent thrombotic events after coronary stenting when added to aspirin. Due to risks of haematological and dermatological side effects, ticlopidine has been largely replaced by clopidogrel.

All thienopyridine drugs are biologically inactive pro-drugs and are metabolised to the active form by the cytochrome (CY) P450 system in the liver. Consequently, the onset of the antiplatelet effect of thienopyridines is slower than that of aspirin. Between patients there is a considerable difference in maximal magnitude of effect, and in the time of onset of antiplatelet effect. In the case of clopidogrel, the onset of action can be advanced by increasing the loading dose from 300 mg to 600 mg.⁵

A third thienopyridine, prasugrel, is currently being investigated in a phase III trial in patients undergoing percutaneous coronary intervention.

Glycoprotein IIb/IIIa receptor blockers

The final common pathway in platelet activation is the activation of the glycoprotein IIb/IIIa surface receptor. Aggregating platelets are glued to each other by fibrinogen, and the glycoprotein IIb/IIIa receptor is the receptor for fibrinogen. Despite dual antiplatelet treatment with aspirin

plus a thienopyridine, platelets can still be activated through stimuli that are insensitive to these drugs, leading to activation of this receptor. Therefore, a new class of antiplatelet drugs blocking the glycoprotein IIb/IIIa receptor was developed. Currently, three different agents for intravenous use are in clinical use. The first, abciximab, is a chimeric antibody that irreversibly binds and inactivates the glycoprotein IIb/IIIa receptor. The other two, tirofiban and eptifibatide, are non-antibody agents that competitively bind the glycoprotein IIb/IIIa receptor. Oral agents in this class have been developed as well. However, these never found their way into practice because of a lack of clinical benefit or even the presence of clinical harm.

PRIMARY PREVENTION

Currently the data from six large trials including over 85 000 individuals are available, comparing active treatment with aspirin to control in the primary prevention of cardiovascular disease (fig 2). Doses between 50–500 mg per day were used.⁶ Despite the large number of patients included in these trials, the benefit of aspirin in the primary prevention of cardiovascular disease remains controversial. This is at least partly due to the fact that aspirin is associated with an increased risk of bleeding complications: absolute annual risk 0.09% in aspirin patients versus 0.05% in controls. Moreover, despite the reduction of thrombotic events, overall mortality was not affected. The decision to use aspirin in primary prevention should therefore be based on the cardiovascular risk of the patient, to ensure that the benefits of aspirin outweigh the risks. The guidelines of the American Heart Association suggest the use of aspirin in apparently healthy patients who have a 10 year risk of cardiovascular events of 10% or higher. The risk calculation is based on the Framingham Heart Study. Factors included are age, sex, blood lipid values, smoking status, blood pressure, and diabetic status.

Interestingly there appears to be a sex-specific effect in the protective action of aspirin. In men, primary preventive use of aspirin only reduces the risk of myocardial infarction (relative reduction 32%), but not of stroke. On the other hand, in women

aspirin only reduces the risk of stroke (relative reduction 19%), but not of myocardial infarction. The cause of this phenomenon remains uncertain. A possible explanation is that in the low risk, young study population of the Women's Health Study, the incidence of stroke is clearly higher than of myocardial infarction, and therefore it is easier to demonstrate a preventive effect on strokes. The exact opposite holds true for men.⁷

The use of clopidogrel in addition to aspirin for primary and secondary prevention has recently been investigated in the large CHARISMA trial.⁸ Overall, the study showed no benefit for clopidogrel. Moreover, in the primary prevention subgroup, which consisted of individuals with multiple risk factors for cardiovascular events, dual treatment increased the risk of all cause mortality from 3.8% to 5.4%.⁸ Therefore, clopidogrel in addition to aspirin should be avoided in primary prevention treatment, even in high risk individuals.

STABLE CORONARY ARTERY DISEASE Aspirin

The only trial comparing antiplatelet treatment with placebo in patients with stable chronic angina pectoris (SAPAT: Swedish Angina Pectoris Aspirin Trial), showed a clear reduction in the primary end point of fatal or non-fatal myocardial infarction or sudden death (relative reduction 34%).⁹ This implies that all patients with stable coronary disease should receive aspirin.

Thienopyridines

The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial compared aspirin with clopidogrel for secondary prevention in stabilised vascular patients. The overall results of the study were in favour of clopidogrel, with a 9% relative reduction of vascular events.¹⁰ However, patients were stratified for indication of antiplatelet treatment, which allows for separate analysis for each one of the three indications. The three different indications for inclusion were: (1) myocardial infarction ≤ 35 days before inclusion; (2) ischaemic stroke in the past six months; or (3) peripheral artery disease. For the latter indication clopidogrel was superior. On the other hand, in the strata of patients with stroke, or myocardial infarction, there were no significant differences in efficacy between the

Figure 2 Primary prevention of vascular events with aspirin. BDT, British Doctors Trial; HOT, Hypertension Optimal Treatment; PHS: Physicians' Health Study⁶; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial; WHS: Women's Health Study. CI, confidence interval; OR, odds ratio.

treatments. Therefore, based on these results, and on cost-effectiveness, aspirin remains the preferred treatment for stabilised patients. In the case of contraindications for aspirin (for example, allergy), clopidogrel is a good alternative.

Since dual antiplatelet treatment reduces the risk of thrombotic events in patients with different types of ACS, the CHARISMA trial tested the hypothesis whether in 15 603 stable vascular patients this would also hold true. However, in contrast to unstable patients, clopidogrel on top of aspirin was not superior to aspirin alone in patients with stable cardiovascular disease, and was associated with a relative increase of moderate to severe bleeding of 50%.⁸

PERCUTANEOUS CORONARY INTERVENTION

Aspirin

Thrombotic risk after elective balloon angioplasty without stenting is adequately treated using single antithrombotic treatment with aspirin. However, nowadays percutaneous coronary intervention (PCI) is almost routinely accompanied by stent placement to reduce the risk of restenosis. Since monotherapy with aspirin is associated with a high risk of stent thrombosis, up to almost 20% in the early days of stenting, more aggressive treatment is indicated.

Thienopyridines

Antithrombotic treatment in addition to aspirin initially consisted of heparin followed by oral anticoagulation. This type of treatment seemed effective against stent thrombosis, but was also associated with a high rate of bleeding complications, especially at the puncture site. Randomised trials comparing aspirin plus oral anticoagulation versus ticlopidine plus aspirin were strongly in favour of the latter, both with respect to thrombotic complications (fig 3) and bleeding complications.¹¹

Due to the risk of haematological side effects, ticlopidine has been largely replaced by clopidogrel. The CLASSICS trial, a safety study, showed that clopidogrel compared to ticlopidine nearly halved the complication rate: 9.1% v 4.6% major bleedings, neutrocytopenia, thrombocytopenia, and early discontinuation of study drug.

Figure 3 Superiority of dual antiplatelet treatment compared to aspirin plus oral anticoagulation for coronary stenting.¹¹ ASA, aspirin; MACE, major adverse cardiac events; OAC, oral anticoagulation.

Direct placebo-controlled randomised evidence for a loading dose of clopidogrel before PCI is lacking. In a subgroup analysis, administration of a 300 mg clopidogrel loading dose >6 hours before PCI was superior to initiation after PCI, whereas initiation only 3–6 hours before PCI was not. These results have led to widespread application of clopidogrel loading before intervention. More recently, randomisation to a high loading dose of 600 mg clopidogrel 4–8 hours before intervention was shown to be superior to a standard 300 mg loading dose in preventing periprocedural myocardial infarction.¹² This benefit is possibly explained by the faster onset of action, and the more complete antiplatelet effect of 600 mg compared to 300 mg.⁵ Therefore, when a rapid onset of action is required—for example, in urgent or primary PCI—the higher loading dose is preferred. For high risk patients undergoing urgent PCI, and for all patients undergoing primary PCI, additional treatment with glycoprotein IIb/IIIa blockers is recommended.

With respect to duration of treatment after PCI no comparative data are available. Depending on the indication for PCI, and the type of stent used, the recommendations in the guidelines vary (table 1).¹³

Glycoprotein IIb/IIIa receptor blockers

With the use of dual oral antiplatelet treatment after PCI with stenting the risk of periprocedural complications is low. The addition of a glycoprotein IIb/IIIa receptor blocker may be considered to reduce this risk further. This strategy, however, was not shown to be clinically superior to aspirin plus pre-PCI initiated clopidogrel in low to intermediate risk patients, nor in diabetic patients.¹⁴ In diabetic patients there does seem to be a preventive effect on in-stent restenosis.¹⁴ Reasons for this phenomenon are speculative. Importantly, these data are derived from a study where only 10% of the patients were treated with drug eluting stents. Currently, diabetic patients are frequently treated with drug eluting stents which reduces the risk of restenosis.

It seems that treatment with these agents should be reserved for those patients at increased risk of periprocedural events—that is, those undergoing PCI of a venous graft, of complex lesions, or PCI in the setting of unstable angina, or evolving myocardial infarction.¹⁵

CORONARY ARTERY BYPASS GRAFTING

Aspirin

Coronary artery bypass grafting (CABG) nowadays is especially indicated in patients with extensive coronary artery disease and reduced left ventricular function when PCI is deemed insufficient, or for patients with left main stem disease. Although the use of internal mammary arteries is currently the standard treatment, frequently the use saphenous vein grafts is unavoidable in order to achieve complete revascularisation. Venous graft occlusion rates are strongly reduced by the use of aspirin (table 2).¹⁶ Moreover, mortality is halved by early administration of aspirin after CABG.

Exact recommendations on the dose of aspirin cannot be given, but doses varying from 75–325 mg daily seem to be comparably effective and safe.

Clopidogrel

The role of clopidogrel has not been extensively studied in the setting of CABG. It does, however, appear that preoperative

Table 1 Recommendations of the European Society of Cardiology on the use of clopidogrel in patients undergoing percutaneous coronary intervention plus stent

Indication	Loading dose	Timing of loading dose	Treatment duration
Elective PCI with BMS	300 mg	>6 hours before PCI	4 weeks
Elective PCI with DES	300 mg	>6 hours before PCI	6–12 months
Non-ST elevation ACS	300 mg	At hospital admission, if clinically justifiable	9–12 months
ST elevation ACS	600 mg	Immediately after first medical contact, if clinically justifiable	9–12 months

ACS, acute coronary syndrome; BMS, bare metal stent; DES, drug eluting stent; PCI, percutaneous coronary intervention.

clopidogrel on top of aspirin is associated with an increased risk of perioperative bleeding complications. Therefore, if possible, clopidogrel should be stopped at least five days before surgery. Moreover, in ACS patients on dual antiplatelet treatment, post-CABG restarting of clopidogrel does not appear to yield additional benefit.

ACUTE CORONARY SYNDROMES

For all types of ACS, aspirin constitutes one of the key pharmacological interventions. In patients with non-ST elevation ACS, aspirin yields a relative reduction of death and infarction of 50%.³ In patients with ST elevation myocardial infarction aspirin reduces mortality by 25%, irrespective of whether or not patients receive fibrinolysis.¹⁷ Although there are no randomised trials on the use of aspirin in the setting of primary PCI, it should always be part of treatment in all patients with myocardial infarction.

Antiplatelet treatment in addition to aspirin for the different types of ACS and for the different treatment strategies will be discussed below.

NON-ST ELEVATION ACUTE CORONARY SYNDROMES

Thienopyridines

In the large CURE trial, dual antiplatelet treatment with aspirin and clopidogrel led to a relative risk reduction of 20% for the combined end point of cardiovascular death, myocardial infarction and stroke compared to aspirin alone: 11.4% to 9.3%. These results were consistent between the subgroups of patients managed invasively and conservatively.

At the trade-off for better protection against thrombotic events, the risk of major bleeding was increased by an absolute 1% in the clopidogrel group (2.7% to 3.7%), though intracranial bleeding was not affected.

The addition of clopidogrel to aspirin for non ST-elevation ACS is recommended both in the case of a planned conservative approach, as well as in the case of a planned invasive strategy.

As mentioned above, attention should be paid to those undergoing CABG with respect to the bleeding risks.

Glycoprotein IIb/IIIa receptor blockers

A meta-analysis of the randomised trials in non-ST elevation ACS showed that the rate of death and myocardial infarction at 30 days was relatively reduced by 9% with the use of glycoprotein IIb/IIIa blockers in addition to heparin. This was almost completely accounted for by patients who underwent an early PCI. Importantly, the trials in this meta-analysis mainly stem from the era before addition of clopidogrel to aspirin became standard.

In the ISAR-REACT 2 trial, 2022 non-ST elevation ACS patients were randomised to abciximab or placebo; all were pretreated with 600 mg clopidogrel and all underwent an early percutaneous intervention.¹⁵ The primary outcome of death, myocardial infarction and urgent target vessel revascularisation was reduced from 11.9% to 8.9%, mainly driven by a reduction in myocardial infarction. The reduction was completely accounted for by the subgroup of patients with raised pre-procedural troponin values.

Currently, it seems that the use of glycoprotein IIb/IIIa receptor blockers should be restricted to invasively managed ACS patients with positive cardiac markers. Alternatively, heparin plus glycoprotein IIb/IIIa blockers can be replaced with bivalirudin alone. In the ACUTY trial this approach was shown to be comparably efficacious, but with a better safety profile with respect to bleeding. In case of a conservative treatment, glycoprotein IIb/IIIa receptor blockers yield no benefit.

ST ELEVATION ACUTE CORONARY SYNDROMES

The main aim of treatment for acute ST elevation myocardial infarction (STEMI) is to open the occluded coronary artery as soon as possible. Currently, two reperfusion strategies are available: fibrinolysis and primary PCI.

Table 2 Low dose aspirin versus control and the effect on saphenous vein graft patency

Study	Initiation of aspirin	Daily aspirin dose	Timing of angiography (months)	Total number of anastomoses	Aspirin % occluded	Control % occluded
Lorenz <i>et al</i> , 1984	2 h after CABG	100 mg	4	138	19	35
Goldman <i>et al</i> , 1989	12 h before CABG	325 mg	12	685	13	23
Sanz <i>et al</i> , 1990	7 h after CABG	150 mg	1	1495	14	18
Gavaghan <i>et al</i> , 1991	<1 h after CABG	324 mg	12	690	6	12
Hockings <i>et al</i> , 1993	7 d before CABG	100 mg	6	273	5	9
Overall				3281	11	18

CABG, coronary artery bypass grafting; d, days; h, hours.

Fibrinolysis

Thienopyridines

Recently, clopidogrel has made its way into the treatment of patients with STEMI who received fibrinolysis. In the angiographic CLARITY-TIMI 28 trial immediate administration of clopidogrel (300 mg loading dose, followed by 75 mg daily) after fibrin specific fibrinolysis, led to a reduced incidence of occluded infarct related arteries 2–8 days after fibrinolysis: from 21.7% to 15.0%.¹⁸ Although the study was too small for clinical conclusions, it did provide a possible mechanistic rationale for the use of clopidogrel in STEMI. The COMMIT study randomised over 45 000 patients with mostly STEMI, to clopidogrel without a loading dose or to placebo.¹⁹ Mortality at 28 days was modestly but significantly reduced by the early addition of clopidogrel to standard treatment: 8.1% to 7.5%. Of note, only about half of the patients in the COMMIT trial had received fibrinolysis, but within the subgroup of patients who did, the combined primary end point was significantly reduced in the clopidogrel group.¹⁹ Major bleedings were not increased by clopidogrel, but most of the participants were younger than 75 years.

Glycoprotein IIb/IIIa inhibitors

The observation in experimental models that platelet-rich thrombi are resistant to alteplase, initiated studies using the most potent antiplatelet agents to increase patency rates. Due to excessive bleeding with the use of full dose lysis plus glycoprotein IIb/IIIa inhibitors, only combination regimens using a reduced dose lytic were eventually tested in large clinical trials. The angiographic trials preceding these large clinical studies were promising, but the large clinical trials failed to show a benefit for combination therapy.

Primary PCI

Thienopyridines

Since stenting is almost standard procedure nowadays, dual antiplatelet treatment with aspirin and clopidogrel should be used in the majority of patients. It has not been investigated whether pre-treatment with a loading dose clopidogrel is beneficial for this indication, but doing so seems logical.

Glycoprotein IIb/IIIa receptor blockers

A meta-analysis of the five placebo-controlled randomised trials showed an overall favourable trend with respect to mortality at 30 days for glycoprotein IIb/IIIa inhibitors in primary PCI, with evident reductions in mortality for patients with a high a priori risk. For the combined end point of death and infarction abciximab conferred a relative reduction of 34%. These trials generally started administration of abciximab in the catheterisation laboratory, except for a small subgroup in the ADMIRAL trial in which treatment was initiated in the ambulance or emergency room. The observation that this latter subgroup had superior preprocedural patency rates as compared to later or no treatment was investigated in five randomised trials, using tirofiban or abciximab. Meta-analysis ($n = 931$) confirmed the impact of early initiation on pre-procedural TIMI grade 3 flow: 20% *v* 12%. Mortality at 30 days tended to be reduced as well.

In conclusion, abciximab reduces mortality in high risk patients and ischaemic events in a larger group of STEMI patients treated with primary PCI. Early initiation is recommended to improve preprocedural TIMI grade 3 flow.

No reperfusion treatment

Despite the importance of early reperfusion, still a large proportion of patients with STEMI does not receive reperfusion treatment for several reasons. In these patients adequate antithrombotic treatment is also very important. Thienopyridines have not specifically been tested in this setting, but treatment with tirofiban has been studied in the TETAMI trial. Tirofiban on top of aspirin plus heparin or enoxaparin was not superior to placebo. This finding corroborates the results of the studies in non-ST elevation acute coronary syndromes, where glycoprotein IIb/IIIa blockers were not beneficial in conservatively managed patients.

ANTIPLATELET DRUG RESISTANCE

Aspirin

Many patients on aspirin experience (recurrent) ischaemic events. Should we, or should we not, call this aspirin resistance? It seems insufficient to base the definition merely on clinical events; it should also encompass pharmacological, mechanistic effects of aspirin that are associated with clinical thrombotic risk. It is generally accepted that inhibition of platelet thromboxane formation is the main effect. Hence, measurement of in vitro thromboxane formation has classically been used to assess the effect of aspirin. However, possible additional properties that may be of importance for the clinical efficacy of aspirin—for example, anti-inflammatory or anti-thrombin effects—are neglected by this test.

Currently, a clear definition of aspirin resistance is lacking, but some consensus exists regarding the elements that should be represented in it. First, there should be a measurable lack of aspirin-effect that is reproducible, specific, and reliable. Secondly, this lack of measured effect should independently and consistently correlate with atherothrombotic risk.

In the past frequently the measurement of in vitro thromboxane production was used to assess the effect of aspirin. However, in vitro thromboxane production has never been linked with clinical outcome, perhaps partly due to the fact that this test does not reflect overall thromboxane production in subjects. Therefore, nowadays much research focuses on in vivo aspirin-resistant thromboxane biosynthesis.

A potential source for this is COX-2 mediated thromboxane production. For example, in smokers COX-2 contributes significantly to in vivo thromboxane production. A second mechanism is pharmacological interference, especially by non-steroidal anti-inflammatory drugs, reducing the ability of aspirin to reach its target site in COX-1. A third mechanism is extraplatelet production of TXA-2. Endothelial cells and plaque monocytes and macrophages are capable of producing prostaglandin H₂, the direct precursor of TXA-2. Prostaglandin H₂ may be transferred from these cells to platelets, and in the platelets TXA-2 is formed independently of COX-1. Finally, genetic polymorphisms of COX-1 may contribute to varying susceptibility of COX-1 to aspirin. Despite the fact that overall high residual in vivo thromboxane production is associated with increased risk of thrombotic events, the relative importance of these individual pathways with respect to this risk is presently uncertain.

Besides aspirin insensitive thromboxane biosynthesis, other causes for aspirin resistance should also be considered. First, platelets may have increased sensitivity to stimuli that are

insensitive to aspirin—that is, ADP or thrombin. Secondly, there may be an overabundance of these aspirin insensitive stimuli. Finally, increased platelet turnover, such as after CABG, may cause reduced efficacy of aspirin. Low dose aspirin is rapidly cleared from the circulation. When platelet turnover is very fast, platelets may appear in the circulation in the absence of aspirin, and are therefore not inhibited.

To date, only two clinical studies have shown a relation between test results and clinical thrombotic risk. The first was a prospective observational study of 326 patients and used optical platelet function testing. An aspirin resistant subgroup was identified and showed a twofold risk of thrombotic events. However, only a small minority of all events could be predicted with this approach. The other study used the urinary assessment of 11-dehydro TXB-2 (11-d-TXB-2), reflecting in vivo TXA-2 production. In retrospect, patients in the highest quartile had a 1.8 fold higher risk of thrombotic events compared to those in the lowest quartile. Like many other prognostic markers, urinary 11-d-TXB-2 indicates an increased group risk, but its use for individual risk assessment appears limited.

In conclusion, aspirin resistance is shaping up to be a true clinical entity. Possible causes are being explored, and easy to perform individually predictive tests of aspirin resistance are currently being investigated, as well as alternative antithrombotic strategies.

Thienopyridines

The issue of clopidogrel resistance has also received much attention. To date, only one small clinical trial has shown a relation between ADP-induced platelet aggregation and clinical events.²⁰

Several mechanisms may be involved in clopidogrel resistance. Firstly, drug-drug interactions at the level of the CYP450-3A4 were suggested, especially with atorvastatin. Initial studies indicated a reduced inhibitory effect of clopidogrel when combined with atorvastatin. However, in later mechanistic and large clinical studies these findings could not be substantiated.

Differences in the metabolic activity of the CYP450-3A4 system are a second possible mechanism associated with a varying antiplatelet effect. Many genetic variants of CYP450-3A4 have been discovered; the impact on the efficacy of clopidogrel remains to be demonstrated though.

Finally, response to clopidogrel may vary due to genetic polymorphisms of the P2Y₁₂-receptor on the platelet surface.

Inter-individual differences in the antiplatelet effect of clopidogrel are likely to be multifactorial. Moreover, at present it is uncertain whether high platelet activity during dual antiplatelet treatment is associated with an increased risk of thrombotic events. The value of measuring antiplatelet effect and consequent individualisation of antiplatelet treatment—for example, dose adjustment—has not been studied.

CONCLUSION

For almost all patients at increased risk of thrombotic events, aspirin is one of the main therapeutic interventions. For those at modest risk of events—for example, in primary prevention—attention should be paid as to whether the antithrombotic benefits outweigh the risk of bleeding complications. Thienopyridines, nowadays mainly clopidogrel, are primarily

indicated as monotherapy in the case of contraindications for aspirin. In the case of gastrointestinal bleeding resulting from treatment with aspirin, replacement with clopidogrel is not necessarily indicated, since continued use of aspirin plus gastric protection has a superior safety profile. Clopidogrel on top of aspirin is recommended in high risk acute coronary syndromes, and should be given immediately. Dual antiplatelet treatment must be continued for 6–12 months. Dual treatment should also be given in PCI with stenting, with glycoprotein IIb/IIIa inhibitors in the case of a clinically high risk profile. In primary PCI for ST elevation myocardial infarction, standard use of abciximab has been proven efficacious, and infusion should be initiated as early as possible to improve pre-procedural patency.

Despite notable improvements in outcome after thrombotic events brought about by antiplatelet treatment over the last decades, some patients may not benefit as much as others—a phenomenon sometimes referred to as antiplatelet drug resistance. Further research to refine its definition, and elucidate the underlying pathophysiological mechanisms, may be the next step to a more individualised optimisation of future antithrombotic treatment.

Additional references appear on the *Heart* website—<http://www.heartjnl.com/supplemental>.

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Additional references appear on the *Heart* website—
<http://www.heartjnl.com/supplemental>