We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

3,800 Open access books available
116,000 International authors and editors
120M Downloads

154 Countries delivered to
TOP 1% Our authors are among the most cited scientists
12.2% Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
1. Introduction

Platelet activity has a very important role in the pathogenesis of atherosclerosis disease. In addition to being part of the coagulation system, they contribute to all phases of the atherosclerosis process (1). The “intervention” in the platelet activity has been played a central role in the treatment of coronary artery disease (CAD) (2).

Aspirin is considered the foundation antiplatelet therapy for patients at risk of cardiovascular events. However, in the last few decades many different agents were introduced to have a more effective antiplatelet action and improve treatment outcomes in coronary syndromes.

In this chapter you will find a systematic review of all the antiplatelet agents available: mechanism of action, pharmacokinetics, side effects, evidence of effectiveness and their use in clinical settings. A special emphasizes will point out agents that are in investigational stage and what are the future perspectives.

1.1 Platelet mechanisms of action

Platelets play a critical role in the normal coagulation system by “preventing” bleeding after blood vessels are damaged. In addition they contribute to different phases of the atherosclerotic process (1). Rupture of a previously formed atherosclerotic plaque exposes collagen, smooth-muscle cells and von Willebrand factor (vWF) all of which trigger platelet activation and massive aggregation (3). The result of this accumulation of platelets is thrombosis. Acute coronary syndrome (ACS) is a consequence of the occlusion of an atherosclerotic vessel by the thrombotic process. As described before, collagen and vWF in addition to thromboxane A2 (TXa2), thrombin and adenosine diphosphate (ADP) are the most powerful platelet activators (4). When a platelet is activated a conformational change occurs in a receptor located in the platelet membrane called glycoprotein IIb/IIIa which promotes platelet aggregation (5).

Antiplatelet agents that target critical steps of the thrombotic mechanism described above have been developed in the last three decades. However, treatment with these agents can sometimes increase the risk of “undesirable” bleeding complications (6).

2. The traditional anti-platelet agents

Many anti-platelet agents have been tested and used as an effective treatment in arterial thrombosis. Acetyl salicylic acid, commonly known as aspirin was the first anti-platelet
agent used and proven to be effective to reduce the incidence of myocardial infarction and stroke in many high risk vascular patients (2). The recurrence of vascular events in patients treated with aspirin alone ranges between 10 – 20% within five years of the initial event (2-7).

Aspirin is effective by blocking the synthesis of TXa2, a powerful platelet activator. In the last decade, the thienopyridines such as **clopidogrel** have been used to improve outcomes in the treatment of ACS. This anti-platelet agent irreversibly blocks the P2Y12 receptor, precluding the platelet activation by ADP (2). Its anti-platelet mechanism of action clearly differs from aspirin. In the majority of cardiovascular patients the combination of clopidogrel and aspirin has additive beneficial effects when compared with clopidogrel or aspirin alone (8). Clopidogrel also has some limitations, which have prompted the development of newer anti-platelet agents which interact at different sites of the coagulation cascade.

The following figure reflects the site of action of the common antiplatelet agents (figure 1)

3. The thromboxane A2 antagonist

**Dipyridamole** (Persantine) acts as a thromboxane synthase inhibitor, therefore lowering the levels of TXA2 and thus stops the effects of TXA2 as a platelet activator (9). Also can causes systemic vasodilation when given at high doses over a short period of time. The latter, due to the inhibition of the cellular reuptake of adenosine into platelets, red blood cells and endothelial cells leading to increased extracellular concentrations of adenosine (9). It also inhibits the enzyme adenosine deaminase, which normally breaks down adenosine into inosine. This inhibition leads to further increased levels of extracellular adenosine, producing a strong vasodilatation (9).
<table>
<thead>
<tr>
<th>Antiplatelet agents nowadays</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibits the synthesis of TXa2</strong></td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td><strong>TXa2 antagonist</strong></td>
</tr>
<tr>
<td>Dipyridamole</td>
</tr>
<tr>
<td>Terutroban</td>
</tr>
<tr>
<td><strong>P2Y 12 antagonist</strong></td>
</tr>
<tr>
<td>Ticlopidine</td>
</tr>
<tr>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Prasugrel</td>
</tr>
<tr>
<td>Ticagrelor</td>
</tr>
<tr>
<td>Cangrelor</td>
</tr>
<tr>
<td><strong>Glycoprotein IIb/IIIa antagonist</strong></td>
</tr>
<tr>
<td>Abciximab</td>
</tr>
<tr>
<td>Tirofibin</td>
</tr>
<tr>
<td>Eptifibatide</td>
</tr>
<tr>
<td><strong>Protease-activated receptor 1 antagonist</strong></td>
</tr>
<tr>
<td>Vorapaxar</td>
</tr>
<tr>
<td><strong>Direct thrombin Inhibitor</strong></td>
</tr>
<tr>
<td>Bivalirudin</td>
</tr>
</tbody>
</table>

Modified release dipyridamole is used in conjunction with aspirin (under the trade names Aggrenox in the USA or Asasanti Retard in the UK) in the secondary prevention of stroke and transient ischemic attack. This practice has been confirmed by the ESPRIT trial (9). A triple therapy of aspirin, clopidogrel and dipyridamole has been investigated, but this combination led to an increase in adverse bleeding events (10).

Via the mechanisms mentioned above, when given as 3 to 5 min infusion it rapidly increases the local concentration of adenosine in the coronary circulation which causes vasodilation. Vasodilation occurs in healthy arteries, whereas stenosed arteries remain narrowed. This creates a "steal" phenomenon where the coronary blood supply will increase to the dilated healthy vessels compared to the stenosed arteries which can then be detected by clinical symptoms of chest pain, electrocardiogram and echocardiography when it causes ischemia. Flow heterogeneity (a necessary precursor to ischemia) can be detected with gamma cameras and SPECT using nuclear imaging agents such as Thallium-201 and Tc99m-Sestamibi (9).

**Terutroban** is a selective antagonist of the thromboxane receptor. It blocks thromboxane induced platelet aggregation and vasoconstriction (11). As of 2010, it is being tested for the secondary prevention of acute thrombotic complications in the Phase III clinical trial. However, the recent publication of the finalized trial PERFORMS shown no clinical advantage in comparison with patients with aspirin monotherapy in preventing strokes (12). At the time of this publication its use in clinical practice is not approved in the USA.

### 4. Other P2Y 12 antagonist

**Ticlopidine** an anti-platelet drug in the thienopyridine family inhibits platelet aggregation by altering the function of platelet membranes by irreversibly blocking ADP receptors. This
prevents the conformational change of glycoprotein IIb/IIIa which allows platelet binding to fibrinogen (13). It is used in patients in whom aspirin is not tolerated, or in whom dual anti-platelet therapy is desirable (in combination with Aspirin). Because it has been reported to increase the risk of thrombotic thrombocytopenic purpura (TTP) and neutropenia, its use has largely been supplanted by the newer drug, clopidogrel, which is felt to have a much lower hematologic risk (14).

**Prasugrel**, a novel thienopyridine was approved for clinical use in the USA by the Food and Drug Administration (FDA) in 2010. Unlike clopidogrel, which undergoes a two-step, CYP450-dependent conversion to its active metabolite, prasugrel only requires single-step activation. Prasugrel is a more potent platelet inhibitor with faster action and inhibition. Also, it has been estimated that due to its “easy metabolism” its genetic resistance is less likely (15). In other words, prasugrel has a significantly lower incidence of hypoResponsiveness in comparison with clopidogrel (15). However, the risks of bleeding in these patients are greater than clopidogrel (16).

**Ticagrelor** is the most novel class of anti-platelet drugs, the cyclopentatriazolopyrimidines, which also inhibit the P2Y12 receptor as the thienopyridines. However, it has a simpler and faster metabolism (rapid onset of action) high potency and most importantly reversibility (17). The latter, makes this drug safer in regards of bleeding complications.

**Cangrelor**, an ATP analog, is an investigational intravenous anti-platelet drug. This agent has biphasic elimination and possesses the advantages of high potency, very fast onset of action and very fast reversibility after the discontinuation (16).This gives a considerable advantage over other ADP antagonist in patients who might need immediate surgery. However, after initial treatment, patients who received intravenous infusion of Cangrelor often require continued treatment with one of the oral P2Y12 antagonists, something that one must take into consideration (16).

### 5. Glycoproteins IIb/IIa antagonist

**Abciximab**, more known as the ReoPro is an antibody against glycoprotein IIb/IIIa receptor. It had a lot of popularity within interventional cardiologist 10 years ago. It is barely used today. It was replaced by newer IV agents. Abciximab has a plasma half-life of about ten minutes, with a second phase half-life of about 30 minutes. However, its effects on platelet function can be seen for up to 48 hours after the infusion has been terminated, and low levels of glycoprotein IIb/IIIa receptor blockade are present for up to 15 days after the infusion is terminated (18).

**Tirofiban** (Aggrastat) is a synthetic, non-peptide inhibitor acting at glycoprotein (GP) IIb/IIIa receptors. It has a rapid onset and short duration of action after proper intravenous administration. Platelet activity returns to normal 4 to 8 hours after the drug is withdrawn (19).

**Eptifibatide** (Integrilin) is the newer anti-platelet drug which inhibits the glycoprotein IIb/IIa inhibitor. It belongs to the class of the so-called arginin-glycin-aspartat-mimetics and reversibly binds to platelets. Eptifibatide has a short half-life, 3 to 5 hours after the discontinuation platelet activity recovers to normal levels (20). The drug is the third inhibitor of GPIIb/IIIa that has found broad acceptance within interventional cardiologists nowadays.

### 6. Protease-activated receptors antagonist

**Vorapaxar** (formerly SCH 530348) is a thrombin receptor (PAR-1) antagonist based on the natural product himbacine. It is an experimental pharmaceutical treatment for acute coronary syndrome as a very powerful platelet inhibitor (21). In January 2011, the clinical trial was
halted for patients with stroke and mild heart conditions due to safety reasons. It is unknown if it will continue.

7. Direct thrombin inhibitors

Bivalirudin (Angiomax) is a specific and reversible intravenous direct thrombin inhibitor. Clinical studies demonstrated consistent positive outcomes in patients with stable angina, unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) undergoing PCI in 7 major randomized trials (22). Coagulation times and platelet activity return to baseline approximately 1-6 hour following cessation of bivalirudin administration (23).

8. Conclusions

Antiplatelet therapy plays a crucial role in the treatment of coronary patients. The continuous introduction of new agents is geared to improve results in patient ongoing percutaneous coronary interventions. However, the side effects of these should be monitored closely. In the end, the ideal management of patients with acute coronary syndrome should be to be a collaborative effort between cardiologist and surgeons to assure the best outcomes possible.

9. References


[18] Tcheng, JE; Kandzari, DE; Grines, CL; Cox, DA; Effron, MB; Garcia, E; Griffin, JJ; Guagliumi, G et al. "Benefits and risks of abciximab use in primary angioplasty for acute myocardial infarction: the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial." Circulation 2003;108 (11): 1316–23


This book has been written with the intention of providing an up-to-the-minute review of acute coronary syndromes. Atherosclerotic coronary disease is still a leading cause of death within developed countries and not surprisingly, is significantly rising in others. Over the past decade the treatment of these syndromes has changed dramatically. The introduction of novel therapies has impacted the outcomes and surviving rates in such a way that the medical community need to be up to date almost on a "daily bases". It is hoped that this book will provide a timely update on acute coronary syndromes and prove to be an invaluable resource for practitioners seeking new and innovative ways to deliver the best possible care to their patients.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:
