The Future of Antiplatelet Therapy in Cardiovascular Disease

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Abstract
Mechanisms of platelet inhibition are reviewed with emphasis on the pharmacokinetic and pharmacodynamic determinants of clinical efficacy and safety of antiplatelet drugs. Current developments in antiplatelet therapy are discussed in relation to both primary and secondary prevention of atherothrombotic complications. Interindividual variability in response to antiplatelet agents and new drug targets are outlined within the context of optimizing the balance between the cardiovascular benefits and bleeding risks of antiplatelet therapy. Recent advances in the pharmacogenetics of thienopyridines open the realistic prospect of a personalized choice of the most appropriate antiplatelet agent and tailored dose adjustment for an individual patient.
THE ROLE OF PLATELETS IN PRIMARY HEMOSTASIS AND ATHEROTHROMBOSIS

Platelets are anucleate progeny of megakaryocytes (1), exporting a complex repertoire of enzymes, receptors, and stored autacoids while retaining the capacity of signal-dependent translation and consequent protein synthesis (2). Their main physiologic task is to ensure primary hemostasis. However, platelets are also prominent components of thrombi developing over ruptured atherosclerotic lesions in the brain, heart, and peripheral arteries (3). Moreover, platelets appear to contribute to the development of atherosclerosis by secreting mediators of cell adhesion, proliferation, and inflammatory response (4).

The initial tethering of platelets at sites of vascular injury is mediated by the glycoprotein (GP)Ib-IX-V receptor complex, which binds von Willebrand factor (vWF) (Figure 1), whose abnormalities generate a bleeding diathesis (5). Subendothelial collagen exposed by damaged vessel engages platelets via GPVI and GPIa/IIa receptors (6) (Figure 1a). Most platelet agonists interact with G-protein-coupled receptors (GPCR) ultimately leading to a decrease in cyclic AMP (cAMP) and/or Ca\(^{2+}\) mobilization (7). Initial events trigger the platelet synthesis and release of several autocrine and paracrine mediators, including adenosine diphosphate (ADP), thrombin, epinephrine, and thromboxane (TX) A\(_2\). At least two ADP receptors are expressed by platelets: P2Y\(_1\) couples to G\(_{\alpha}\)q and contributes to initial aggregation (Figure 1b); P2Y\(_{12}\) couples to G\(_{\alpha}\)q12 and decreases cAMP, thus amplifying aggregation and platelet secretion. TXA\(_2\), originated from arachidonic acid (AA) via cyclooxygenase (COX) (Figure 1a,c), can diffuse through the membranes, activating the same or neighboring platelets (Figure 1a). The TXA\(_2\) receptor (TP) has two splice variants, TP\(_{\alpha}\) and TP\(_{\beta}\), that differ in their cytoplasmic tail (Figure 1c), both coupled to G proteins (G\(_{q}\) and G\(_{12/13}\) families). TPs trigger phospholipase C, phosphoinositides, IP\(_3\), and diacyl-glycerol cascade, ultimately resulting in protein kinase C activation, and Ca\(^{2+}\) mobilization (Figure 1c). Thrombin, generated at the site of vascular injury, represents the most potent platelet activator (Figure 1d), acting through the proteolytic cleavage of two protease-activated receptors (PARs) at their N-terminal exodomain, PAR-1 and PAR-4. PAR-1 is activated by lower thrombin concentrations and couples to several G proteins (G\(_{12/13}\), G\(_{q}\), and G\(_{i}\)), thus generating shape change, release reaction, Ca\(^{2+}\) mobilization, and cAMP decrease. Thus, these mediators amplify the intensity and duration of the initial activating signal by recruiting neighboring quiescent platelets and strengthening the hemostatic plug. The final common pathway is the activation of the integrin GPIIb/IIIa, which becomes competent to bind fibrinogen with high affinity (Figure 1a) (7). The peptide sequence RGD (Arg-Gly-Asp) of adhesive proteins binds to the high-affinity state of GPIIb/IIIa. Fibrinogen contains two RGD sequences on its \(\alpha\)-chain, one in the N-terminal and one in the C-terminal region. Fibrinogen-mediated bridging of adjacent platelets via activated GPIIb/IIIa is the final mediator of aggregation. The importance of GPIIb/IIIa is reflected by the severe bleeding phenotype of GPIIb/IIIa-deleted mice and Glanzmann’s thrombasthenia resulting from GPIIb/IIIa mutations (8). Other adhesive proteins, such as vWF, fibronectin, and vitronectin, also bind GPIIb/IIIa, facilitating aggregation (Figure 1a) (8).

Several modifiable conditions (cigarette smoking, obesity, hypertension, hyperlipidemia), disease states (diabetes mellitus, renal disease), and aging are associated with platelet activation and represent risk factors for atherothrombotic complications (4). Many of the same factors also increase the risk of bleeding complications (9, 10).
Platelet activation and aggregation: agonists, receptors and effectors. (a) The activation, adhesion, and aggregation of platelets is triggered by agonists interacting with specific membrane receptors leading to inside-out change in the ligand-binding properties of GPIIb/IIIa, which conformationally switches to a high-affinity state for adhesive proteins such as fibrinogen, vWF, fibronectin, and vitronectin. Panels b, c, and d depict the outside-in signaling mediated by ADP, TXA₂, and thrombin, respectively. Abbreviations: ADP, adenosine diphosphate; cAMP, cyclic adenosine monophosphate; TX, thromboxane; TP, thromboxane receptor; PKC, protein kinase C; PAR, protease-activated receptor; TXS, thromboxane synthase; PGH₂, prostaglandin H₂; COX, cyclooxygenase; AA, arachidonic acid; PLA₂, phospholipase A₂; GP, glycoprotein; vWF, von Willebrand factor; CD40L, CD40 ligand; Fbg, fibrinogen.

MECHANISMS OF PLATELET INHIBITION: PHARMACOKINETIC AND PHARMACODYNAMIC DETERMINANTS OF CLINICAL EFFICACY

The mechanisms by which antiplatelet drugs interfere with platelet activation and aggregation involve targeting enzymes or receptors that are critical for the synthesis or action of important mediators of these functional responses (11). The interaction between the antiplatelet drug and its molecular target largely depends on the following determinants: (a) the availability of the active moiety of the drug at its receptor site, as a function of drug absorption, liver metabolism,
and elimination, i.e., pharmacokinetics (PK); (b) the mechanism of transient or permanent inhibition of the target and the rate of its renewal, i.e., pharmacodynamics (PD); and (c) genetic variation of the drug target and/or drug-metabolizing enzymes, i.e., pharmacogenetics. The anucleate nature of blood platelets and their variable daily turnover are important determinants of the persistence of the antiplatelet effect of irreversible blockers (e.g., aspirin and thienopyridines), which is largely unrelated to their PK features (11).

**COX-1 Inhibition**

All traditional nonsteroidal antiinflammatory drugs (NSAIDs), including aspirin, are inhibitors of platelet COX-1. However, aspirin permanently inactivates the enzyme, other NSAIDs act as reversible inhibitors. Virtually complete (≥97%) and persistent (≥24 h) inactivation of platelet COX-1 by low-dose aspirin (75–100 mg once daily) reflects cumulative acetylation of a critical serine residue near the catalytic site of the enzyme that blocks access of the substrate to its cyclooxygenation (9). Aspirin is equally potent in acetylating COX-1 and COX-2, when tested in vitro. However, its unique mechanism of action and unusual PK features (short half-life; presystemic encounter with the platelet target in the portal blood prior to first-pass liver metabolism) allow selective, cumulative inhibition of platelet COX-1 at low doses while substantially sparing vascular COX-2 (9, 11). Although the effect of aspirin on COX-1-dependent TXA2 production is saturable at daily doses as low as 30–50 mg, its inhibitory effect on COX-2-derived PGI2 production is dose dependent up to daily doses of 650–1300 mg (9, 11).

The strikingly nonlinear relationship between inactivation of platelet COX-1 and inhibition of TXA2-dependent platelet function by low-dose aspirin (12) has three important practical implications. First, a substantial loss of platelet inhibition is associated with less than maximal inactivation of COX-1. Second, recovery of platelet function is disproportionately rapid upon drug withdrawal. Third, the requirement for virtually complete and persistent inhibition of platelet COX-1 cannot be met by most traditional NSAIDs, allowing their COX-2-dependent cardiotoxicity to be unmasked (11).

**P2Y12 Blockade**

The interaction of ADP with one of its platelet receptors, P2Y12 (Figure 1b), can be blocked irreversibly by the active metabolites of thienopyridines (ticlopidine, clopidogrel, and prasugrel) or antagonized reversibly by novel drugs in phase III clinical development (cangrelor, ticagrelor) (13). Thienopyridines inhibit ADP-dependent platelet function through an irreversible modification of platelet P2Y12, operated by short-lived active metabolites generated by liver cytochrome P-450 (CYP) isozymes. Although conceptually analogous to aspirin in terms of PK/PD dissociation (short half-life, long duration of action), the inhibition of ADP-dependent platelet function by clopidogrel is less predictable than the inhibition of TXA2-dependent platelet function by aspirin. Insufficient availability of the active metabolite of clopidogrel at conventional therapeutic doses results in incomplete inactivation of platelet P2Y12. However, because of the linear relationship between P2Y12 inactivation and inhibition of ADP-dependent platelet function, even incomplete inactivation of the drug target results in a measurable clinical effect (11). Genetic variation of the liver enzymes responsible for the metabolism of clopidogrel as well as drug-drug interactions are important determinants of the highly variable circulating levels of its active metabolite (14) (Figure 2). These recent findings have important implications for the interindividual variability in the antiplatelet effect of clopidogrel (see below).

The PK advantages of prasugrel over clopidogrel, which enable more efficient metabolic activation by liver enzymes, allow the achievement of substantially higher plasma levels of its active metabolite, resulting in more complete
Mechanisms underlying the interindividual variability in response to clopidogrel. Both pharmacogenetic mechanisms [e.g., reduced-function polymorphisms of cytochrome P450 (CYP) isozymes] and pharmacokinetic mechanisms (e.g., drug interactions with inhibitors of CYP isozymes, such as some proton pump inhibitors) may be responsible for impairment of the two-step conversion of clopidogrel to its active metabolite. The resulting incomplete inactivation of platelet P2Y12 is associated with impaired inhibition of ADP-dependent platelet aggregation. In a pharmacogenetic substudy of the TRITON-TIMI38 trial (28), clopidogrel-treated carriers of the reduced-function CYP2C19*2 allele had lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major cardiovascular events than did clopidogrel-treated noncarriers.

and less variable inactivation of the same drug target (13).

The less stringent requirements for P2Y12 versus COX-1 blockade may explain the more consistent antplatelet effects of reversible P2Y12 blockers compared to reversible COX-1 inhibitors. Large randomized phase III trials of ticagrelor are currently testing the long-term efficacy and safety of this novel antplatelet strategy. However, two short-term phase III trials of the intravenous P2Y12 blocker, cangrelor, have been discontinued owing to less-than-expected efficacy.

**Thromboxane Receptor Blockade**

A potential limitation in the antplatelet effect of aspirin is related to the existence of extraplatelet, nucleate sources of TXA2 biosynthesis that are less affected than platelet TXA2 production by the once-daily regimen of administration and by the low dose administered (11). Moreover, F2-isoprostanes and other structurally related isoeicosanoids represent aspirin-insensitive agonists of the platelet thromboxane receptor (TP) (Figure 1c) that are produced nonenzymatically through a process of oxygen radical-catalyzed lipid peroxidation (4).

A potent, selective TP antagonist could effectively block the interaction of both aspirin-sensitive and aspirin-insensitive agonists with this important platelet receptor. One such compound, terutroban, is currently in phase III clinical development. However, the PERFORM trial (15) of terutroban versus...
aspirin in 18,000 stroke patients was recently halted on the basis of an interim analysis failing to support the superiority hypothesis.

**Thrombin Receptor Antagonism**

Thrombin interacts with two platelet receptors, called protease activated receptor (PAR)–1 and –4 (Figure 1d), that are activated through proteolytic cleavage (16). PAR-1 is the major human platelet receptor, exhibiting 10–100 times higher affinity for thrombin than PAR-4 (16). Two thrombin receptor antagonists (TRAs) with PAR-1 selectivity are currently under development. The rationale for adding a TRA to conventional antiplatelet treatment relies on the hypothesis that PAR-1 antagonism might increase antithrombotic efficacy by targeting a powerful platelet-activating pathway without increasing bleeding risk. This assumption is based on the consideration that thrombin generation and PAR-1 activation might occur somewhat later during primary hemostasis and on the findings that TRAs do not affect bleeding times nor ADP- or collagen-induced platelet aggregation ex vivo (17).

SCH530348, a synthetic analogue of himbacine, is an oral TRA with a Ki of 2.7 nM (17, 18) and a half-life of 126–269 h. It inhibits platelet function for up to four weeks after its withdrawal (13, 18). SCH530348 has recently completed a placebo-controlled dose-ranging phase II study in patients undergoing a percutaneous coronary intervention (PCI) and receiving standard antithrombotic therapy (18). PD data from this study, based on thrombin-induced optical platelet aggregation ex vivo, identified 40 mg and 2.5 mg as suitable loading and maintenance doses, respectively. This dosing regimen is currently being investigated in placebo-controlled phase III trials in patients with acute coronary syndromes (ACS) undergoing PCI (19) and in high-cardiovascular-risk patients (20). These trials are scheduled to be completed by 2011. Another oral TRA, E5555, is in phase II evaluation in ACS patients. This compound has a shorter half-life and faster recovery of platelet function after its withdrawal than SCH530348 (13).

**GPIIb/IIIa Blockade**

Three structurally unrelated compounds, abciximab, eptifibatide, and tirofiban, are currently available for intravenous administration. Their PK/PD features were selected for providing short-term, high-grade blockade of platelet GPIIb/IIIa to counteract platelet-mediated thrombosis that may occur in response to mechanical disruption of coronary plaques during and immediately after PCI (11). It is important to emphasize that the clinical development of these antiplatelet drugs took place before dual antiplatelet therapy with aspirin and clopidogrel became standard of care in patients undergoing PCI. The extent to which GPIIb/IIIa blockade remains safe and effective is likely to vary with the increasing intensity of platelet inhibition achieved by newer regimens of dual (e.g., aspirin and prasugrel) or triple (e.g., aspirin, clopidogrel, and PAR-1 antagonist) antiplatelet therapy.

At least four different GPIIb/IIIa blockers were developed as oral antiplatelet agents for long-term therapy (11). In part because of inadequate PK/PD features, none of these compounds was shown superior to aspirin or placebo in phase III trials in ACS. The occurrence of a significantly higher rate of major bleeding complications associated with these GPIIb/IIIa blockers versus placebo illustrates an important point, i.e., the potential dissociation of bleeding liability from antithrombotic efficacy.

**Modulation of Platelet Cyclic AMP**

A brake to platelet activation and aggregation can be placed through elevation of intraplatelet levels of cyclic AMP. This can be achieved by stimulating adenylate cyclase with PGE1, PGI2, or their synthetic analogs, or by inhibiting phosphodiesterase(s) with dipyridamole or cilostazol (11). These drugs tend to have both antiplatelet and vasodilator effects. Among them, only dipyridamole has been subjected to large randomized clinical trials for the secondary prevention of atherothrombosis (11). Inadequate PK features of the original
formulation of dipyridamole and, perhaps, inadequate dosage were likely responsible for the initial failure to demonstrate a statistically significant clinical benefit in patients with ischemic heart disease. Development of a modified-release formulation of dipyridamole with improved bioavailability in a fixed combination with low-dose aspirin has led to successful demonstration of efficacy and safety in patients with prior stroke or transient ischemic attack (11) and in ameliorating hemodialysis graft patency (21).

New Drug Targets

The activation of vWF is crucial in initiating platelet adhesion to the injured vessel (Figure 1a), especially under high-shear-rate conditions, such as in arterial stenosis. The A1 domain exposed on vWF by high shear rate binds the GPIb platelet receptor (22). Aptamers are a novel class of oligonucleotides antagonizing the A1 domain of vWF. An A1 antagonist would potentially display arterial selectivity and specifically target the initial phase of thrombus formation (adhesion) while sparing other activating targets. ARC1779, a parenteral aptamer, did not cause serious adverse events or spontaneous bleedings in phase I studies (22). It has a half-life of ~2 h and caused >95% inhibition of vWF activity at the higher dose, which returned to baseline by 12–16 h after the infusion (22). vWF-mediated, shear-dependent platelet function displayed a parallel inhibition and recovery (22). A recently terminated phase II trial randomized patients with myocardial infarction undergoing PCI to three different doses of ARC1779 versus the active comparator abciximab (23).

Another agent under development is the C1qTNF-related protein-1 (CTRP-1), which prevents collagen-induced platelet aggregation by specific blockade of vWF binding to collagen (24), thereby hampering platelet adhesion. In studies of carotid thrombosis in nonhuman primates, CTRP-1 effectively prevented thrombus formation (24). Additional platelet targets, such as PAR-4 and P2X₁, are currently being explored in preclinical models of thrombosis.

INTERINDIVIDUAL VARIABILITY IN RESPONSE TO ANTIPLATELET AGENTS

For any given drug, there may be wide variation in its PK handling among individuals. Interindividual PK variability results in different plasma concentrations of the drug or its active metabolite(s) in different individuals given the same dose. Moreover, considerable interindividual variation in drug response remains after the concentration of the drug in plasma has been adjusted to a target value, i.e., different individuals may respond differently to the same plasma concentration of the drug (PD variability). Thus, less-than-expected response (be it biochemical, functional, or clinical) to a standard drug regimen in an individual patient is not surprising nor unique to any drug class. Antiplatelet drugs do not escape this general rule of drug therapy (25).

In the case of aspirin, once noncompliance has been rigorously excluded with biochemical tests (e.g., measurement of serum TXB₂), less-than-complete inhibition of platelet TXA₂ production and TXA₂-dependent aggregation is a rare phenomenon (11, 12). A PD interaction with other NSAIDs (e.g., ibuprofen and naproxen), competing at a common docking site within the COX-1 channel, may explain an important fraction of this phenomenon, often inappropriately referred to as aspirin “resistance” (11). Accelerated renewal of COX-1, due to enhanced platelet regeneration, might be expected to shorten the duration of COX-1 inactivation by low-dose aspirin and, perhaps, dictate a shorter dosing interval in clinical settings characterized by accelerated platelet turnover.

Marked interindividual variability has been reported in clopidogrel PK, i.e., in the amount of intact prodrug that reaches the CYP-dependent pathway of metabolic activation, and in the fraction of prodrug transformed into the active metabolite (26, 27). A relatively
common loss-of-function genetic variant of CYP2C19 explains a major fraction of this variability (28). Disease-related changes in clopidogrel bioavailability, as suggested by preliminary findings in diabetic patients (27), and drug-drug interactions at CYP2C19 and other CYP isozymes could also contribute to this variability (14). Lower levels of the active metabolite are associated with less inhibition of ADP-dependent platelet function with a linear relationship between the two. Impaired platelet inhibition is associated with an increased rate of atherothrombotic complications (28) (Figure 2).

BALANCING THE BENEFITS AND BLEEDING RISKS OF ANTIPLATELET THERAPY

The efficacy and safety of aspirin as an antiplatelet agent have been evaluated in several populations, ranging from apparently healthy persons at low risk of vascular complications (so-called primary prevention) to high-risk patients presenting with or surviving an acute myocardial infarction or an acute ischemic stroke (so-called secondary prevention). Studies have ranged from a few weeks to 10 years in duration (9, 11).

It is interesting to compare the effects of low-dose aspirin in primary prevention with the well-known benefits in secondary prevention (10). In the six primary-prevention trials among 95,000 low-risk individuals, with mean follow-up of 6.9 years, aspirin allocation yielded a 12% relative risk reduction in serious vascular events (myocardial infarction, stroke, or vascular death) from an annual rate of 0.57% to 0.51%. This cardioprotective effect was mainly due to a reduction in nonfatal myocardial infarction, from 0.23% to 0.18% per year. The net effect on stroke was not significant (from 0.21% to 0.20% per year), reflecting a small reduction in presumed ischemic stroke and counterbalancing effects on hemorrhagic stroke and other (probably ischemic) stroke. There was no reduction in vascular mortality, which was 0.19% per year with or without aspirin. Aspirin allocation increased gastrointestinal (or other extracranial) bleeds by about half, from 0.07% to 0.1% per year.

In 16 long-term secondary-prevention trials in 17,000 high-risk patients with prior myocardial infarction or prior stroke or transient cerebral ischemia, with mean follow-up of 2.5 years, aspirin allocation yielded 19% fewer serious vascular events (from 8.2% to 6.7% per year), with similar proportional reductions in coronary events (20% relative risk reduction) and ischemic stroke (22% relative risk reduction) but a nonsignificant increase in hemorrhagic stroke (10). Although the 19% proportional reduction in serious vascular events was similar to that observed in primary prevention, the absolute benefit of aspirin was about 25 times larger in secondary prevention (15 versus 0.6 fewer vascular events per 1000 per year). In both primary- and secondary-prevention trials, the proportional reductions in serious vascular events appeared similar for men and women and for older and younger people. The risks of serious vascular events and of major extracranial bleeds were predicted by the same independent risk factors (age, male gender, diabetes mellitus, current smoking, blood pressure and body mass index), so those with high risk of vascular complications also had a high risk of bleeding (10).

Whereas for secondary prevention the net benefits of adding aspirin to other preventive measures (e.g., statin) would substantially exceed the bleeding hazards, irrespective of age and gender, for people without pre-existing vascular disease the benefits and hazards of adding long-term aspirin would be of similar magnitude (10).

PRIMARY PREVENTION IN PATIENTS AT ENHANCED RISK OF VASCULAR COMPLICATIONS

To maximize the cardioprotective benefit over the bleeding hazard of low-dose aspirin in primary prevention, most guidelines recommend that aspirin be given to those with risk of coronary events exceeding an arbitrary threshold
(from as low as 0.6% to as high as 2.0% per year) (29–31). These guidelines implicitly assume either that the absolute risk of bleeding complications is approximately constant irrespective of variable coronary risk, or that it depends solely on age. However, the recently published Antithrombotic Trialists’ (ATT) overview (10) showed that other risk factors for coronary events are also risk factors for bleeding. As a result, even for patients at moderately increased risk of coronary events, the absolute benefits and hazards of low-dose aspirin added to a statin-based regimen of primary prevention are likely to be approximately evenly balanced (10). Further primary-prevention trials of aspirin are currently ongoing with the aim of recruiting people who are at relatively high cardiovascular risk (expected annual rate of major vascular events ≥2%) because of diabetes mellitus (ASCEND and ACCEPt-D), advanced age (ASPREE), or a cluster of risk factors that do not include diabetes (ARRIVE). Although a subgroup analysis of the six primary-prevention trials is consistent with some net benefit of aspirin in adults with diabetes but no known vascular disease (10), the evidence from three placebo-controlled trials that recruited only patients with diabetes (32–34) has been inconclusive. The unpromising results of these trials may well reflect their relatively limited sample size, but it is also conceivable that low-dose aspirin is less effective in people with diabetes because of abnormalities in platelet regeneration, potentially limiting the duration of the antiplatelet effect of a standard once-daily regimen of the drug.

**ACUTE TREATMENT AND SECONDARY PREVENTION IN HIGH-RISK PATIENTS**

Low-dose aspirin remains the mainstay of antiplatelet treatment for patients with ACS and acute myocardial infarction (9, 11). Moreover, aspirin at the recommended dose of 75–100 mg daily represents the first option for the secondary prevention of recurrent vascular events in patients surviving a myocardial infarction or ischemic stroke, with clopidogrel providing a valid alternative (35, 36).

The complementary mechanisms of action of clopidogrel and aspirin have led to testing of the efficacy and safety of their combination in several high-risk settings (37–40). The relative risk reduction of major vascular events associated with the combination of clopidogrel and aspirin, compared with aspirin alone, was relatively modest and inconsistent (Figure 3). The additional benefit of dual antiplatelet therapy versus aspirin alone (37–40) was only a fraction of the benefit achieved by aspirin versus placebo in the same clinical settings (41, 42), raising the possibility that the role of ADP in atherothrombosis may have been underestimated on the basis of clopidogrel trials because of incomplete and variable blockade of ADP-induced platelet aggregation by the drug (4).

Consistent with this hypothesis, a novel thienopyridine, prasugrel, which causes a higher level of inhibition of ADP-induced

![Figure 3](https://www.annualreviews.org/doi/10.1146/annurev-med-050709-130406)
platelet aggregation and a less variable response than a standard regimen of clopidogrel, reduced major vascular events by $\sim 20\%$ versus clopidogrel in ACS patients with scheduled PCI (43). As expected from a regimen of intensified platelet inhibition, prasugrel increased major bleedings by about one third and disproportionately increased the risk of fatal bleeding versus clopidogrel (43). Prasugrel has been approved by the U.S. Food and Drug Administration and European Medicines Agency based on the results of this pivotal phase III trial. When considering the choice of antiplatelet regimens for the treatment of ACS patients undergoing PCI, clinicians need to balance the potential benefits and bleeding risks of intensive platelet inhibition (43). In contrast to clopidogrel (28), common reduced-function genetic variants of CYP isozymes did not affect active metabolite levels, inhibition of ADP-induced platelet aggregation, or cardiovascular event rates in subjects treated with prasugrel (44).

The concept that less variable and more profound inhibition of platelet P2Y$_{12}$ results in improved vascular outcomes has been validated by the PLATO study, a phase III randomized trial of ticagrelor versus clopidogrel in 18,624 ACS patients (45), which demonstrated a 16% reduction in major vascular events including death from cardiovascular causes. As compared with clopidogrel, ticagrelor was associated with more frequent non-procedure-related bleeding, but it did not increase the risk of bleeding in patients undergoing coronary-artery bypass grafting (45). The potential advantages and drawbacks of reversible versus irreversible blockade of platelet P2Y$_{12}$ need to be investigated further at comparable levels of P2Y$_{12}$ inhibition.

The efficacy and safety of triple antiplatelet therapy, with the addition of the PAR-1 antagonist SCH530348 to a standard regimen of aspirin and clopidogrel, are currently being evaluated in ACS patients undergoing PCI (19). The theoretical safety advantage of adding a PAR-1 antagonist to traditional antiplatelet therapy vis-à-vis intensifying inhibition of ADP-dependent platelet function with prasugrel or ticagrelor remains untested and will likely represent the next step in head-to-head comparisons of antiplatelet regimens.

**CONCLUSIONS**

The field of antiplatelet therapy has undergone very substantial changes during the past 20 years, moving from one to eight antiplatelet drugs in the armamentarium with at least five additional compounds in phase III clinical development. Although beating aspirin was the name of the game until recently, optimizing combination (dual or triple) antiplatelet therapy represents the next challenge. Attempts to separate improved antithrombotic efficacy from enhanced bleeding liability have met limited success thus far. A PAR-1 antagonist added to traditional antiplatelet therapy holds promise in this respect (18), but we should not overinterpret the results of phase II studies, given the relatively rare occurrence of major bleeding complications and limited sample size of these studies. Quantitative assessment of bleeding risk has lagged behind the successful development and validation of tools for assessing the risk of ischemic complications. Much of the relevant information on the major determinants of bleeding risk is actually available from both observational studies and randomized trials, and bleeding scores are being developed (46).

Drug-drug interactions are increasingly being recognized as important determinants of less-than-expected inhibition of platelet aggregation by aspirin (47, 48) and clopidogrel (49, 50). It should be emphasized that concomitant drug treatment may alter the benefit/risk balance of antiplatelet therapy, either by reducing the benefit because of PK (e.g., clopidogrel) or PD (e.g., aspirin) drug interactions, or by modifying the baseline risk of vascular events (e.g., statin) (10) and bleeding complications (e.g., oral anticoagulants, NSAIDs) (51, 52). In this context, the challenge of combining novel anticoagulants (e.g., factor Xa inhibitors) (13) with...
intensified regimens of antiplatelet therapy will require more sophisticated tools for assessing the ischemic and hemorrhagic risk of the individual patient. The pharmacogenetics of liver CYP-isozymes responsible for the metabolic activation of thienopyridines has contributed to illuminating important sources of interindividual variability in response to clopidogrel. Although many pivotal questions remain unanswered (53), the prospect of a personalized choice of the most appropriate P2Y12 inhibitor and tailored dose adjustment for an individual patient appears realistic.

Ongoing studies of the recovery rate of platelet COX-1 activity during the 24-h dosing interval of aspirin administration in clinical settings characterized by enhanced platelet regeneration (e.g., type 2 diabetes mellitus and essential thrombocythemia) may provide valuable information for tailoring the dosing regimen as a function of platelet turnover. Finally, it can be anticipated that the availability of more effective and/or safer antiplatelet agents may allow the role of platelets to be investigated in other important areas of vascular disease, such as the development and progression of atherosclerosis (4).

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Contents

Using Genetic Diagnosis to Determine Individual Therapeutic Utility
  C. Thomas Caskey ................................................................. 1

Emotion Recollected in Tranquility: Lessons Learned from the COX-2 Saga
  Tilo Grosser, Ying Yu, and Garret A. FitzGerald ...................... 17

Progressive Multifocal Leukoencephalopathy in Patients on Immunomodulatory Therapies
  Eugene O. Major ................................................................. 35

The Future of Antiplatelet Therapy in Cardiovascular Disease
  Carlo Patrono and Bianca Rocca ............................................. 49

Pharmacogenetics of Warfarin
  Farhad Kamali and Hilary Wynne ........................................... 63

Heparin-Induced Thrombocytopenia
  Gowthami M. Arepally and Thomas L. Ortel ................................ 77

Regulation of Phosphate Homeostasis by PTH, Vitamin D, and FGF23
  Clemens Bergwitz and Harald Jüppner .................................... 91

Alveolar Surfactant Homeostasis and the Pathogenesis of Pulmonary Disease
  Jeffrey A. Whitsett, Susan E. Wert, and Timothy E. Weaver ........ 105

Diagnosis and Treatment of Neuropsychiatric Disorders
  Katherine H. Tuber, Robin A. Hurley, and Stuart C. Yudofsky ........ 121

Toward an Antibody-Based HIV-1 Vaccine
  James A. Hoxie ........................................................................ 135

HIV-1 Vaccine Development After STEP
  Dan H. Barouch and Bette Korber ........................................... 153

Growing Up with HIV: Children, Adolescents, and Young Adults with Perinatally Acquired HIV Infection
  Rohan Hazra, George K. Siberry, and Lynne M. Mofenson ............ 169
H5N1 Avian Influenza: Preventive and Therapeutic Strategies Against a Pandemic
Suryaprakash Sambhara and Gregory A. Poland ........................................... 187

Revascularization for Coronary Artery Disease: Stents Versus Bypass Surgery
Spencer B. King III, John Jeffrey Marshall, and Pradyumna E. Tummala .......... 199

Controversies in the Use of Drug-Eluting Stents for Acute Myocardial Infarction: A Critical Appraisal of the Data
Rabul Sakkuya and Laura Mauri ................................................................. 215

Arrhythmogenic Cardiomyopathy: Etiology, Diagnosis, and Treatment
Srijita Sen-Chowdhry, Robert D. Morgan, John C. Chambers, and William J. McKenna .......................................................... 233

Contemporary Use of Ventricular Assist Devices
Cesare M. Terracciano, Leslie W. Miller, and Magdi H. Yacoub ......................... 255

Stress Cardiomyopathy
Yoshihiro J. Akashi, Holger M. Nef, Helge Möllmann, and Takashi Ueyama .................. 271

Stem Cells in the Treatment of Heart Disease
Stefan Janssens ...................................................................................... 287

Biological Mechanisms Linking Obesity and Cancer Risk: New Perspectives
Darren L. Roberts, Caroline Dive, and Andrew G. Renehan ............................. 301

Hepatocellular Carcinoma: Novel Molecular Approaches for Diagnosis, Prognosis, and Therapy
Augusto Villanueva, Beatriz Minguez, Alejandro Forner, Maria Reig, and Josep M. Llovet ............................................................... 317

Molecular Diagnosis and Therapy of Kidney Cancer
W. Marston Linehan, Gennady Bratslavsky, Peter A. Pinto, Laura S. Schmidt, Len Neckers, Donald P. Bottaro, and Ramaprasad Srinivasan ........................................ 329

Myelodysplastic Syndromes
Bart L. Scott and H. Joachim Deeg ................................................................. 345

Nanotechnology Applications in Surgical Oncology
Sunil Singhal, Shuming Nie, and May D. Wang ................................................. 359

Emerging Molecular Targets for the Treatment of Nonalcoholic Fatty Liver Disease
Giovanni Musso, Roberto Gambino, and Maurizio Cassader ............................... 375

Metabolic Surgery to Treat Type 2 Diabetes: Clinical Outcomes and Mechanisms of Action
Francesco Rubino, Philip R. Schauer, Lee M. Kaplan, and David E. Cummings .... 393
Genetic Aspects of Pancreatitis
   David C. Whitcomb ................................................................. 413

Anorexia Nervosa: Current Status and Future Directions
   Evelyn Attia ................................................................. 425

Structural Variation in the Human Genome and its Role in Disease
   Pawel Stankiewicz and James R. Lupski .................................. 437

Surgical Innovations Arising from the Iraq and Afghanistan Wars
   Geoffrey S.F. Ling, Peter Rhee, and James M. Ecklund .................. 457

Medicare Part D: Ongoing Challenges for Doctors and Patients
   Gretchen Jacobson and Gerard Anderson .................................. 469

Indexes

Cumulative Index of Contributing Authors, Volumes 57–61 ................ 477
Cumulative Index of Chapter Titles, Volumes 57–61 .......................... 481

Errata

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