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Antiplatelet Drugs in Coronary Artery Disease

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1. Introduction

Overview of diverse functional aspects

Human platelets (PLTs) are anucleate, discoid small cells (2 - 4 μm by 0.5 μm) that normally circulate at concentrations of 150 - 400 x 10^9/L for a maximum of 10 days. They are primed to undergo explosive activation following damage from the vessel wall and play a central role in both primary hemostasis and arterial thrombosis, including adhesion, aggregation, and coagulation but also chemotaxis, inflammation, and proliferation.

The normal vascular endothelium produces potent PLT inhibitors such as nitric oxide, prostacyclin and natural ADPase (CD39). However, once sub-endothelial components like collagen, fibronectin, laminin, or von Willebrand factor (vWF) become exposed, PLTs undergo a highly regulated set of functional responses including adhesion, followed by spreading, release reactions (degranulation), induction of pro-coagulant activity, microparticle formation, and clot retraction. These activities result in rapid formation of a vascular (white) plug, which then is stabilized by the activation of soluble plasma components resulting in the formation of fibrin and the inclusion of erythrocytes and leukocytes. This red plug initiates the healing process during which a part of fibrin is degraded again by fibrinolysis. Under physiological conditions thrombus formation is strongly limited to the region of the damaged vessel wall by inhibitory mechanisms of intact endothelial cells and the coagulation cascade.

PLTs are enriched in surface glycoprotein (GP) receptors that mediate interactions among PLTs themselves, with the sub-endothelium and with white blood cells. PLTs also contain specific granules for the storage of calcium (Ca^{++}), adenine/guanine nucleotides, and serotonin (dense bodies) and the storage of coagulation factors (e.g. vWF, FV), multimerin, thrombospondin-1, fibrinogen, IgE, growth factors (e.g. PDGF, TGF-β, ECGF, EGF, VEGF, bFGF, IGF-I), and cytokines (e.g. PF4, RANTES) (α granules). Serotonin (5-hydroxytryptamine) acts predominantly as a local vasoconstrictor but has also pro-inflammatory properties by stimulation of monocytes and attraction of T lymphocytes (IL-16). Contents of α granules mediate e.g. host defense, recruitment and activation of leukocytes as well as regulation of tissue repair by mitogenic effects on smooth muscle cells, macrophages, monocytes, and fibroblasts. Other important pro-inflammatory mediators are present in the cytosol (IL-1β, CD40L) and are generated from mRNA (relict from megacaryocytes) and are released upon PLT activation. CD40L stabilizes aggregation by interference with GP IIb-IIIa and stimulates endothelial cells to express ICAM-1, VCAM-1,

E-selectin, and the vitronectin receptor, thus modulates leukocyte-endothelium and PLT-endothelium interactions.

Due to specific binding between sub-endothelial agents and specific GP receptors, PLTs begin to slow down and transiently adhere or roll along the damaged area of the vessel wall. Under conditions of high shear, as found in the arterial circulation, the initial PLT-sub-endothelium interactions are exclusively mediated by vWF present in bridges between sub-endothelial collagen and GP Ib (V-IX) of the adhering PLTs. The following steps of activation via various signal transduction pathways (outside-in signaling) and the elevation of cytoplasmatic Ca^{++} levels are then mediated by other receptor-ligand interactions. When the cytoplasmatic Ca^{++} concentration exceeds a certain threshold, cytoskeletal changes occur, which mediate shape change from discoid to sphere, pseudopod formation, and conformational change of the fibrinogen receptor GP IIb-IIIa (receptor activation). Only the activated GP IIb-IIIa complex is able to bind soluble plasma fibrinogen (and vWF under high shear conditions) leading to further spreading of the stimulated PLTs along the site of injury and ultimate aggregation characterized by fibrinogen bridges between the activated GP IIb-IIIa complexes on adjacent PLTs. Simultaneous release and surface exposure of granule components (e.g. ADP and serotonin from dense bodies, vWF and p selectin from α-granules) and cyclooxygenase (COX)-related thromboxane A_2 (TxA_2) formation/expression result in further recruitment, activation and aggregation of other PLTs near to the growing plug. At least, internal, anionic, negatively charged phospholipids are exposed by transbilayer flip flop of the inner membrane leaflet and pro-coagulant microvesicles are generated. The exposure of anionic phospholipids, mainly phosphatidylserine, provides a surface upon which PLTs can support thrombin generation by accelerating the tenase and prothrombinase reactions of the plasmatic coagulation pathway. Thrombin, the key enzyme of the coagulation cascade and the most potent PLT agonist, interacts with two binding sites on PLTs, a) the region of GP Ib (high affinity) and b) a specific epitope of the thrombin receptor (moderate affinity). Binding of thrombin leads to cleavage of the extracellular domain (protease-activated receptor PAR), whereby the generated free polypeptide (SFLLRN-x) can directly activate further thrombin receptors (thrombin-receptor activating peptide TRAP). Human PLTs express two kinds of PARs activated either by lower (PAR-1) or higher concentrations of thrombin (PAR-4). Receptor activation by thrombin results in further activation of GP IIb-IIIa, TxA_2 formation, and secretion of granular components such as ADP that promotes recruitment and activation of adjacent PLTs into the vicinity of the growing plug and the inclusion of leukocytes. Thrombin also converts soluble fibrinogen into insoluble fibrin, which is cross-linked by the thrombin-activated FXIII to confer stability of the otherwise fragile plug/thrombus. At last, the activated PLTs rearrange their intracellular actin/myosin cytoskeleton, which leads to clot retraction. The latter is inhibited by blockade of GP IIb-IIIa receptors representing central links between the contractile elements.

Adhesion

As described, adhesion is mediated by GPs of the PLT surface that recognize specific structural components of the extracellular matrix such as collagen and elastic fibrils embedded in a gel of proteoglycans and water. This first contact *(contact phase)* between PLTs and the sub-endothelium is mediated by interaction between GP Ib-V-IX (vWF receptor belonging to the leucine-rich GPs) with collagen-bound vWF. Thus, the main task of GP Ib-V-IX is the adhesion of circulating PLTs to immobilized vWF despite high shear

forces. GP Ib-V-IX consists of four subunits: the central part is GP V surrounded by GP Ib_{α} and GP Ib_{β}, which are covalently linked to each other by disulfide bridges and non-covalently bound to GP IX. GP Ib_{α} possesses binding sites for vWF and thrombin. In contrast to GP IIb-IIIa, whose surface expression increases after thrombin activation, the surface density of GP Ib-V-IX is reduced by receptor internalization after PLT activation. Recent evidence suggests that, apart from GP Ib-V-IX, another PLT membrane receptor for collagen, GP VI, is strictly required for the initial PLT tethering following vascular injury. Both receptors appear to act in concert to recruit PLTs to the sub-endothelium in-vivo. GP VI mediates the activation (opening) of other adhesive receptors (GP IIb-IIIa, GP Ia-IIa) by shifting them from a low to a high affinity binding state required for stable PLT arrest. GP VI belongs to the immunoglobulin superfamily and forms complexes with the FcR γ-chain at the cell surface. In the absence of GP VI, PLTs completely failed to adhere and aggregate on the damaged vessel wall. Further immunoglobulin adhesion receptors, PECAM (PLT-endothelial cell adhesion molecule)-1 and ICAM (intracellular adhesion molecule)-2 probably mediate adhesion to leukocytes and PLT related inflammation, but their global role for PLT function is mostly unknown.

The contact phase is stabilized via further adhesion to collagen, fibronectin, laminin, and thrombospondin *(stabilization phase)*. Binding of collagen leads to the formation of pseudopods (shape change) and peptide as well as GP IIb-IIIa activation via tyrosine phosphorylation *(activation phase)*. Starting from released arachidonic acid (AA) the adhering PLTs form TxA_2, which slows down the blood flow due to its vasoconstricting activity. Additionally TxA_2 induces the release of soluble granule components like ADP *(secretion phase)* leading to the recruitment of still resting PLTs that then become activated and aggregate with already adhering PLTs through activated GP IIb-IIIa. By spreading of the PLT aggregate over the complete sub-endothelium, the vessel wall lesion is separated from blood flow, and blood loss is kept as low as possible.

Aggregation

Aggregation depends on three conditions: shear force, Ca^{++}, and fibrinogen. The latter are stored in PLT granules and are released in high concentrations during PLT activation. While the *primary aggregation phase* is reversible and characterized by "loose links" via fibrinogen bridges, the *secondary aggregation phase* is irreversible and induced by the degranulation process. GP IIb-IIIa, a β_3 integrin, plays a central role in aggregation. 60,000 to 100,000 GP IIb-IIIa receptors can be detected per PLT. 70% are bound to the surface, and 30% are only released from intracellular stores (open canalicular system, α-granules) upon PLT activation. Circulating PLTs carry resting, not activated GP IIb-IIIa complexes (low affinity functional state) that only can bind immobilized fibrinogen. The binding sites for soluble fibrinogen become accessible after conformational change during activation, which strongly depends on Ca^{++} (high affinity functional state). The binding of fibrinogen to the activated receptor induces a further conformational change (ligand-occupied functional state) with exposure of cryptic epitopes (LIBS = ligand-induced binding site) and transmembrane signal transduction (post-occupancy) events.

Activation

Upon changes in biochemical pathways several soluble PLT agonists (e.g. ADP, thrombin, TxA_2) are formed, which bind to specific G protein-linked receptors. Via signal transduction pathways, each agonist amplifies the activation step through the formation of *second*

messengers. One of these messengers, phospholipase C, forms inositol 1,4,5 triphosphate (IP_3) and diacylglycerol (DAG), whereby IP_3 enhances the intracellular Ca^{++} concentration and DAG activates proteinkinase C, which in turn phosphorylates a series of further signal proteins that control the degranulation process and the activation of GP IIb-IIIa. Cytoplasmatic Ca^{++} activates phospholipase A_2, which leads to the liberation of AA from phospholipids of the cell membrane. Aspirin-sensitive COX-1 and thromboxane synthetase then form TxA_2, which has vasoconstricting activity and stimulates the secretion of granule components after interaction with specific TxA_2 receptors. Two TxA_2 receptors can be distinguished on the PLTs surface (TPα and TPβ), of which TPα is most important. COX-1-inhibition results in reduced secretion and inhibition of secondary aggregation. Receptors that directly inhibit PLTs stimulate adenylate cyclase (increased formation of cAMT) via G_S proteins and are activated by PLT antagonists like adenosine, β-adrenergic substances, prostacyclin, prostaglandin E_1, and theophylline.

PLTs are presently the only cells that express ADP specific receptors (P_2Y_1, P_2Y_{12}, P_2X_1). Like other activation receptors, ADP receptors are linked to G-proteins. Due to their key role in the pathogenesis of arterial thrombosis, they are of particular pharmacological interest. The P_2Y_1 receptor is linked to the initiation of shape change, mediation of Ca^{++} mobilization and activation of phospholipase C. Activation of P_2Y_{12} inhibits cAMP formation via inhibitory G-proteins and is predominantly responsible for TxA_2 formation, p selectin surface expression and conformational changes of GP IIb-IIIa (receptor activation), thus sustained PLT aggregation. All of these mechanisms are affected by thienopyridines. Like P_2Y_1, P_2X_1 mediates Ca^{++} influx and shape change but seems not to be influenced by thienopyridines.

Secretion

During adhesion, PLTs begin to release stored components from the granules in the order dense bodies, α-granules, and lysosomes. Dependent on ATP and Ca^{++} the degranulation process initiates the secondary, irreversible phase of aggregation and reinforces the activation/recruitment of further circulating PLTs as well as fibrin formation resulting in thrombus consolidation. As described above, the interaction of released ADP (from PLTs, damaged vessel wall cells, endothelial cells, red blood cells) with its specific purinergic receptors plays a central role in this process. Released serotonin reinforces vasoconstriction and thus slows down the blood flow. Released α-granule contents attract leukocytes and fibroblasts (β-TG, PF4), promote mitogenic and proliferative effects in fibroblasts and smooth muscle cells (growth factors like PDGF), or exhibit pro-inflammatory activity (IL-1). P selectin is found in both PLTs (α-granules) and endothelial cells (Weibel-Palade bodies) and is expressed on cell surface only after cellular activation. P selectin is the decisive receptor for PLT adhesion to leukocytes and triggers inflammatory reactions but also plays a central part in vascular repair processes. Interestingly, p selectin is significantly increased in all states of coronary artery disease: stable angina (showing also increased TxA_2 formation and fibrinogen binding due to increased GP Ib and GP IIb-IIIa expression [1-3]), unstable angina (showing also increased LIBS expression [4]), and acute myocardial infarction (AMI). Here, increased p selectin levels are indicative for an increased thrombotic re-occlusion risk [5]. When coronary stenting is combined with dual antiplatelet therapy, p selectin expression and GP IIb-IIIa activation are as low as after conventional coronary angioplasty [6-8]. Besides p selectin, thrombin promotes chemotaxis of monocytes and mitogenesis in lymphocytes and mesenchymal cells (smooth muscle cells, fibroblasts). In addition, released coagulation factors (vWF, fibrinogen, FV, PAI-1) fulfill pro-coagulant or anti-fibrinolytic

tasks. The pro-coagulant activity can be reinforced by microparticle formation, small membrane vesicles extruded from activated PLTs that exhibit a high binding affinity for FVa and FVIIIa, thus facilitating the formation of the tenase and prothrombinase complexes. Lysosomal enzymes like collagenease or elastase degradate surrounding fibrils and induce changes in atherosclerotic plaques.

2. The role of platelets in atherogenesis

Role of the arterial plaque

In contrast to stable angina pectoris, which is generally caused by a reduced oxygen supply to the myocardium due to coronary vasoconstriction, acute coronary syndromes (ACS) arise from an acute plaque rupture within an epicardial coronary artery with subsequent PLT aggregation and thrombus formation. Reperfusion strategies aim to dissolve the thrombotic plaque either through administration of fibrinolytic agents or direct coronary interventions. Paradoxically, despite a sufficiently reestablished blood flow, reperfusion injury occurs and myocardial dysfunction can progress. This is mainly triggered by activated PLTs released from the plaque area or the circulation itself (cardiovascular risk factors are per se associated with an increased basal activity of circulating PLTs [9,10]). Activated PLTs in turn promote inflammatory reactions within the ischemic myocardium, thus plug growing. Consequently, up to 50% of all patients with successful revascularization and normal epicardial blood flow following interventional therapy do not have adequate tissue reperfusion [11,12].

Following a modern concept of atherogenesis, apart from endothelial dysfunction (characterized by decreased vasodilatation upon stimulation with acetylcholine and increased pro-coagulant inflammatory activities) lipid deposition on the intima is one of the first pathological events in the genesis of an arterial plaque. The lipid-rich nucleus is separated from blood flow by a fibrous cap and rich in free cholesterol crystals, cholesteryl esters, oxidized LDL and monocytes/macrophages. The latter undergo phagocytosis of fatty acids and oxidized LDL and differ to foam cells. Additionally, there are particularly heavy PLT deposits and high amounts of tissue factor, which favors thrombin formation. Thrombin, in turn, activates additional PLTs and supports their aggregation to already adhering PLTs (recruitment), which, in parallel, stimulate the migration of smooth muscle cells and fibroblasts by a PDGF-dependent mechanism. After intima proliferation and monocyte migration increased shear forces (high blood flow or tension) and the liberation of proteolytic enzymes (plasminogen activator, metalloproteinases) can promote plaque rupture with all known sequelae. PLTs are not just involved in thrombotic complications by formation of vascular occlusions but also trigger plaque progression and promote myocardial malperfusion by participation in recurrent vasoconstrictions and local/systemic inflammatory reactions.

PLT-mediated microembolization

The regeneration of the afflicted myocardial area largely depends on the integrity and recovery of the microcirculation distal to the stenosis. Importantly, there is an increased embolization of thrombotic material from the arterial plaque lesion during plaque growing and particularly in the reperfusion phase after coronary interventions. This may promote intermittent coronary vasospasms distal to the stenosis through the release of serotonin and TxA_2 resulting in inadequate perfusion, myocardial ischemia, tissue damage, unstable angina or non-ST-segment elevation myocardial infarction. On the other hand, the contact of

intact endothelial cells with activated PLTs has the potential to modify chemotactic, proteolytic and adhesive properties inducing increased surface expression of endothelial adhesion receptors (VCAM-1, ICAM-1, vitronectin receptor), which participate in the recruitment of PLTs to the inflamed endothelium. Additionally, the elevated release of endothelial pro-inflammatory substances (MIP-1, IL-6, IL-8) supports chemotaxis, adhesion, and transmigration of monocytes.

PLT-mediated inflammation

The exposure of sub-endothelial compounds is not required for PLT adhesion in acute inflammatory processes such as ischemia/reperfusion. E.g., p selectin expression of inflamed endothelial cells has been demonstrated to mediate PLT rolling through GP Ib indicating that the vWF receptor mediates both PLT adhesion to the sub-endothelial matrix and to "intact" endothelial cells. Additionally, endothelial adhesion receptors that bridge PLTs via fibrinogen are up-regulated in response to endothelial inflammation (e.g. by IL-1β or CD40L of activated PLTs or thrombin). In this manner, PLTs (if activated or resting) adhere to the vessel wall and promote the recruitment of neutrophils and monocytes by the release of a variety of pro-inflammatory mediators and growth hormones. Furthermore, adhering PLTs can induce up-regulation of NF-κB in endothelial cells leading to further inflammatory changes in the vessel wall. High doses of ASA (≥ 900 mg/d) can influence the NF-κB activation, thus promote the stillstand of atherosclerotic plaque progression [13]. Consequently, cardiac patients with elevated systemic CRP levels benefit especially from antiplatelet therapy with ASA [14]. Another strategy to limit reperfusion injury uses monoclonal antibodies to adhesion receptors such as p selectin (present on endothelial cells and PLTs), CD11/CD18 (present on leukocytes), and the vitronectin receptor (present on endothelial cells). Abciximab not only blocks GP IIb-IIIa on PLTs, but also the vitronectin receptor on endothelial cells explaining its favorable effect on myocardial perfusion, microcirculation, and recovery of left ventricular function [14-17].

3. Antiplatelet substances

Acetylic salicylic acid (ASA)

Of the five main groups of antiplatelet substances **(Tab.1.)**, ASA is probably the most important drug. Its use is considered as the gold standard in primary and secondary prophylaxis of coronary syndromes [18]. However, from the results of collagen and AA-induced aggregation, up to 30% of all patients respond insufficiently to ASA and may profit from a combined (dual) antiplatelet therapy to effectively reduce arterothrombotic events.

ASA selectively and irreversibly inhibits COX, an ubiquitous enzyme existing in two isoforms: COX-1 (forms short living prostaglandins (PgG_2, PgH_2) from which thromboxane synthetase forms TxA_2) and COX-2 (forms prostaglandins mainly in leukocytes that are involved in inflammatory and pain processes). After oral administration ASA is rapidly (5-16 min) and completely absorbed. Due to the hepatic first pass effect the bioavailability drops to about 50% **(Tab.2.)**. Thereafter, COX-1 of all bypassing PLTs is irreversibly acetylated at Ser_{529}. ASA thereby inhibits the production of the potent PLT activator TxA_2. However, with stronger agonists than TxA_2, especially thrombin, PLT aggregation is not markedly inhibited by ASA. ASA also inhibits synthesis of prostaglandins in endothelial cells (prostacyclin, a potent PLT inhibitor and powerful vasodilatator) and stomach mucosa cells (cytoprotective prostaglandins). Of note, in the absence of protein biosynthesis, COX-1

Mode of action	Substances
Increase of cyclic nucleotides	
• Activation of adenylat cyclase	PGE_1 (Alprostadil) PGI_2 (Epoprostenol) prostaglandin (Iloprost)
• Inhibition of phosphodiesterase	theophylline, dipyridamole
• Activation of guanylyl cyclase	NO, nitrate derivates, molsidomine
Interaction with arachidonic acid metabolism	
• Inhibition of cyclooxygenase	acetylsalicylic acid (ASA), sulphinpyrazone, indomethazine, ω3-fatty acids
• Inhibition of thromboxyne synthetase	dazoxibene, ozagrel
• Antagonism of TxA_2 receptor	ridogrel, nidrogrel
Interaction with aggregation receptors	
• Inhibition of ADP receptor	ticlopidine, clopidogrel
• Inhibition of thrombin receptor	peptide antagonists
• Inhibition of serotonin receptor	ketanserine
Inhibition of aggregation	
• Inhibition of fibrinogen receptor (GP IIb-IIIa)	i.v. moAB: abciximab (ReoPro) i.v. cyclic peptide: eptifibatide (Integrillin) i.v. peptide mimetics: tirofiban, lamifiban oral peptide mimetics: xemilofiban, orbofibane, gantofibane, roxifiban
Inhibition of adhesion	
• Inhibition of vWF receptor (GP Ib-V-IX)	recombinant vWF fragment
• Inhibition of collagen receptor (GP Ia-IIa)	antibodies, peptides

i.v. intravenous; moAB monoclonal antibody;

Table 1. Classification of antiplatelet substances [8]

	ASA	ticlopidine	clopidogrel	prasugrel
Bioavailability (%)	90	80-90	> 50	> 50
Protein binding (%)	50-80	98	94-98	98
Half life (h)	0,5	12,6	7-8	> 12
Metabolism	hepatic	hepatic	hepatic	hepatic
Active metabolites	no	no	yes	yes
Inhibited aggregation (onset)	minutes	< 4days	2 hours	< 30 minutes
Inhibited aggregation (steady state)	hours	8-11 days	3-7 days	2 days
Inhibited aggregation (duration)	7 days	5 days	2-3 days	7 days
Recommended daily dose (mg)	75 - 325	500 (2 x 250)	75	10

Impairment of hepatic function can diminish the antiplatelet effect. The onset of action of thienopyridines can be accelerated by higher initial doses. Compared to clopidogrel, prasugrel treatment is associated with more rapid, potent and prolonged PLT inhibition. Preliminary evidence suggests a similar safety profile compared to clopidogrel.

Table 2. Pharmacologic properties of oral antiplatelet drugs [8,23]

inhibition in anucleated PLTs persists for a cellular lifetime compared with nucleated vascular endothelial and stomach mucosa cells, which recover COX-1 activity shortly after exposure to ASA. Daily doses of 30-70 mg ASA are sufficient for complete inhibition of TxA_2 synthesis, whereas increasing doses can promote gastrointestinal side effects. The recommended daily dose ranges therefore from 75 to 325 mg. Other side effects include intracerebral hemorrhage (≤ 0.5%), hypersensitivity, respiratory alkalosis, and renal and liver dysfunction (cave Reye's syndrome in children characterized by encephalopathy with liver damage). Higher doses of ASA inhibit the nuclear factor κB (NF-κB) that regulates transcription of many inflammatory cytokines (e.g. MCP-1) and of immunoglobulin adhesion receptors (VCAM-1). Additionally, in ACE-inhibitor-treated patients, ASA should be replaced with thienopyridines, since much of the hemodynamic benefits of ACE inhibitors would be lost by the addition of ASA [19].

Thienopyridines (TPs)

TPs including drugs under late state development (cangrelor, elinogrel) inhibit PLT adhesion by inhibition of the ADP receptor P_2Y_{12} mediating recruitment and aggregation of further PLTs into the vicinity of a growing plug. After oral administration the antiplatelet effect is exerted by active metabolites formed by cytochrom (CYP) P450 activity upon hepatic metabolism **(Tab.2.)**. Since statins are also metabolized by CPY-P450 (mainly CYP3A4), co-administration is associated with decreased antiplatelet efficacy [20]. While ticlopidine (oral, approved), clopidogrel (oral, approved) and parasugrel (oral, approved) act irreversibly, ticagrelor (oral, approved), cangrelor (intravenous), and elinogrel (oral or intravenous) lead to reversible P_2Y_{12} receptor blockade.

In contrast to ASA, TPs do not influence the COX pathway in endothelial cells (no effect on prostacyclin production) but hinder the rapid degradation of extracellular ADP by impairment of ectoADPse released from the damaged vessel wall. Considerably more than ASA, TPs reduce key factors of arterial thrombosis: shear force-induced PLT activation, PLT-leukocyte formation, and inflammation [21]. Consequently, *ticlopidine*, the first developed TP, was found to be superior to ASA in reducing thrombotic risks (mainly stroke) during different pathological conditions including percutaneous coronary intervention (PCI) [22]. However, due to its unfavorable safety profile (20% diarrhea, 10% skin eruptions, 2.5% neutropenia and thrombotic-thrombocytopenic purpura) and its delayed onset of action (4-7 days), ticlopidine has been replaced by clopidogrel in routine clinical use.

Clopidogrel, a second generation TP, is equally effective as ticlopidine but has a markedly better tolerability profile. Additionally, clopidogrel achieves a significant antiplatelet effect even on the first day of treatment. Bleeding problems are as frequent as under ASA [23]. Clopidogrel, together with ASA, constitutes the current standard of care for high risk patients with cardiovascular diseases and has considerably improved the antithrombotic therapy after coronary stenting. Despite this, a considerable number of patients with recurrent ischemic cardiovascular events remains, which may only in part be attributed to suboptimal PLT inhibition. Less than 60% inhibition of ADP induced PLT aggregation following 75 mg/d clopidogrel in healthy volunteers [24] or 300 mg clopidogrel loading in PCI patients [25] indicates an incomplete P_2Y_{12} receptor blockade. In addition, inhibited ADP induced PLT aggregation < 10% is observed in 10-30% of treated patients [26-31], probably due to poor compliance, drug-drug interactions, genetic receptor polymorphisms, or variability in CYP P450 activity or intestinal absorption. Poor responsiveness to

clopidogrel was shown to be associated with recurrent cardiovascular events including stent thrombosis [32] and may be overcome by increased clopidogrel doses. This was demonstrated in the CLEAR PLATELETS study, where higher loading doses of clopidogrel prior to PCI acted more rapidly and increased the inhibitory effect on PLTs [25]. During maintenance, however, there was no significant difference in the composite end point (AMI, stroke, vascular death) between the double and the standard dose of clopidogrel [33]. Thus, the search for TPs (third generation) with less response variability is an ongoing feature.

Compared to clopidogrel, *cangrelor* exhibits more consistent and greater PLT inhibition as well as short onset and offset of action. The CHAMPION trials, however, were stopped early because of lack of efficiency [34,35]. Cangrelor is still being studied as a bridge for clopidogrel prior to surgery [36]. *Prasugrel* also combines a rapid onset of action (< 30min) with less response variability (0.3%) and a prolonged duration of action (> 3 days). While ticlopidine and clopidogrel require two CYP P450-dependent steps to form active metabolites (mainly CYP 3A4), prasugrel requires only one step (CYP3A4 or CYP2B6). This leads to less CYP P450 dependency and higher amounts of active metabolites [37] translating into a 10-fold (clopidogrel) to 100-fold (ticlopidine) greater potency [38]. As shown in the recent PRINCIPLE-TIMI 44 and TRITON-TIMI 38 studies [39,40], prasugrel increased the efficiency of PCI and improved cardiovascular outcomes (by 20%) but was associated with a significant increase in major bleedings [41]. This was reinforced by the recent CHARISMA trial testing prolonged dual antiplatelet therapy with ASA + prasugrel vs. ASA + clopidogrel [42], although the JUMBO-TIMI 26 trial demonstrated a similar bleeding risk compared to standard clopidogrel [43]. Prasugrel should not be used in adults > 75 years of age or < 60 kg of body weight and in those who have had a recent TIA/stroke or an increased bleeding risk. Like prasugrel, *ticagrelor* acts more potent and rapid but does not significantly increase major bleeding events. Drawbacks, however, are increased incidences of dyspnea and ventricular pauses [36]. The PLATO study demonstrated significantly increased reduction rates of cardiovascular syndromes and mortality vs. clopidogrel (- 16%), while bleeding events were as frequent as under prasugrel [44]. In addition to cangrelor, prasugrel, and ticagrelor *elinogrel* rapidly achieves nearly complete PLT inhibition even in subjects with low responsiveness to clopidogrel [45]. Patients undergoing PCI had greater PLT inhibition under elinogrel (100/150 mg twice daily) than under standard clopidogrel without exhibiting more bleeding events [46]. These results gave promise for further Phase III trials.

Fibrinogen receptor antagonists (FRAs)

FRAs currently prescribed only during PCI reversibly block one of the final steps of PLT activation irrespective of the stimulus. This is the binding of fibrinogen to GP IIb-IIIa mediating adhesion to the injured vessel wall or interactions with PLTs and other blood cells. Blockade of GP IIb-IIIa further leads to an attenuated formation of pro-coagulant microparticles and inhibits PLT-dependent formation of thrombin. Thus, in addition to inhibition of aggregation, an anticoagulant activity can also be achieved by the administration of FRAs. Side effects include hypotension, vertigo, vomiting, headache, and thrombocytopenia. Bleeding complications must be considered under ongoing therapy (especially in thrombocytopenic, female and elderly patients).

Chimeric monoclonal antibodies directed against the vicinity of the fibrinogen recognition (RGD) region (abciximab) can be distinguished from small low molecular mass antagonists (SMAs) including cyclic peptides (eptifibatide) or non-peptide molecules (tirofiban) with a

tyrosine like structure **(Tab.3)**. In contrast to SMAs that bind specifically to the RGD region (competitive inhibition) abciximab binds to a different site, even when the binding pocket is occupied by fibrinogen or vWF (steric inhibirion).

	abciximab	**eptifibatide**	**tirofiban**	**lamifiban**
Molecular mass (Dalton)	45.000	800	495	468
Receptor specificity	CR	no CR	no CR	no CR
Onset of action (after i.v. bolus)	minutes	minutes	minutes	minutes
Reversibility	slow (> 12 h)	rapid (< 6 h)	rapid (< 6 h)	rapid (< 6 h)
Half life **plasma (normally a few hours)** **receptor (normally a few hours)**	 short long	 DD DD	 DD DD	 DD DD
Intrinsic activity (LIBS expression)	+	+	+	+
Recommended dose **Initial bolus (μg/kg) prior to PCI** **MD (μg/kg/min) for 12-48 (72) h**	 250 0.125	 90.0 – 180.0 0.5 – 2.0	 0.4 – 10.0 0.10 – 0.15	 - 0.01 - 0.07

PCI percutaneous coronary intervention; CR cross reaction with the vitronectin (endothelium cells) and the MAC-1 receptor (leukocytes); DD dose dependency; MD maintenance dose
GP IIb-IIIa blockers administered intravenously (i.v.), have proven efficacious in mitigating arterial thrombosis in acute coronary syndromes and coronary interventions such as balloon dilatation and stent implantation but are associated with an increased bleeding risk. Currently, i.v. GP IIb-IIIa blockers are prescribed in high risk patients with acute coronary syndromes immediately before and after coronary intervention (for 24-72 h). Oral GP IIb-IIIa blockers have failed to demonstrate any benefit.

Table 3. Pharmacologic properties of intravenous (i.v.) GP IIb-IIIa antagonists [8]

In order to achieve an effective antithrombotic protection, a receptor blockade of at least 80% should be achieved. A blockade > 90% increases the risk of bleeding. This makes the dosing difficult. The latter is controlled by ADP-induced aggregation that should be carried out in hirudine- or PPACK-anticoagulated blood due to the Ca^{++} dependency of receptor binding. Unlike abciximab, the function of SMAs depends on the achieved plasma concentration. Excretion modalities are linked directly to body weight and are inversely correlated with age. Unlike SMAs that rapidly dissociate from the receptor, 70% of all GP IIb-IIIa receptors are still inhibited for up to 12 hours after termination of abciximab (PLT bound abciximab even lasts for up to 2 weeks). Thus, receptor blockade with abciximab can be reduced in patients with a strongly elevated PLT count. Due to the fact that internal GP IIb-IIIa receptors cannot adequately be blocked, TRAP-induced aggregation is only very incompletely be inhibited by standard doses of FRAs (in contrast to ADP induced aggregation that must completely be inhibited). Consequently, patients with ACS experience a markedly lower inhibition of aggregation than do patients with stable coronary artery disease. This suggests that higher doses of FRAs are required under conditions of increased PLT activation, especially with thrombin (occurring e.g. during fibrinolysis therapy). Additionally, the release of internal GP IIb-IIIa receptors can lead to a significant residual aggregation and thrombus formation despite the administration of FRAs.

Novel antiplatelet strategies

Currently, two groups of PLT inhibitors are approved for clinical use in ACS patients: ASA and oral TPs. These agents have shown improved short- and long-term clinical outcomes

but are associated with increased bleeding events. Thus, there is a need for new antiplatelet agents with higher PLT inhibition capacity and less bleeding risk.
A new TxA_2 receptor antagonist was tested in animals and has demonstrated fast and potent antiplatelet efficacy [47] comparable to that of ASA plus clopidogrel [48]. Additional desired effects were an improved endothelial function [49], an inhibited TxA_2-induced vasoconstriction [50], and a favorable bleeding risk profile [48]. *Picotamide*, already marketed in Italy, combines both TxA_2 receptor and thromboxane synthetase blockade and, unlike ASA, preserves prostacyclin formation in endothelial cells. Picotamide was shown to reduce atherosclerotic plaque progression, cardiovascular events and mortality without increased bleedings in ASA-refractory patients with peripheral artery disease without [51,52] or with diabetes [53]. Selective inhibition of the thrombin specific PAR-1 receptor *(vorapaxar, atopaxar)* represents a further strategy to reduce ischemic events and was tested in two Phase-II trials (TRA-PCI and LANCELOT-ACS) as secondary prophylaxis of ACS or on the top of standard antithrombotic therapy including ASA, clopidogrel and the heparin of choice. Despite significant dose-dependent increases in abnormal liver function parameters and QT elongation, there was a trend towards lower adverse cardiac events without increased bleeding events in the verum- vs. the placebo treated groups [54,55]. The first developed phosphodiesterase (PDE) inhibitor with an antiplatelet effect was *dipyridamole*. Together with ASA, dipyridamole demonstrated efficacy in the prevention of stroke [56]. However, ASA plus dipyridamole was not superior to clopidogrel in the prevention of recurrent stroke as seen in PRoFESS [57]. *Cilostazol*, a selective PDE III inhibitor, increases cAMP levels in PLTs, endothelial and smooth muscle cells leading to vasodilatatory and antiplatelet properties. Recent studies have shown that the addition of cilostazol to ASA and clopidogrel (triple antiplatelet therapy), particularly in diabetic patients, reduced risk of stent thrombosis (even of drug eluting stents) and increased cardiac outcomes after PCI without increased bleeding complications. However, due to headache, palpitations, and diarrhea, withdrawal of cilostazol approximated 15% [58,59]. Further antiplatelet strategies including blockade of inflammatory substances such as p selectin [60] or collagen receptors [61] are currently under clinical development. An accurate evaluation of the balance between the anti-ischemic effect and the hemorrhagic risk of these new drugs is highly warranted.

Antiplatelet-therapy-inherited bleeding risk

Sufficient hemostasis requires normal PLT function in at least 20% of circulating PLTs [62]. As the effects of antiplatelet drugs are not reversible by other drugs, PLT transfusions are the only manner to rapidly restore normal hemostasis. Today, prevention of cardiac events, especially stent thrombosis, is considered as being highly dependent on antiplatelet therapy during the first year after coronary intervention. In this period, however, up to 5% of patients have to undergo surgery for non cardiac reasons, whereby elderly patients, women, patients with anemia, renal dysfunction, and hypertension are at especially increased risk for perioperative bleeding. Not only does bleeding constitute an immediate threat, but is also associated with increased re-infarction and cardiac morbidity (5-fold/year) both in the short as well as the long term [63]. For this reason, the inherited bleeding risk of all antiplatelet drugs has to be outweighed against the concomitant cardioprotective effect **(Tab.4.)**. Of note, antiplatelet replacement by heparin does not provide protection against the risk of coronary artery or stent thrombosis. Based on a retrospective evaluation, we recommended discontinuation of antiplatelet therapy for at least 2 days prior to elective

Pharmacological properties	Indication (RRR)	Bleeding risk
GP IIb-IIIa antagonists		
Fibrinogen receptor antagonists	IST (50%)	SP: 3 - 4% (mostly catheters)
Clopidogrel (300 mg LD, 75/d mg MD)		
ADP receptor antagonist	AMI in ACS (18%) IST, recurrent ST (30%)	SP: 1 – 2% (higher plus ASA) ICH: 0.35% GIT: 0.68% GIT ulcers: 0.68% IOBL: 50% (ASA + clopidogrel) *
Acetylic salicylic acid ASA (100 – 325 mg/d)		
COX-1 inhibitor	Prim. prevention (40%) Sec. prevention (20%)	SP: 1 ‰/year ICH: 0.49% GIT: 2.66% GIT ulcers: 1.15% IOBL: 20%*

PCI percutaneous coronary intervention; LD loading dose; MD maintenance dose; AMI acute myocardial infarction; ACS acute coronary syndrome; ST stent thrombosis; IST immediate stent thrombosis; SP spontaneous; ICH intracranial hemorrhage; GIT gastrointestinal; intraoperative blood loss; * without bleeding-related increase in mortality.
The risk of cardiac events is maximal (increased up to 5-10-fold) in malignancy, diabetes mellitus, the early postoperative state and during stent re-endothelialization, especially of high risk stents (proximal, multiple, or overlapping stents, small vessels, bifurcated lesions). In these settings, the risk for stent thrombosis averages 35%. The associated mortality reaches 20-40%

Table 4. Relative risk reduction (RRR) and bleeding risk of common antiplatelet substances [59]

surgery [64]. However, since antiplatelet agents are maximally helpful when the thrombotic risk is highest, long-term dual antiplatelet therapy should be pursued until surgery, especially during stent re-endothelialization (4 – 6 weeks after bare metal stents, 12 months after drug-eluting stents). Due to the rise in fibrinogen, CRP and PAI-1, the risk of plaque rupture and consecutive thrombosis is maximal (2-4-fold higher) in the early postoperative setting. Here, the mortality rate due to stent thrombosis is estimated to about 20-40% [65]. After withdrawal of ASA, the cardiac complication rate increases 3-fold, and ASA should never be stopped when prescribed for secondary prophylaxis of ACS or in patients with stents. When prescribed for primary prevention, there is no evidence that ASA withdrawal 7 days prior to surgery is harmful. Clopidogrel withdrawal during the first month after coronary intervention makes patients 10 times more likely to die. When necessary, ADP receptor blockers could be bridged with short acting GP IIb-IIIa antagonists like eptifibatide. After surgery, both drugs ASA and clopidogrel should be resumed within 12-24 hours.

4. Antiplatelet therapy and coronary heart disease

Primary and secondary prophylaxis of cardiac syndromes

Since > 50 years ASA reduces vascular death by 15% and non-fatal vascular events by 30% as evidenced by meta-analyses of over 100 randomized trials [66,67]. ASA may also be of

benefit in the primary prevention of cardiovascular events but the effect is more modest and its recommendation in this setting is highly debated due to the probably offset of the cardioprotective effect by bleeding complications [68,69]. Additionally, total mortality remains unaffected. Based on these and further data [70-74] daily doses of 160-325 mg ASA are recommended for all subjects > 50 years of age, who are at increased risk of AMI. Higher doses are not more effective in the prevention of cardiovascular events and may be associated with more serious side effects (reduced patient compliance) [33]. Younger subjects should use ASA only, when manifestations of atherosclerotic diseases (e.g. TIA, unstable angina) are present [8].

The CAPRIE study [75] examined the prophylactic efficacy of clopidogrel in comparison to ASA in patients with a history of ischemic stroke, prior AMI or symptomatic peripheral artery disease (PAD). In comparison to ASA (325 mg/d), a significant 8.7% risk reduction of non-fatal and fatal vascular deaths was found for clopidogrel (75 mg/d), which thereby occupies a firm place in secondary prophylaxis of cardiovascular events but is only marginally superior over ASA. Although not significant, ASA showed a trend towards better efficacy after prior AMI, whereas patients with PAD appeared to more profit from clopidogrel than from ASA. Despite this, a large portion of patients remains for whom no satisfactory therapeutic success can be obtained with ASA or clopidogrel monotherapy. Since both antiplatelet drugs have different target receptors and mechanisms of action (COX-1 inhibitor vs. P_2Y_{12} ADP receptor blockade), their combination as dual antiplatelet therapy offers additive effects and provides greater inhibition of PLT aggregation than therapy with either agent alone. As a consequence, the CURE study [76] demonstrated a risk reduction of 20% in patients with unstable angina, when ASA was combined with clopidogrel. The subsequent CREDO trial [77] showed that dual antiplatelet therapy reduced the risk of major adverse cardiovascular events after angioplasty compared with ASA alone. The tolerability profile was good, and major bleedings increased by only 1% as demonstrated in CLARITY-TIMI 28 [78] and COMMIT [79]. In the CHARISMA trial, however, patients with established vascular disease demonstrated a markedly increased bleeding risk, and no additional benefits were achieved with dual antiplatelet therapy over ASA therapy alone (probably due to clopidogrel resistance) [42]. Long-term dual antiplatelet therapy was beneficial only for high-risk patients with clinically evident atherothrombosis, especially for the prevention of stroke in cases with atrial fibrillation [80].

Fibrinolysis

Thrombin liberation in the region of the lysed thrombus may promote increased activation of circulating PLTs [81]. Moreover, due to high amounts of PAI-1, the PLT-rich core (white) thrombus is practically resistant to fibrinolytic agents. For these reasons, a successful reperfusion upon fibrinolysis can be achieved in only 50% of AMI and a TIMI-3 flow, which is a decisive survival parameter, is only insufficiently restored. For these reasons, antiplatelet drugs have been administered together with fibrinolytics: full dose fibrinolytics plus partial dose FRAs [82] or reduced-dose fibrinolytics plus full dose FRAs [83]. Pooled results from these studies and equivalent data suggest that FRAs together with ASA significantly increase the efficacy of fibrinolytics, reduce fatal and non fatal re-infarctions and the need for urgent revascularization [84-86]. Drawbacks, however, were increased intracranial bleeding and unaffected re-infarction rates after 30 days asking for safety and long-term efficacy of this combination [87].

Percutaneous transluminal coronary angioplasty (PTCA)

Pretreatment with ASA as well as with TPs significantly lower (up to 70%) the incidence of early acute thrombotic occlusions after PTCA [8]. Since the additional administration of FRAs to ASA and/or clopidogrel as well as to standard therapy including anticoagulants, nitrates, and beta-blockers, further reduce (40%) early cardiac incidents (partly, however, at cost of increased bleeding events [88-105]), the ACC/AHA guidelines recommend the addition of a FRA to ASA and heparin to patients in whom catheterization and coronary intervention are planned [106]. Furthermore, eptifibatide or tirofiban together with ASA and heparin should be given to patients with continuing ischemia or elevated troponin levels, in whom invasive management is not planned. Clopidogrel administered before cardiac catheterization enhances perioperative bleeding, if angiography reveals that bypass grafting is required rather than percutaneous coronary intervention. Thus, the American College of Chest Physicians (ACCP) guidelines recommend withholding clopidogrel until the coronary anatomy is determined [107]. Despite the efficacy of antiplatelet therapy concerning early thrombotic occlusions after PTCA, studies on the prevention of later re-stenosis (> 6 month) were disappointing [108,109]. Due to an excessive fibroproliferative response, up to 30% of PTCA patients developed recurrent ischemia and re-stenosis [110]. Only the results of the TACTICS study [104] showed that in patients with ACS early invasive strategy combined with immediate administration of FRAs was significantly better concerning late vascular deaths than the "wait and see" approach. Patients with elevated troponin levels had the greatest benefit from this strategy [8].

Coronary stenting

2 million patients of Western Countries undergo coronary dilatation each year [77], and coronary stents are placed in over 90% of these patients [111]. One of the greatest fears is subacute stent thrombosis triggered within minutes to hours after coronary intervention by activated PLTs. Predictors for increased risk of re-thrombosis are elevated GP IIb-IIIa expression or PLT degranulation markers prior to PCI as well as high post-interventional PLT reactivity to ADP [112]. Thus, long-term antiplatelet therapy is mandatory for the success of coronary stenting.

One of the first trials on stent thrombosis showed that ticlopidine (vs. anticoagulants) reduced the risk [113]. Thereafter, numerous clinical trials have demonstrated the superiority of dual antiplatelet therapy [114-116]. Based on these data, the American Heart Association/American College of Cardiology guidelines recommend ASA plus a 300 mg or 600 mg (better PLT inhibition) clopidogrel loading, followed by a 75 mg clopidogrel maintenance for 12 months for all patients undergoing PCI and/or stenting [117]. Recently, prasugrel demonstrated even higher efficiency than clopidogrel (plus 52%) irrespective of the clopidogrel loading dose: 300 mg [40] or 600 mg [39], however at cost of increased bleeding (2.4% vs. 1.8%, p=0.03) [40]. Moreover, the additional application of FRAs prior to PCI has significantly increased clinical outcomes as seen by improvements in early and late TIMI 3 flow rate, global left ventricular function, early re-stenosis, and recurrent ischemia [89,91,92,105,118,119] in spite of bleeding complications [92]. Abciximab could promote the re-establishment of the microcirculation, thus the functional recovery of the infarcted heart region. From the STOP-AMI trial [120] stenting + abciximab + dual antiplatelet therapy was superior over fibrinolysis with respect to myocardial salvage and the accumulation of death and thromboembolic complications for up to 6 months (p=0.02) and resulted in superior

inhibition of inflammation [28]. In the ERASER study [121], however, the rate of late re-infarction (> 6 month) remained unaffected.

5. Conclusion

Despite its efficacy, ASA is a relatively weak antiplatelet drug, and ADP receptor antagonists like clopidogrel are only marginally superior to ASA in the reduction of AMI and stroke. Furthermore, adverse ischemic events probably due to drug resistance remain a serious clinical problem. The combination of different antiplatelet substances may implicate additive properties and is proven to be beneficial for patients, in whom monotherapy is not sufficient (non-responders) or who implicate a high thrombotic risk after coronary interventions. Given the predominate role of PLTs in the mechanism of stent thrombosis, dual antiplatelet therapy has reduced its incidence to less than 1.5% in most recent studies. Meanwhile, the combination of several (even three) antiplatelet drugs has become the standard of care in these situations. A future challenge, however, is to depict patients at especially high risk for post-interventional thrombotic complications, who may have additional benefit from the optimal antiplatelet therapy, probably with new antiplatelet regimens.

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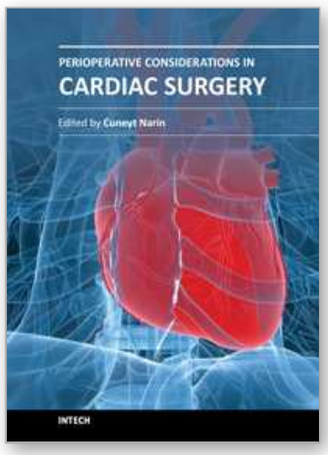

Perioperative Considerations in Cardiac Surgery

Edited by Prof. Cuneyt Narin

ISBN 978-953-51-0147-5
Hard cover, 378 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

This book considers mainly the current perioperative care, as well as progresses in new cardiac surgery technologies. Perioperative strategies and new technologies in the field of cardiac surgery will continue to contribute to improvements in postoperative outcomes and enable the cardiac surgical society to optimize surgical procedures. This book should prove to be a useful reference for trainees, senior surgeons and nurses in cardiac surgery, as well as anesthesiologists, perfusionists, and all the related health care workers who are involved in taking care of patients with heart disease which require surgical therapy. I hope these internationally cumulative and diligent efforts will provide patients undergoing cardiac surgery with meticulous perioperative care methods.

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