Platelet aggregation inhibitors in prevention and treatment of coronary thrombosis

M.E.R. Gomes, F.W.A. Verheugt*

Department of Cardiology (540), Heart Centre, University Medical Centre, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, the Netherlands, tel.: +31 (0)24-361 42 20, fax: +31 (0)24-354 05 37, e-mail: f.verheugt@cardio.umcn.nl, * corresponding author

ABSTRACT

Platelet aggregation plays a key role in the development of complications of atherosclerosis. By inhibiting platelet aggregation in a pharmacological way complications such as myocardial infarction and sudden death may be prevented. This goes for primary as well as secondary prevention. The most relevant substances for this goal are aspirin, clopidogrel and the new glycoprotein IIb/IIIa inhibitors.

INTRODUCTION

In the Western world atherosclerosis is the leading cause of severe morbidity and mortality. Though much of the pathophysiological mechanism of atherosclerosis is still unknown, a multifactor model seems appropriate. In many cases this chronic condition will be complicated by thrombosis, the so-called atherothrombosis. Antithrombotic medication is the cornerstone in the prevention and treatment of this severe complication of atherosclerosis. Within the arsenal of antithrombotic medication, platelet aggregation inhibitors have taken a prominent position, because they are highly effective and easy to use. In this review we summarise the latest developments in coronary thrombosis, discussing successively the pathophysiology, causes and consequences of atherothrombosis on one hand and the pharmacology, efficacy, most commonly occurring side effects, contraindications and interactions of the main antithrombotic agents on the other hand. Finally, the place of antiplatelet therapy within the total spectrum of antithrombotic treatment is discussed.

PATHOPHYSIOLOGY, CAUSES AND CONSEQUENCES OF Atherosclerotic CORONARY THROMBOSIS

Pathophysiology

Atherosclerosis causes arterial stenosis. Although the early stages of atherosclerosis are usually benign, sudden changes in flow can result in rapid progression of the stenosis and can even give total occlusion of the vessel by thrombus. This total occlusion will result in ischaemia and ultimately infarction. When the onset of the ischaemia is sudden and there is no collateral circulation, the infarcted area will be large and may result in pump failure, severe ventricular arrhythmias, (fatal) cerebral infarction or the loss of limbs, gut or retina. The reason for thrombus formation on an atherosclerotic plaque of a vessel with reduced diameter is not yet clarified. Atherosclerotic plaques are covered with an incomplete endothelial layer. The uncovered subendothelial structures such as collagen and tissue factor seem to stimulate platelet adhesion and aggregation and the activation of the coagulation system by the aggregated platelets, all of which cumulate in the formation of platelet-rich thrombi at the site of the atherosclerotic plaque. This thrombus can in turn result in total occlusion.

Causes of coronary thrombosis

There are two main theories on the cause of coronary thrombosis. The first theory assumes that local factors induce coronary thrombosis. This theory is supported by the findings of pathologists in patients with diseases due to coronary thrombosis and those who have received fibrinolytic therapy. In these patients total coronary artery occlusion has almost always occurred at a site with severe stenosis. The second theory assumes that there is a state
of elevated platelet aggregatebility. This is supported by the fact that some patients have a myocardial infarction without significant coronary artery disease. Also the circadian variation with a morning increment in the frequency of myocardial infarction, sudden death and ischaemic cerebrovascular events seems to support this theory. Elements of both theories probably play a role in coronary thrombosis.

**Consequences of coronary thrombosis**
Thrombus formation in coronary arteries can give severe complications. Among these complications acute coronary syndromes with ST elevation (acute transmural infarction) and without (unstable angina pectoris or non-Q-wave infarction) can be distinguished. Randomised controlled trials have shown that mortality rates of acute myocardial infarction were 30% within the first hour after onset in patients prior to hospital admission, 10% during hospital admission and 10% during the first year after discharge. About 10% of patients with unstable angina pectoris develop a myocardial infarction.

**PHARMACOLOGY**
Three groups of platelet aggregation inhibitors are available.

**Aspirin and dipyramidole**
The first group is represented by aspirin and dipyramidole. Aspirin reduces the synthesis of prostaglandins by acetylating cyclo-oxygenase. As a result the formation of prostacyclin (PGI₂), which has a vasodilatory and platelet aggregation inhibiting function, and thromboxane A₂ (TxA₂), which has a vasoconstrictive and platelet aggregation stimulating function, is inhibited (figure 1). Due to the fact that cyclo-oxygenase production is regulated on a nuclear level, the effect of aspirin on nucleus-containing cells is only of short duration (a few hours). For cells without a nucleus, such as platelets, the effect is sustained for its lifetime, which is about seven days. The effect of aspirin is immediate and continuous until at least 50% of the platelets have been replaced. At a very low dose (from 9 mg/day) aspirin removes all thromboxane A₂ from plasma, without reducing prostacyclin levels. The clinical effectiveness of this dosage is, however, still under debate. A dose of 30 mg/day has shown to be clinically effective in neurology and 75 mg/day in cardiology. Laboratory findings have shown that dipyramidole reduces platelet adhesion to rough surfaces without a direct effect on platelet aggregation. For this reason dipyramidole is used in the secondary prevention of transient ischaemic attacks (TIA) or cerebrovascular accidents (CVA). For acute coronary syndrome, dipyramidole has no proven clinical benefit.

**Clopidogrel and ticlopidine**
The second group consists of clopidogrel and ticlopidine. Due to its side effects ticlopidine is not registered in the Netherlands and is therefore not discussed in this article. Clopidogrel is a so-called prodrug which is metabolised in the liver. It is a powerful inhibitor of adenosine diphosphate (ADP) induced platelet aggregation, without reducing thromboxane A₂ induced platelet aggregation. It also has an indirect inhibitory effect on the glycoprotein IIb/IIIa receptor. It has no influence on platelet collagen adhesion (no reduction of intracellular cyclic adenosine monophosphate), humoral haemostasis or fibrinolysis. Its effect is best assessed by measuring bleeding time. It has a stronger effect on bleeding time than aspirin. Clopidogrel reaches a maximum effect three to five days after administration, which may reduce its usefulness in the acute setting. Clinical effectiveness can be enhanced using a loading dose.

**Glycoprotein IIb/IIIa inhibitors**
The third group contains the glycoprotein IIb/IIIa inhibitors. By preventing fibrinogen mediated cross-linkage of platelets by means of the platelet glycoprotein IIb/IIIa receptor, these agents inhibit the final common pathway of platelet aggregation, independent of the kind of stimuli (thromboxane, collagen and catecholamines). Glycoprotein IIb/IIIa inhibitors do not influence platelet adhesion. Theoretically, glycoprotein IIb/IIIa inhibitors can prolong bleeding time indefinitely. By recombinant
technique, parts of the monoclonal antibodies against the glycoprotein IIb/IIIa receptor have been attached to the Fab-fragment of the human immunoglobulin G (IgG) molecule. Abciximab is an example of such an antibody and is administered intravenously. Eptifibatide, lamifiban and tirofiban represent a group of substances that inhibit the glycoprotein IIb/IIIa receptor competitively, resulting in an effect of only a few hours. These agents are also administered intravenously. Glycoprotein IIb/IIIa inhibitors that can be administered orally are lefradafiban, orbofiban, sibrafiban and xemilofiban. They have a long $t_{1/2}$ and are cleared by the kidney. These agents are not registered in the Netherlands.

**EFFECTIVENESS AND MOST COMMONLY OCCURRING SIDE EFFECTS**

We will now describe the effectiveness of antiplatelet agents in primary prevention of coronary heart disease, the direct treatment of acute coronary syndromes and in secondary prevention. Additionally, their most important side effects will be discussed. For the explanation of the abbreviations used, see **table 1**.

**Effects on primary prevention**

In 2001 a meta-analysis was performed from four randomised controlled clinical trials concerning the effectiveness of aspirin in the primary prevention of coronary heart disease.4 This meta-analysis showed that aspirin gives a significant reduction of cardiovascular events and myocardial infarction, without affecting mortality. Treatment was useful in patients with an absolute risk for cardiovascular events of 1.5% or more per year (NNT=44 for five years). For patients with an absolute risk of 1% per year or less, treatment with aspirin was of limited value. A more recent meta-analysis, assessing the efficacy of aspirin in the primary prevention of cardiovascular disease events, showed that aspirin reduces myocardial infarction by an average of 28% (95% CI 11 to 40%) in healthy individuals with a wide range of cardiovascular risk.5 Neither mortality nor stroke were significantly decreased in either of these trials. They calculated that for preventing 6-20 myocardial infarctions, one has to treat 1000 patients with an absolute risk for coronary heart disease of 5% for a period of five years with aspirin (number needed to treat=NNT=50-167). On the other hand in this group 0-2 cerebral haemorrhages will be induced (number needed to harm=NNH= 2500) as well as 2-4 severe gastrointestinal bleedings (NNH=250-500). In patients with an absolute risk of 1% for a period of five years, 1-4 myocardial infarctions will be prevented (NNT=250-1000), at the cost of 0-2 cerebral haemorrhages (NNH=2500) and 2-4 gastrointestinal bleedings (NNH=250-500), resulting in a benefit to harm ratio $<1.0$. With regards to the major side affects, excess gastrointestinal bleeding in the above trials ranges from 0.4 (pNS) to 1.7 (p$<0.05$) per 1000 patients treated per year. In the HOT trial excess risk was similar in males and females. In the same trial elderly (>65 years) had slightly more excess bleeding (1.7%, p=0.03) than younger individuals (1.4%, p=0.002) per 1000 person-years. Excess cerebral bleeding in the above trials varied from -0.12 (pNS) to 0.2 (pNS) per 1000 patients treated per year. Regarding the benefits and haemorrhagic risks, aspirin should not be given to each healthy individual in the primary prevention of cardiovascular disease events. Only in those with a certain amount of cardiovascular risk will the benefit of aspirin outweigh the haemorrhagic risk. In the Physicians’ Health Study, of all the parameters assessed (age, smoking, diabetes, family history, plasma lipid level, blood pressure, alcohol used, exercise and body mass), only blood lipid levels and age showed a significant interaction with aspirin benefit. Whereas lipid levels showed a negative interaction (the higher the plasma cholesterol, the less benefit from aspirin), age was a clear indicator of increased benefit. Aspirin showed to be effective from the age of 50, with the protective effect of aspirin for the elderly (over the age of 65 to 70) seeming likely. Protective benefit in women below the age of 50 seems unlikely, but above this age their protective benefits seem to be similar to those in men.5

Additionally individuals at risk can be identified using some form of risk calculation. In conclusion low-dose aspirin is indicated in the prevention

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**Table 1**

**Abbreviations and explanation**

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
<th>FORMULA</th>
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<tbody>
<tr>
<td>Relative risk (RR)</td>
<td>The risk for a certain event in the experimental group (Y) $R_y$ divided by the risk in the control group (X) $R_x$</td>
<td>$RR=R_y/R_x$</td>
</tr>
<tr>
<td>Absolute risk (AR)</td>
<td>The frequency of occurrence of an event in a specific period of time</td>
<td></td>
</tr>
<tr>
<td>Absolute risk reduction (ARR)</td>
<td>The risk for an event in the control group (X) $R_x$ minus the risk in the experimental group (Y) $R_y$</td>
<td>$ARR=R_y-R_x$</td>
</tr>
<tr>
<td>Number needed to treat (NNT)</td>
<td>The number of patients needed to be treated for a period of time to prevent one event</td>
<td>$NNT=1/(R_y-R_x)$</td>
</tr>
<tr>
<td>Number needed to harm (NNH)</td>
<td>The number of patients in which during active treatment (H_y) in one extra person a complication occurs compared with the controls (H_x)</td>
<td>$NNH=1/(H_y-H_x)$</td>
</tr>
</tbody>
</table>

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| JUNE 2003, VOL 61, NO. 6 | 187 |
of myocardial infarction in persons at higher cardiovascular risk, i.e. males and females over the age of 50 years with a cardiovascular risk of more than 1%/year. Additional risk analysis can be performed using the risk calculation tables.

**Direct treatment of acute coronary syndromes**
Aspirin should be administered to every patient under suspicion of acute coronary syndrome, because it is the only substance that gives an instant inhibition of platelet aggregation. In most countries 75 to 325 mg/day is administered after a loading dose of 160-200 mg. After admission clopidogrel or a glycoprotein IIb/IIIa inhibitor can be added.

**Effects on secondary prevention**

**General**
In 1994 a meta-analysis of 145 randomised trials (over 100,000 patients) comparing platelet aggregation inhibitors against each other and against placebo in patients with an increased risk for vascular events, a protective effect in secondary prevention of cardiovascular or cerebrovascular events was found when treated with aspirin (75-325 mg/day) or another platelet aggregation inhibitor for a few years. For the endpoints of myocardial infarction, CVA and mortality, the following NNTs were calculated: nonfatal myocardial infarction NNT=25 (one month of treatment), prior myocardial infarction NNT=25 (two years of treatment), unstable angina pectoris NNT=20 (six months treatment), miscellaneous with an increased risk, e.g. operation, stable angina pectoris, NNT=50 (one year of treatment). There was no relation with age, sex, hypertension or diabetes. In 2002 a consecutive meta-analysis was performed by the same group of investigators. They now analysed 287 randomised trials (over 200,000 patients) comparing different doses of platelet aggregation inhibitors with placebo in patients with an increased risk for vascular events. The authors came to a similar conclusion as in their meta-analysis of 1994, with NNTs now being respectively: 26 for myocardial infarction (one month of treatment), 28 for patients with a prior myocardial infarction (27 months of treatment) and miscellaneous 45 (22 months of treatment). The authors could not show a dose-effect relationship for aspirin, when comparing a dose of less than 75 mg with a dose of 75 mg or more in the secondary prevention of cardiovascular events. They stated that in the literature there was insufficient evidence of the efficacy of an aspirin dose of less than 75 mg, to conclude that the effectiveness was similar to that of a dose of 75 mg or more.

**Aspirin and clopidogrel**
Only one study compared the efficacy of clopidogrel with aspirin. In this study (with a mean follow-up time of 1.9 years) the effects of clopidogrel and aspirin were compared in 19,000 patients with a recent CVA, myocardial infarction or peripheral vascular disease. The authors concluded that in 9.8% of the patients treated with clopidogrel the primary combined endpoint had occurred (nonfatal cerebral or myocardial infarction or death by a cardiovascular event), compared with 10.7% of the patients treated with only aspirin (NNT=110). For total mortality these numbers were 5.8% and 6.0% respectively (NNT=500). Severe haemorrhages occurred in 112 patients in the clopidogrel group and 149 patients in the aspirin group. In another study assessing 12,000 patients with acute coronary syndrome without ST elevation, patients were administered clopidogrel with aspirin or aspirin alone within 24 hours after the initial symptoms (table 2). After 12 months a nonfatal CVA, nonfatal myocardial infarction or death by cardiovascular event had occurred in 9.3% of the patients using clopidogrel, compared with 11.4% of the patients without clopidogrel (NNT=48). There was a significantly larger number of severe haemorrhages (patients in need of transfusion) in the group using clopidogrel (3.7% versus 2.7%, NNH=100), but there was no difference in the number of life-threatening haemorrhages.

**Dipyramidole**
This agent is only used in the secondary prevention of CVA and TIA and will not be further discussed in this article.

**Glycoprotein IIb/IIIa inhibitors and aspirin**
The combination of aspirin with an intravenously administered glycoprotein IIb/IIIa inhibitor has been compared with aspirin alone in patients with acute coronary syndromes with or without ST elevation and in patients who underwent a PTCA (table 2). In almost all of these studies both groups (experimental and control) were given a combination of aspirin and heparin as the standard treatment. The mean follow-up was 30 days. In a meta-analysis the effect of an intravenously administered glycoprotein IIb/IIIa inhibitor was assessed in patients with acute coronary syndromes without ST elevation. Six randomised placebo-controlled trials were studied with a total of 31,402 patients. Five of these trials were double-blinded. The authors concluded that within 30 days after randomisation the primary combined endpoint of death or myocardial infarction was reached in 10.8% of the patients treated with the glycoprotein IIb/IIIa inhibitor, compared with 11.8% in the controls (NNT=106). There was no statistically significant difference with regards to the endpoint death (2.06% in the treated group versus 3.66% for the controls, RR 0.90, CI 0.80-1.02). After 30 days the treated group showed more severe haemorrhages than the control group (2.4% versus 1.4%, NNH=121). Of all patients 38% underwent a percutaneous coronary intervention (PCI) or bypass operation. In these patients, compared with the patients without intervention, the treatment seemed effective. The efficacy of oral glycoprotein IIb/IIIa inhibitors has also been assessed in...
Table 2
Large randomised trials on platelet aggregation inhibitors in acute coronary syndromes with or without ST elevation or PCI

<table>
<thead>
<tr>
<th>STUDY (YEAR)</th>
<th>AGENT</th>
<th>DEATH AND (RE)INFARCTION (n/N)</th>
<th>RR</th>
<th>AR</th>
<th>ARR</th>
<th>NNT</th>
<th>NNH a</th>
</tr>
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<td></td>
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<tr>
<td>Clopidogrel</td>
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<tr>
<td>CURE10 (2001)</td>
<td>clopidogrel</td>
<td>450/5202</td>
<td>209/2598</td>
<td>0.80 [0.72-0.90]</td>
<td>0.02</td>
<td>0.02</td>
<td>48</td>
</tr>
<tr>
<td>Intravenous glycoprotein IIb/IIIa receptor antagonists</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GUSTO-IV ACS12 (2001)</td>
<td>abciximab</td>
<td>450/5202</td>
<td>209/2598</td>
<td>0.80 [0.72-0.90]</td>
<td>0.02</td>
<td>0.02</td>
<td>48</td>
</tr>
<tr>
<td>PARAGON20 (1998)</td>
<td>lamifiban</td>
<td>172/1524</td>
<td>89/738</td>
<td>0.80 [0.75-0.84]</td>
<td>0.02</td>
<td>0.02</td>
<td>48</td>
</tr>
<tr>
<td>PARAGON-B4 (2002)</td>
<td>lamifiban</td>
<td>278/2628</td>
<td>296/2597</td>
<td>0.93 [0.86-0.99]</td>
<td>0.01</td>
<td>106</td>
<td>121</td>
</tr>
<tr>
<td>PRISM21 (1998)</td>
<td>tirofiban</td>
<td>94/1616</td>
<td>115/1616</td>
<td>0.80 [0.72-0.90]</td>
<td>0.02</td>
<td>0.02</td>
<td>48</td>
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<tr>
<td>PRISM-PLUS22 (1998)</td>
<td>tirofiban</td>
<td>114/1118</td>
<td>96/779</td>
<td>0.80 [0.72-0.90]</td>
<td>0.02</td>
<td>0.02</td>
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<tr>
<td>PURSUIT23 (1998)</td>
<td>eptifibatide</td>
<td>872/6209</td>
<td>745/4739</td>
<td>0.93 [0.86-0.99]</td>
<td>0.01</td>
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<tr>
<td>Meta-analysis24 (2002)</td>
<td></td>
<td>1980/18297</td>
<td>1550/13107</td>
<td>0.93 [0.86-0.99]</td>
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<td>FROST25 (2000)</td>
<td>lefradafiban</td>
<td>17/401</td>
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<td>OPUS-TIMI 1626 (2000)</td>
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<td>302/6867</td>
<td>133/3421</td>
<td>0.93 [0.86-0.99]</td>
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<td>SYMPHONY27 (2000)</td>
<td>sibrafiban</td>
<td>467/6095</td>
<td>214/3074</td>
<td>0.93 [0.86-0.99]</td>
<td>0.01</td>
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<td>SYMPHONY-228 (2001)</td>
<td>sibrafiban</td>
<td>339/4406</td>
<td>136/2231</td>
<td>0.93 [0.86-0.99]</td>
<td>0.01</td>
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<tr>
<td>Meta-analysis29 (2002)</td>
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<td>1125/17769</td>
<td>487/8836</td>
<td>1.16 [1.04-1.28]</td>
<td>0.01</td>
<td>106</td>
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<tr>
<td><strong>ACUTE CORONARY SYNDROMES WITH ST ELEVATION</strong></td>
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<td>ASSENT-32 (2001)</td>
<td>abciximab</td>
<td>177/2017</td>
<td>208/2038</td>
<td>0.85 [0.78-0.93]</td>
<td>0.01</td>
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<td>ENTIRE30 (2002)</td>
<td>abciximab</td>
<td>14/241</td>
<td>20/242</td>
<td>0.85 [0.78-0.93]</td>
<td>0.01</td>
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<tr>
<td>GUSTO-V31 (2001)</td>
<td>abciximab</td>
<td>616/8328</td>
<td>726/8260</td>
<td>0.85 [0.78-0.93]</td>
<td>0.01</td>
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<td>INTRO-AMI32 (2002)</td>
<td>eptifibatide</td>
<td>16/204</td>
<td>7/101</td>
<td>0.85 [0.78-0.93]</td>
<td>0.01</td>
<td>106</td>
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<td>SPEED33 (2001)</td>
<td>abciximab</td>
<td>5/115</td>
<td>9/109</td>
<td>0.85 [0.78-0.93]</td>
<td>0.01</td>
<td>106</td>
<td>121</td>
</tr>
<tr>
<td>TIMI-1434 (2000)</td>
<td>abciximab</td>
<td>12/150</td>
<td>9/150</td>
<td>0.85 [0.78-0.93]</td>
<td>0.01</td>
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<tr>
<td>Meta-analysis35 (2001)</td>
<td></td>
<td>840/11055</td>
<td>979/10900</td>
<td>0.85 [0.78-0.93]</td>
<td>0.01</td>
<td>106</td>
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<tr>
<td><strong>PERCUTANEOUS CORONARY INTERVENTION</strong></td>
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<tr>
<td>Meta-analysis36 (2001)</td>
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</table>
| The results mentioned in this table correspond in part with the Cochrane Collaboration. The primary endpoint (death and reinfection) is displayed for the experimental as well as the control group, as the number of patients with this primary endpoint compared with the total number of patients in each individual group (n/N). The result of the relative risk (RR) and the absolute risk (AR) are presented by way of graphics. The size of the squares represents the number of contestats in each study. The horizontal lines through each square correspond with the 95% CI. With regards to the AR, there is no statistically significant effect when the squares enclose the vertical line. The squares at the left side of the vertical line indicate a tendency to treatment preference, whereas the squares at the right side of the vertical line indicate control preference. The results of the intravenously administered glycoprotein IIb/IIIa inhibitors in acute coronary syndromes without ST elevation have been slightly adjusted. The same goes for the results of the oral glycoprotein IIb/IIIa inhibitors in acute coronary syndromes without ST elevation and those of the intravenous glycoprotein IIb/IIIa inhibitors. For all results statistical tests for heterogeneity were performed. These were all negative, which indicates that the results of all studies point in the same direction.

a. The number needed to harm regards to major bleedings. b. The values of the ARR and NNT are negative because the treatment is not effective. c. Only the data of the control group which were given heparin are displayed. d. Of these studies, in which 'dose-finding' was also assessed, only the results of the period hereafter (dose-confirmation) were analysed. e. Only the results of the two largest trials are shown, due to the fact that of the remaining studies not all data could be calculated. f. Of this study only the number of patients who died were included. g. This meta-analysis gives insufficient data for some outcomes.

patients with acute coronary syndromes without ST elevation.0-11 Four randomised, double-blind phase III studies were analysed in a meta-analysis assessing over 33,000 patients.12 The authors concluded that the use of oral glycoprotein IIb/IIIa inhibitors gives an increase in mortality and myocardial infarction. The use of intravenously administered glycoprotein IIb/IIIa inhibitors has also been analysed in patients with an acute coronary
syndrome with ST elevation (transmural infarctions). In the literature there are six randomised controlled open trials assessing over 23,000 patients. The results summarised in table 1 show a positive effect on the combined endpoint death and reinfarction. For the endpoint death there is no significant difference, with 5.69% for the treated group versus 5.75% for the controls (RR 1.00, CI 0.90-1.11). Because of their open character, these studies have less relevance than the double-blinded trials. Finally the effect of intravenously administered glycoprotein inhibitors was assessed in patients that underwent a PTCA. In a meta-analysis on glycoprotein IIb/IIIa inhibitors in acute coronary syndromes, a subgroup of 6337 patients was analysed who underwent a PCI during hospital admission. After 30 days these patients showed a strong reduction in mortality and myocardial infarction, compared with patients who had only used standard medication, with odds ratios of 0.82 (0.71-0.96) versus 0.95 (0.80-1.03) respectively. Glycoprotein IIb/IIIa inhibitors showed an additional benefit when their use was continued during PCI, compared with cessation prior to the PCI (OR 0.74 CI 0.57-0.96 versus OR 0.87 CI 0.72-1.06). In practice the (expensive) glycoprotein IIb/IIIa inhibitors are only used by specialised cardiologists (interventional cardiologists and heads of coronary care units).

Aspirin and ticlopidine
Four randomised controlled open trials assessing the efficacy of ticlopidin and aspirin on the endpoints death and (re) infarction in patients who underwent a PTCA with stent implantation showed a positive effect against stent thrombosis. There were significantly more haemorrhagic complications in the ticlopidin group.

OTHER SIDE EFFECTS, CONTRAINDICATIONS AND INTERACTIONS

Aspirin
Side effects
One of the notorious side effects of aspirin is gastrointestinal bleeding. Case-controlled studies about the relation between the risk of hospital admission due to gastrointestinal bleeding and the prophylactic use of aspirin (≥300 mg/day) show that there is an increased risk of bleeding for all doses of aspirin. When used for more than a month the risk seems to increase with the dosage, from 2.3 for a dose of 75 mg/day to 3.9 for 300 mg/day. A meta-analysis of 24 randomised controlled trials (over 66,000 patients) on the relation between the use of aspirin and the occurrence of gastrointestinal bleedings showed that when used for more than one year, there is a significant increase in the number of gastrointestinal bleedings compared with placebo (2.47% versus 1.42%, NNH=106). There was no evidence that a lower dose or tablets with slow release decreased the number of bleedings. For this reason it seems likely that the risk for bleeding is independent of the dose used. In this meta-analysis, studies were excluded that selected specific categories of bleedings, e.g. only large bleedings or bleedings that necessitated hospital admission. Another meta-analysis of five primary prevention studies showed that aspirin does not increase the risk for cerebral haemorrhage (OR 1.4, CI 0.9-2.0), but does increase the risk for a large gastrointestinal bleeding (OR 1.7 CI 1.4-2.1). Total mortality was not influenced. Yet another meta-analysis assessed the risk of cerebral haemorrhage in the use of aspirin. Sixteen randomised placebo-controlled trials with a total of 55,462 patients were analysed, of which 14 were secondary prevention trials. The mean aspirin dose was 273 mg/day and the mean duration of treatment was 37 months. The result showed that the AR for a cerebral haemorrhage increased by 12 per 10,000 persons (NNH=694). It was remarkable that, when using aspirin, the ARR for a nonhaemorrhagic stroke was 0.4% (NNT=250) in this meta-analysis, indicating a beneficial harm-to-benefit ratio. Another aspirin side effect is allergy. Symptoms can range from slight to severe, e.g. anaphylactic shock.

Contraindications
The most important contraindications for aspirin use are gastric ulcers, erosive gastritis, haemorrhagic diathesis, recent cerebral haemorrhage, severe renal insufficiency (renal clearance of <30 ml/min), severe liver insufficiency and the use of anticoagulants. Further contraindications are gastric discomfort or pain, asthmatic attacks, collapse or allergic reactions in former use.

Interactions
The effect of oral anticoagulants can be enhanced by the use of aspirin, increasing the risk for bleeding. In a recently published study on patients with arthritis, authors found that ibuprofen antagonises the aspirin induced irreversible platelet aggregation inhibition. This effect was not found for diclofenac, rofecoxib or paracetamol. The relevance of this finding for day-to-day practice is not yet clear. The simultaneous use of NSAIDs or corticosteroids with aspirin also increases the risk of gastrointestinal ulceration.

Clopidogrel
Side effects
Gastrointestinal side effects such as abdominal pain, dyspepsia, diarrhoea and nausea are the most common side effects of clopidogrel. Gastrointestinal bleedings, purpura or nose bleeds can also occur. Rash and itching have also been described, as well as central and peripheral nervous system disorders.

**Contraindications**
Severe liver insufficiency and haemorrhages such as peptic ulcer or cerebral haemorrhage are contraindications.

**Interactions**
The simultaneous use of clopidogel with aspirin, heparin, thrombolytic agents or NSAIDs increases the chance of haemorrhage.

**Ticlopidine**
**Side effects**
The ticlopidine-induced bone marrow depression that is seen in almost all patients has prohibited large-scale use of this agent.38

**Glycoprotein IIb/IIIa inhibitors**
**Side effects**
The most frequent side effect of abciximab is haemorrhages within 36 hours after administration. Mild trombocytopenia is seen in over 4% of the patients, where a severe thrombocytopenia occurs in 1% of the patients. The other common side effects are hypotension, nausea, vomiting, chest pain, bradycardia and fever. Some people have suggested the administration of an H₂-receptor antagonist or a proton pump inhibitor for the prevention of gastrointestinal bleeding. There is no scientific proof to support this theory.

**Contraindications**
The most important contraindications are recent bleeding or an increased risk for bleeding: internal bleeding, recent CVA or operation, haemorrhagic diathesis, thrombocytopenia, retinopathy and hypertension. Additionally liver and renal insufficiency are absolute contraindications (except for tirofiban).

**Interactions**
There is little known about their interactions. Preferably, these agents should not be used simultaneously with thrombolytic therapy.

**CONCLUSION**
Platelet aggregation plays a key role in the thrombotic complications of atherosclerosis, such as unstable angina pectoris, myocardial infarction, stroke and sudden death. Platelet aggregation can follow many different pathways, of which thromboxane A₂, thrombin, collagen and ADP are the most important. Eventually, by binding to the glycoprotein IIb/IIIa receptor, fibrinogen is used for the final common pathway to create the binding between the platelets. Pharmacological inhibition of platelet aggregation can be achieved by influencing thromboxane A₂ (aspirin), ADP (clopidogrel) or by blocking the glycoprotein IIb/IIIa receptor (abciximab, eptifibatide and tirofiban). Aspirin reduces the risk of myocardial infarction and death in patients with arterial vascular disease. All patients with acute coronary syndromes should therefore be given aspirin as soon as possible and they should continue to use aspirin for the rest of their lives. The same goes for patients with chronic coronary syndromes not yet using aspirin. Aspirin gives an instant effect. If there are contraindications for aspirin, clopidogrel can be given. Ticlopidine is no longer used in the Netherlands because of its side effects. In one study assessing patients with a prior CVA or myocardial infarction, clopidogrel showed less reinfarction and death than aspirin. With aspirin a larger number of bleedings occurred. Additional research is necessary. In acute coronary syndromes without ST elevations the efficacy of clopidogrel with aspirin has been demonstrated compared with aspirin alone in one study, but additional research is also necessary. In clinical practice clopidogrel is not routinely used outside coronary intervention. The most important application of clopidogrel is in secondary prevention, when there is a contraindication for aspirin. A statistically significant decrease in death and reinfarction has been demonstrated with a combination of glycoprotein IIb/IIIa inhibitors plus aspirin, compared with aspirin alone in patients undergoing PTCA. In practice only specialists in cardiovascular medicine (such as interventional cardiologists or heads of coronary care units) use these substances. The value of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes is only small, while there is an increased risk for haemorrhages. It is obvious that there will be no further research on oral glycoprotein IIb/IIIa inhibitors, because of the increase in deaths and re-infarctions.

**NOTE**
This paper is slightly adapted from a previously published paper entitled ‘Preventie en behandeling van coronaire trombose met bloedplaatjesaggregatieremmers’ from prof. dr. F.W.A. Verheugt, under responsibility of the editorial office of the Geneesmiddelenbulletin, 2002;36:133-40.

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