Drugs of the Future 2009, 34(1): 27-41

CCC: 0377-8282/2009
DOI: 10.1358/dof.2009.34.1.1315100

REVIEW ARTICLE

CURRENT STATUS AND FUTURE DIRECTIONS IN ANTIPLATELET THERAPY

*J. Krakat, S. Mousa, R. Root and S.S. Mousa**

The Pharmaceutical Research Institute, Albany College of Pharmacy, Albany, NY, USA. *Correspondence: mousas@acp.edu

CONTENTS

ABSTRACT

Platelets are the principal effectors of cellular hemostasis and key mediators in the pathogenesis of thrombosis. A variety of membrane receptors determine platelet reactivity with numerous agonists and adhesive proteins, and therefore represent key targets for the development of antiplatelet drug therapies. In this regard, several rapid-onset and rapid-offset reversible ADP antagonists are in clinical development, including reversible oral and rapid-acting intravenous $P2Y_{12}$ receptor antagonists. Novel inhibitors of platelet adhesion in early development target vWF–GPIb/IX and collagen–GPVI interactions. Since platelet aggregation also plays such a critical role in the pathogenesis of arterial thrombosis, more potent agents that interfere with platelet aggregation via other pathways (e.g., the thrombin receptor) are also under clinical investigation. However, the major limitation to treatment with multiple antiplatelet agents is the increased bleeding risk associated with the enhanced antiplatelet effect, as exemplified by the clinical conundrum in patients with acute coronary syndrome who may need to undergo coronary artery bypass graft surgery. Aspirin and clopidogrel irreversibly inhibit platelet function, with the maximal antiplatelet effect occurring after 3-5 days. These limitations might be solved with the availability of rapid-onset and rapid-offset ADP antagonists. One issue that deserves further discussion is the duration of therapy. There is conflicting evidence from the MATCH and CARESS trials as to the optimal duration of antiplatelet therapy in cerebrovascular disease. For coronary artery disease, the CHARISMA trial failed to show the benefit of long-term clopidogrel in the overall trial population, although the 80% of patients with clinically evident atherothrombosis experienced a modest reduction in the primary endpoint, and emerging data with drug-eluting stents suggest that dual antiplatelet therapy may be required even beyond 1 year. Clearly, additional studies are necessary to evaluate optimal antiplatelet therapy combinations and duration of therapies to permit maximal benefit with minimum harm in patients with cardiovascular disease. This review provides detailed information on the clinically most useful antiplatelet agents from aspirin to clopidogrel to GPIIb/IIIa antagonists and beyond, as well as several classes of novel antiplatelet drugs in development.

BACKGROUND

Platelets are derived from bone marrow progenitor cells known as megakaryocytes (1). Platelets work alongside the coagulation cascade to maintain normal hemostasis in blood vessels. Healthy individuals are constantly experiencing small breaks and tears in their blood vessels, but the vessels are closed by platelets before serious damage can occur. Vessel injury is a serious condition that initially causes vasospasm, and within seconds the circulating platelets stick to collagen that is exposed by damage to the endothelial cells. With the aid of fibrin, the platelets undergo metamorphosis at the site of injury, causing further activation and aggregation, which ultimately leads to the formation of a platelet plug to stop the bleeding (2). Disease states associated with cuts, plaque rupture, turbulent blood flow and the implantation of artificial materials often affect and are affected by platelet regulation. Heart failure, atrial fibrillation, ischemic stroke, acute coronary syndromes (ACS) and accompanying procedures are some examples of situations where platelet regulation plays an important underlying role. There has also been research to suggest that platelets may play an important role in cancer. In many cases, the exogenous suppression of platelet function in these situations can provide better clinical outcomes.

There are two types of clots that can form in the vasculature: clots made up mainly of fibrin and clots made up mainly of platelets. The vascular clots consisting mainly of platelets are also known as white clots. White clots are usually precipitated by stress on arteries and can be associated with the components of Virchow's triad: altered flow, damaged surface or a hypercoagulable state. There are many disease states that can contribute, directly or indirectly, to cause this

stress on the arterial walls, intensifying the risk of clot formation. Heart failure is a complex disease characterized by high cardiovascular stress, inflammation and turbulent blood flow, all altering platelet activation and aggregation. Atrial fibrillation deters the ability of the heart to pump efficiently, and therefore blood pooling initiates the process of clot formation, amplifying an individual's risk of stroke. Acute coronary syndromes such as unstable angina, non-S-T-segment myocardial infarction (NSTEMI) and STEMI are all caused by some degree of platelet response. Understanding the mechanisms behind these disease states is vital in the utilization of appropriate antiplatelet therapy in order to regain hemostasis in the body.

Obviously, normal hemostasis is not always properly maintained endogenously. Therefore, we utilize antiplatelet medications to attempt to reproduce a balanced coagulable state, decreasing the risk of complications from the disease states mentioned above. Drug therapy to this effect may be targeted at any of the many processes involved in the platelet activation and aggregation cascade (Table I). Thromboxane A_2 and its receptors, ADP and its receptors, the metabolism of cAMP, the exposure and binding of GPIIb/IIIa receptors, and thrombin are all components involved in platelet activation and aggregation, and all can be altered to achieve some level of platelet inhibition.

Aspirin, the first antiplatelet medication discovered, remains the most widely used and the most studied; however, many others have been developed since. The proven efficacy, as well as the low cost and wide availability, of aspirin has set a standard by which all subsequently developed antiplatelet drugs are evaluated. In some cases the use of newer, costlier drugs is justified, while in others it may not be. Furthermore, many disease states are associated with severely accelerated platelet function that may necessitate different combinations of antiplatelet, anticoagulant and thrombolytic drugs to achieve the desired response. The goal of this review is to provide a comprehensive review of current and newer antiplatelet medications (Table I).

THROMBOXANE INHIBITORS

When platelets are activated, prostaglandins are synthesized. Prostaglandin H_2 (PGH_2) is formed via the cylooxygenase-1 (COX-1) pathway, which stimulates the production of thromboxane (TXA_2) via the thromboxane synthase enzyme. Thromboxane then binds to the thromboxane receptors on neighboring platelets, thus amplifying platelet aggregation and further activation (3).

Aspirin (acetylsalicylic acid, ASA) is the only approved inhibitor of thromboxane currently available for clinical use as an antiplatelet agent. Over 100 years of research involving ASA have proven the drug to be beneficial in treating patients undergoing percutaneous coronary intervention (PCI) and suffering from stroke and myocardial infarction (MI), and numerous disease state guidelines have adopted ASA into current treatment protocols based on its history of use. Randomized trials comparing beneficial effects and hazards of different ASA doses have shown that daily doses of 75-150 mg are as effective as higher doses and are associated with fewer adverse

Table I. *Current and future antiplatelet agents with their common or potential indications and advantages.*

Class/drug	Most common/potential clinical indications
Current antiplatelet therapy	
Cyclooxygenase (COX) inhibitors	
Aspirin	Acute and chronic coronary, cerebral and peripheral vascular disease
Triflusal	Secondary prevention of vascular events
Phosphodiesterase inhibitors	
Dipyridamole	Stroke prevention, prosthetic cardiac valves
Pentoxifylline	Peripheral vascular disease
Cilostazol	Peripheral vascular disease, intracoronary stenting
Thienopyridines	
Ticlopidine	Stroke prevention, intracoronary stenting
Clopidogrel	Acute and chronic coronary artery disease, intracoronary stenting
Intravenous GPIIb/IIIa antagonists	
Abciximab	Percutaneous coronary intervention
Eptifibatide	Acute coronary syndromes, percutaneous coronary intervention
Tirofiban	Acute coronary syndromes
Future antiplatelet therapies in development	
$P2Y_{12}$ inhibitors (compared to clopidogrel)	
Prasugrel	Faster onset, greater antiplatelet effect, less variable response
Ticagrelor	Reversible, faster onset and offset, greater antiplatelet effect
Cangrelor (i.v.)	Reversible, shorter half-life, faster onset, greater antiplatelet effect, less variable response
PAR1 (thrombin receptor) antagonists	
Sch-530348	Greater antiplatelet effect, less variable response, potenially lower risk of bleeding (phase III clinical trials)
FR-171113, others	Preclinical and early clinical development

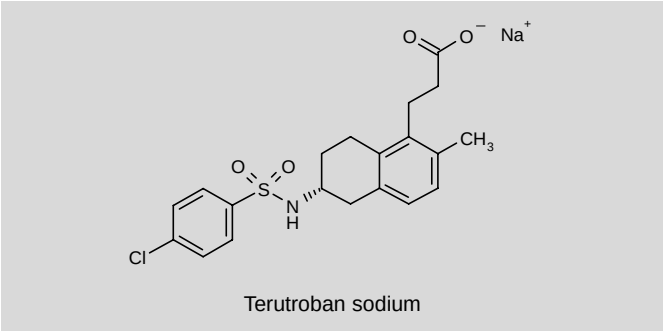
Direct thrombin inhibitors (intravenous and oral) have the potential to have an impact on both coagulation and platelets alone or in combination with aspirin.

effects (4). Because ASA is effective and inexpensive, it has retained its status as the most widely used antiplatelet drug in many clinical situations. In fact, ASA still compares favorably to many of the newer antiplatelet therapies available. Because of this, the practice of using newer drugs in addition to ASA in order to obtain an additive antiplatelet effect has become common (5). Specifically, initial management of ACS, regardless of whether PCI is planned, includes ASA, thienopyridine and an anticoagulant (6).

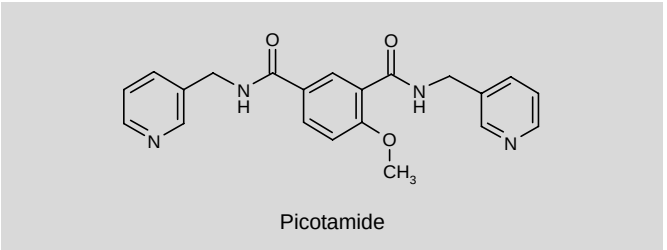
There is not yet significant evidence to support ASA use in other disease states such as heart failure and peripheral vascular disease (PVD), although research is ongoing and there is some debate surrounding these issues. The Anti-Thrombotic Trialists Collaboration (ATTC) meta-analysis demonstrated that ASA does not significantly benefit patients with PVD (5). The same meta-analysis examined ASA use in heart failure patients and showed significant benefits compared to placebo. Other studies, such as WATCH and WASH, gave conflicting outcomes, concluding that ASA use in heart failure patients may increase negative outcomes. Few trials evaluating ASA use in patients diagnosed with heart failure or PVD have been published, and those that have offer conflicting opinions on the subject. Furthermore, many of these studies were underpowered and their methods were insufficient, making it difficult to offer a definitive recommendation regarding ASA use in these disease states.

The topic of "aspirin resistance" has long been of interest due, in part, to the risks involved with suboptimal antiplatelet therapy and also due to a lack of consistent data regarding intersubject variability in the individual response to ASA. The fact that a single definition for this phenomenon has not been agreed upon by experts in the field compounds this issue. The most accurate definition proposed for this phenomenon, without imposing theories about the mechanism behind it, is "the failure of aspirin to inhibit TXA_2 production" (3). Perhaps a more appropriate term for what is commonly referred to as "aspirin resistance" would be "aspirin nonresponsiveness", as this definition correlates with the direct ability or inability of ASA to inhibit thromboxane to affect platelet function. In 2002, Eikelboom et al. displayed an increased risk of cardiovascular complications in ASA-nonresponsive patients (7). While the correlation between ASA nonresponsiveness and cardiovascular risk is not unexpected, the fact that this study, as well as many others on the subject, did not evaluate patient compliance makes it impossible to say for sure that ASA-nonresponsive patients are not simply nonadherent to their ASA therapy. Also, the influence of concomitant therapy and possible drug interactions on ASA effectiveness have not been addressed in a manner satisfactory to the authors of this review. Thus, drug compliance and drug interaction data are characteristics that must be evaluated before any conclusion on the subject is generated.

Nonetheless, ASA remains the benchmark in antiplatelet therapy; however, due to its limitations, the growing incidence of cardiovascular disease and the need for alternate therapies, new inhibitors of TXA_2 are being studied. While ASA acts by inhibiting the synthesis of TXA_2, blocking the receptor at which TXA_2 acts represents another possible mechanism for platelet inhibition. Several compounds have been studied for potential use as antiplatelet agents via inhibition of the TXA_2/PGH_2 (TP) receptor, although, many of these drugs have not made it far in development due to concerns with safety and efficacy (8). **Terutroban sodium** is one such drug that is still being considered. Terutroban has been demonstrated ex vivo to provide long-acting, dose-related inhibition of platelet aggregation and has been shown to be more effective than ASA and at least as effective as clopidogrel for inhibition of aggregation ex vivo (8-10).



Terutroban sodium

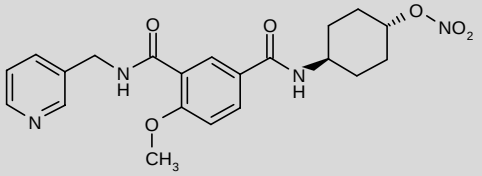


Picotamide

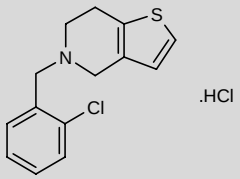
Some compounds block the TP receptor but also inhibit TXA_2 by other mechanisms. **Picotamide** is one such compound that inhibits platelet aggregation as a TP receptor antagonist but which also inhibits TXA_2 synthase without interfering with PGI_2 production (11). Picotamide may also have other antiaggregatory properties that are unrelated to TXA_2, such as the inhibition of serotonin-induced aggregation (12).

The ADEP trial examined the use of picotamide in patients with peripheral arterial disease (PAD), although no compelling evidence was found for its use (11, 13). A substudy of the ADEP trial involving claudicant diabetic patients, however, showed that in this population picotamide can effectively prevent vascular complications, with a 45.2% risk reduction of combined major and minor events observed compared to placebo (11, 13, 14). This inspired the DAVID trial, which compared the effects of picotamide and ASA in diabetic patients with PAD. Patients receiving picotamide displayed a 45% risk reduction of overall mortality versus those taking ASA and also showed a lower incidence of gastrointestinal bleeding. The combined incidence of death and major cardiovascular events, however, was not significantly different between the two groups (15). There is dispute over whether there is a place in therapy for picotamide and more studies are needed to further evaluate the efficacy and limits of use of this compound.

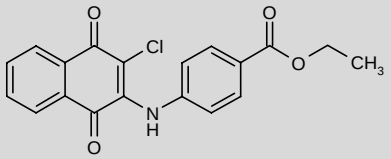
2NTX-99 is a compound synthesized by structurally modifying picotamide in order to add a nitric oxide (NO) donor moiety, thereby possessing three targets for platelet inhibition (16). 2NTX-99 inhibits TXA_2 synthesis, increases PGI_2 synthesis and also supplies exogenous NO, which inhibits the metabolism of cAMP; however, this compound has not been demonstrated to act as a TP receptor antagonist (16). 2NTX-99 has been shown to be an effective platelet inhibitor in animal models, but further development was recently suspended (17).



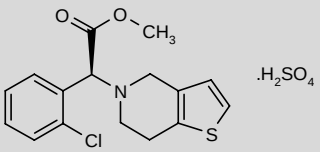
2NTX-99



Ticlopidine HCl



NQ-12



Clopidogrel sulfate

NQ-12 is another compound under investigation for potential antiplatelet properties. NQ-12 has been demonstrated to selectively inhibit TXA_2 synthase without affecting COX, blocking the formation of TXA_2, but not that of PGD_2. NQ-12 may also antagonize TP receptors, although further research needs to be performed to gain a better understanding of the antiplatelet properties of this compound (18).

$P2Y_{12}$ RECEPTOR ANTAGONISTS

Adensosine diphosphate (ADP) plays an important role in promoting and stabilizing platelet aggregation (19, 20). Upon platelet activation, ADP is released from storage granules. ADP then stimulates a number of receptors, including $P2Y_1$ and $P2Y_{12}$ (21). In order for platelets to undergo sustained aggregation due to ADP, both of these receptors must be activated (6, 22-24). The interaction between ADP and the $P2Y_{12}$ receptor contributes to the activation of GPIIb/IIIa receptors, the release of granule contents and the amplification of aggregation (19, 20). Thus, $P2Y_{12}$ receptor antagonism offers dramatic platelet inhibition regardless of the stimulus (8).

Thienopyridines are a class of drugs used to produce antiplatelet effects through specific ADP receptor inhibition. The thienopyridines currently available are all prodrugs requiring bioactivation in the liver by the cytochrome P450 3A4 enzyme. The active metabolites of these drugs then exert their antiaggregatory effects by binding irreversibly to the $P2Y_{12}$ receptor (25, 26). They are commonly used clinically in combination with ASA as part of a dual antiplatelet regimen in patients with ACS (27). **Ticlopidine**, a first-generation thienopyridine was used for its antiplatelet effects before its mechanism of action was determined (20). It may even be said that this drug opened the door to platelet inhibition via specific $P2Y_{12}$ receptor antagonism.

Ticlopidine has been studied for its usefulness in preventing vascular incidents in patients at risk (21). It has been shown to reduce the risk of subsequent events after thromboembolic stroke (28, 29), and also when used in combination with ASA to provide an additive reduction in the risk of recurrent stroke and all-cause mortality following a minor stroke or transient ischemic attack (TIA) (28, 30). Ticlopidine has also been shown to enhance the antiplatelet effects of GPIIb/IIIa inhibitors (28). In the setting of unstable angina, the use of ticlopidine monotherapy has been suggested to be as effective as ASA (28, 31, 32). Ticlopidine has been demonstrated to be effective in patients with PAD, improving pain-free and maximum walking distances in these patients (28, 33, 34), reducing the need for vascular surgery (28, 34), reducing reocclusion after thromboendarterectomy and significantly improving long-term patency of peripheral saphenous vein grafts (28, 35, 36), as well as reducing the high cardiac morbidity in these patients (28, 37, 38). The STIMS trial, which investigated ticlopidine versus placebo in claudicant patients, demonstrated a significant decrease in the risk of fatal vascular events with ticlopidine, and a 41% reduction in the risk of combined vascular morbidity and mortality in those patients that tolerated the drug (38, 39). The combination of ticlopidine and aspirin has been studied extensively in patients undergoing PCI (40-43). While the addition of ticlopidine to aspirin may have shown some benefit in certain patients, the significance of this benefit has been debated (5, 43) and is further clouded by certain drawbacks to the clinical use of ticlopidine.

As many as 20% of patients will not tolerate ticlopidine (38, 39). Skin rash is a common adverse reaction with ticlopidine and diarrhea, nausea and vomiting have been reported to occur in up to 30-50% of patients (28, 44). More seriously, the use of ticlopidine is also limited by a not insignificant incidence of life-threatening side effects including neutropenia (28, 29, 45), bone marrow aplasia and thrombotic thrombocytopenic purpura (28, 46-48). Furthermore, some of the pharmacokinetic and pharmacodynamic properties of ticlopidine also limit its usefulness. The antiaggregatory effect of ticlopidine is not seen until 24-48 h after administration, with the maximal effect occurring 3-5 days after administration. Also, return to baseline values of platelet aggregation has been reported to take up to 4-10 days, with significant antiplatelet activity persisting for more than 72 h after stopping the drug (44).

Due to the drawbacks of ticlopidine, its use has largely been replaced with that of **clopidogrel**, a second-generation thienopyridine (3, 46). While clopidogrel and ticlopidine do not share the same active metabolite, they are similar in that they both require bioacti-

vation and both are inactive in vitro (26). Clopidogrel has proven to be as effective an antiplatelet agent and much safer than ticlopidine, with a lower incidence of serious side effects (6, 49). Clopidogrel also offers a solution to another drawback of ticlopidine. While ticlopidine requires three repeated oral doses, inhibition of platelet aggregation can be observed approximately 2 h after a single i.v. or oral loading dose of clopidogrel (43, 50).

Clopidogrel has been shown to be clinically effective in various settings, and its combination with ASA has become the standard of care for the prevention of stent thrombosis (51). The CAPRIE trial showed a small but significant benefit for clopidogrel over ASA in reducing the risk of ischemic stroke, MI or vascular death in patients with PAD, recent ischemic stroke or MI (52). Whether or not this benefit justifies using clopidogrel over ASA, at a much higher cost, is up for debate, as ASA remains a valid option and is very inexpensive. A secondary analysis from CAPRIE, however, did show that the benefit of clopidogrel was amplified in certain high-risk subgroups of patients. These included patients with a history of prior coronary revascularization, patients receiving concomitant lipid-lowering therapy, diabetic patients and those with a remote prior history of ischemic events (5, 43, 53, 54). The use of clopidogrel in these patients may be justified. No significant differences were seen between clopidogrel and ASA, however, in the prevention of all-cause death, combined stroke, MI and all-cause death, vascular death or combined ischemic stroke, MI, amputation or vascular death (52). In patients with MI and atherothrombotic stroke, the CAPRIE trial showed an insignificant increase and an insignificant decrease in the risk of secondary events following treatment with clopidogrel, respectively (28, 52). Patients with PAD, however, showed a significant benefit from clopidogrel over ASA in reducing the risk for cardiovascular events (52).

When clopidogrel is used in combination with ASA additive antiplatelet effects may be observed. The benefit of this combination when compared to ASA monotherapy, however, may differ among clinical scenarios and it is difficult to offer a general statement on the use of the combination (51). The CURE trial showed that the addition of clopidogrel to standard therapy that included ASA in patients with unstable angina and non-Q wave MI led to a 20% reduced risk of combined stroke, MI or cardiovascular death (43). In patients undergoing PCI, the PCI-CURE study demonstrated that combination therapy with clopidogrel and ASA is effective in reducing cardiovascular death and MI, and this has become the standard of practice (51, 55). The COMMIT trial evaluated the use of clopidogrel and ASA combination therapy in MI and showed that the addition of clopidogrel to ASA was beneficial in further reducing mortality and the incidence of major vascular events. The results of the CHARISMA study, however, suggest that combination therapy with clopidogrel and ASA is associated with an increased risk of bleeding, which can outweigh the benefits of the regimen. Specifically, it has been concluded that a true benefit to using combination therapy over ASA alone is only seen in acute symptomatic patients and not in stable patients. The MATCH trial, which evaluated the combination in patients with cerebrovascular disease, showed no greater reduction in the occurrence of vascular events with combination therapy than with ASA alone; however, an increased risk of bleeding was observed (51). It appears that in order to accurately evaluate whether the addition of clopidogrel to ASA is justified, the clinical setting must first be assessed.

While there may be some controversy surrounding the appropriate use of clopidogrel in addition to or in place of ASA, the second-generation thienopyridine has certainly acquired a place in therapy, as it has proven itself to provide antiplatelet effects while avoiding the serious side effects of its predecessor; however, although clopidogrel may have eliminated many of the problems seen with ticlopidine while preserving its clinical usefulness, it is not without problems of its own. Like ticlopidine, clopidogrel is an irreversible antagonist of the $P2Y_{12}$ receptor, and thus, clopidogrel retains the problem of a long return to baseline aggregation after drug discontinuation (20). This is problematic when a patient on this drug requires emergency surgery, as the persisting platelet inhibition can increase the risk for serious bleeding during surgery. The current American College of Cardiology/American Heart Association guidelines recommend, and recent studies support, waiting 5 days after stopping the drug before performing coronary artery bypass graft (CABG) (56-58). Evidence-based justification of when to use ASA plus clopidogrel versus ASA alone has been recently reviewed (59).

Aside from this drawback, like ASA, a variable interpatient response to clopidogrel has been observed. Recent ex vivo studies have suggested that the standard loading and maintenance doses given for patients undergoing PCI do not provide adequate inhibition of ADP-induced aggregation in some patients (60-62). While it is accepted that there is some variability in the individual patient response to clopidogrel, and that inadequate platelet inhibition has a negative effect on clinical outcome (60, 63), there are many theories as to the mechanism behind this variability. Possible explanations that have been proposed include genetic polymorphisms of CYP3A4, accelerated platelet turnover, reduced CYP3A4 activity, increased ADP exposure, upregulation of the $P2Y_{12}$ pathway, upregulation of the $P2Y_1$ pathway, upregulation of P2Y-independent pathways such as collagen, epinephrine, TXA_2 and thrombin pathways, poor compliance, inadequate dosing, poor absorption and drug interactions involving CYP3A4. Also, many disease states such as ACS, diabetes and elevated body mass index can increase platelet reactivity (63). It should be noted that the results of the CAPRIE trial showed a variability in response to clopidogrel across different subgroups of patients with different underlying disease states, prior events and health risks (52). Convincing evidence has been offered supporting many of these theories and it is quite possible that a number of these mechanisms are involved in determining the response of an individual patient to clopidogrel (63).

In reaction to this interpatient variability in clopidogrel response, studies have been performed evaluating the effect of using loading and maintenance doses exceeding the approved doses. One study has demonstrated that a daily maintenance dose of 150 mg, which is double the standard dose, may provide enhanced platelet inhibition in patients with type 2 diabetes and coronary artery disease who are also taking low-dose ASA (64). This effect needs to be further investigated, however, as it may not extend into the general patient population. A loading dose of 600 mg has been demonstrated to reduce the proportion of nonresponsive patients early in the treatment phase (62), although it has also been demonstrated that patients receiving this higher loading dose experience similar levels of platelet inhibition to those receiving the standard loading dose of 300 mg after 48 h of regular maintenance therapy (65, 66). This agrees with the suggestion that higher loading doses result in faster onset of effects without achieving greater platelet inhibition (6).

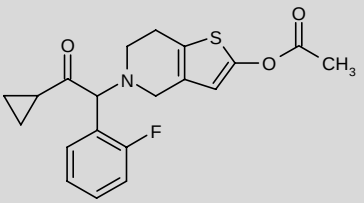
Perhaps the answer to the drawbacks of using clopidogrel can best be found not by giving higher doses, but by developing new antiplatelet drugs targeting the $P2Y_{12}$ receptor. Many are taking this approach and multiple new drugs targeting this receptor are currently in development. The goal of these therapies is to provide potent platelet inhibition with rapidly reversible effects, thus overcoming the two main drawbacks of clopidogrel (20).

Prasugrel is a third-generation oral thienopyridine and, like the other two drugs in this class, it requires bioactivation in the liver (20). Prasugrel differs from clopidogrel, however, in that it is metabolized to its active form in a single step, providing it with a faster onset of action (67-69). Within an hour of administration, prasugrel achieves approximately 70% platelet aggregation inhibition via selective and irreversible blockade of the $P2Y_{12}$ receptor (20). Prasugrel has been demonstrated to produce dose-related antiaggregatory effects and in rat models it has been shown to be approximately 10 times as potent as clopidogrel. The increased potency of prasugrel has been confirmed in human patients with CAD (20, 70). Prasugrel has also been shown to provide more consistent levels of platelet inhibition with less variability than clopidogrel (67). While it is a faster-acting and more potent inhibitor of platelet aggregation, prasugrel is similar to clopidogrel in that its effects have been shown to last 72 h after administration (20) and it may take up to 5 days or longer, depending on the dose, for baseline platelet function to return (27).

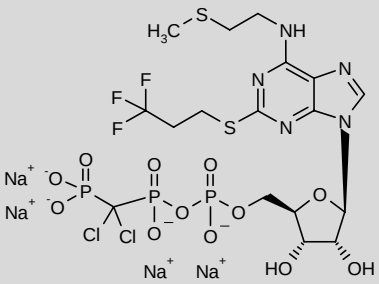
In the TRITON-TIMI-38 trial, which compared prasugrel and clopidogrel in patients with ACS undergoing PCI, prasugrel was shown to provide a significant benefit over clopidogrel in reducing the combined incidence of death, MI and stroke at 12 months, as well as the individual rates of MI, urgent target vessel revascularization and stent thrombosis (20, 71). The combination of prasugrel and ASA has also been shown to provide greater inhibition of platelet aggregation than the combination of clopidogrel and ASA (27, 68).

Wiviott et al. examined the effects of prasugrel or clopidogrel with concurrent ASA in patients with ACS undergoing planned PCI. Prasugrel was shown to have a significantly superior effect to that of clopidogrel in reducing the composite incidence of death from cardiovascular causes, nonfatal MI and nonfatal stroke. Despite its greater efficacy, prasugrel was also associated with a greater risk of fatal and nonfatal major bleeding (71). A similar association between prasugrel and a higher incidence of major bleeding was seen in the TRITON-TIMI-38 trial (20, 71). With the exception of this concerning increased risk of bleeding, the nonhemorrhagic safety profile of prasugrel is similar to that of clopidogrel (20, 27, 71). Nonetheless, the increased risk of bleeding associated with prasugrel raises the question of whether more potent antiplatelet effects will be overshadowed by an increased risk of bleeding.

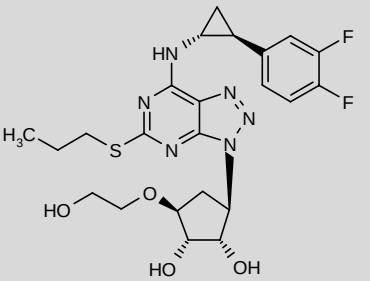
Cangrelor is a selective, competitive and reversible $P2Y_{12}$ antagonist that is administered by i.v. infusion (20, 72, 73). It belongs to a novel class of compounds known as purinoceptor modulators and is derived by modulation of the chemical structure of adenosine triphosphate (ATP), which is a natural antagonist of the $P2Y_{12}$ receptor, although undesirable for therapeutic use (6). Cangrelor does not need to undergo metabolism to become active. It exhibits more potent antiplatelet activity than clopidogrel and offers rapid onset and dose-dependent effects, which can be rapidly reversed. Steady-state levels of platelet inhibition have been observed within 30 min



Prasugrel



Cangrelor tetrasodium



Ticagrelor

of infusion in healthy volunteers (6, 74). The clinical half-life of cangrelor is between 3 and 5 min and its effects can be reversed in approximately 20 min without any rebound increase in thrombosis (6, 20, 73). This may be advantageous for patients who need to achieve rapid platelet inhibition in order to undergo PCI, and also to reverse platelet inhibition rapidly if urgent surgery is required (20).

Cangrelor has been shown to compare favorably with abciximab in patients undergoing PCI from both clinical and safety standpoints (20, 73). Phase II studies have demonstrated the safety and tolerability of cangrelor when used in combination with ASA and anticoagulants in patients with ACS. Research has also been undertaken to evaluate the best way to switch patients from cangrelor to clopidogrel, and it has been suggested that clopidogrel administration should begin upon termination of the cangrelor infusion (75). Two phase III trials investigating cangrelor are currently ongoing (20, 63).

Ticagrelor, also known as AZD-6140, is the first oral, reversible $P2Y_{12}$ receptor antagonist. It is nonthienopyridine belonging to a drug class known as the cyclopentyltriazolopyrimidines (20). Ticagrelor directly and selectively inhibits the $P2Y_{12}$ receptor without the need for hepatic conversion (20, 72) and does not have any sig-

nificant affinity for other P2 receptors (60, 72). Although it is active without conversion, ticagrelor produces one active metabolite, AR-C124910XX, which acts as a $P2Y_{12}$ receptor antagonist with potency equivalent to that of the parent drug. AR-C124910XX has been found to be present in the blood at a third of the concentration of ticagrelor and may be responsible for some of its antiplatelet effects (60, 76).

Ticagrelor has been shown to produce superior inhibition of ADP-induced platelet inhibition compared with clopidogrel and offers less variability in response (20, 60, 65, 76). Even without a loading dose, ticagrelor has an onset of action within 2 h and has been shown to achieve approximately 95% inhibition of platelet aggregation within 2-4 h. The half-life of ticagrelor is approximately 12 h, necessitating twice-daily administration; however, this shorter half-life combined with its reversible receptor antagonism is also responsible for a shorter time for drug offset after discontinuation (20). This characteristic is beneficial when rapid reversal of antiplatelet activity is desired, such as in the setting of emergency surgery.

The DISPERSE-2 trial showed ticagrelor to be superior to clopidogrel in decreasing the occurrence of subsequent MI in patients with non-S-T-segment elevation ACS also receiving ASA; however, there were no significant differences between the groups in the occurrence of other clinical endpoints. A similar incidence of bleeding was seen between the two groups, although higher rates of dyspnea, hypotension and nausea were observed with ticagrelor compared to clopidogrel (20, 56, 60). Ticagrelor is currently involved in an ongoing phase III trial comparing its effects in the clinical setting of ACS and PCI with those of clopidogrel (20, 60).

PHOSPHODIESTERASE INHIBITORS

Antiplatelet effects can be derived by inhibiting phosphodiesterase (PDE), an intracellular enzyme responsible for the degradation of various forms of cyclic AMP (cAMP) and cyclic GMP (cGMP) (2). An increase in the concentration of intraplatelet cAMP in turn inhibits the mobilization of free calcium, thus inhibiting platelet activation (4). Drugs utilizing this mechanism are not commonly used as monotherapy, as other mechanisms of platelet function are left unregulated.

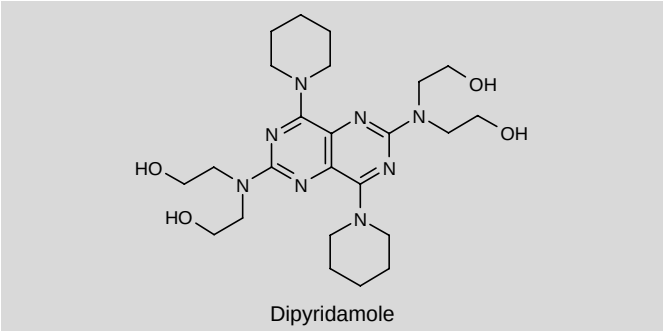
Dipyridamole is a pyrimidopyridine derivative with antiplatelet and vasodilating properties due to an increase in intracellular cAMP. The exact mechanism by which dipyridamole exerts this effect, however, is unknown, although several actions have been observed in vitro that may be responsible. These include inhibition of platelet PDE, direct stimulation of prostacyclin release from endothelial cells and inhibition of adenosine uptake by platelets, although none of these actions have been demonstrated in vivo at doses used in clinical practice (4).

The ATTC meta-analysis showed no significant difference between the effects of dipyridamole alone and ASA alone on serious vascular events, including stroke, MI and vascular death. In fact, the meta-analysis did not dismiss the possibility that dipyridamole is less effective than ASA (4, 5). Similar results were seen in the European Stroke Prevention Study 2 (ESPS-2) (77, 78). This suggests that dipyridamole alone should generally not be considered an alternative to ASA. One analysis used the results of ESPS-2 and CAPRIE to create an indirect comparison between sustained-release dipyridamole and clopidogrel. Clopidogrel was shown to be more beneficial with regard to clinical events compared to dipyridamole; however, these findings were not significant (77).

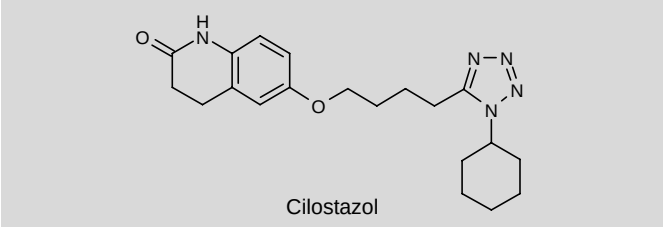
While dipyridamole monotherapy has not been shown to be clinically effective, the results of ESPS-2 suggested that the addition of sustained-release dipyridamole to ASA may provide added protection against stroke, although no benefit was seen with regards to other vascular endpoints when dipyridamole was added to ASA therapy (77, 78). Nonetheless, the observed efficacy of combined sustained-release dipyridamole and ASA in the secondary prevention of stroke has led to the introduction of a combined dosage form (79).

Cilostazol, a quinolinone, is a potent antiaggregatory agent that acts by selective inhibition of PDE3, which is the most abundant PDE isoform present in platelets (79, 80). Cilostazol has been demonstrated to provide significant benefit in patients suffering from intermittent claudication (53, 79, 81, 82). It has also been shown to be useful in preventing restenosis after balloon angioplasty or stent implantation, having effects comparable to ASA or ticlopidine (80, 83-85). Trials investigating the combined use of cilostazol and ASA after coronary artery stenting have shown no substantial differences in the benefits observed compared with those observed with a combination of ASA and ticlopidine. This suggests that, in this setting, cilostazol may be as useful as ticlopidine (79, 83, 85).

Cilostazol has recently been studied as part of a triple therapy regimen with ASA and either clopidogrel or ticlopidine for the prevention of in-stent neointimal hyperplasia, as measured by quantitative coronary angiography and intravascular ultrasound. The addition of cilostazol to double therapy with ASA and either clopidogrel or ticlopidine was shown to provide a significantly greater reduction in neointimal volume within the stented segment, leading to a larger luminal volume compared to double therapy with ASA and a thienopyridine, although no significant difference was seen between the two groups regarding the incidence of clinical events (80).



Dipyridamole



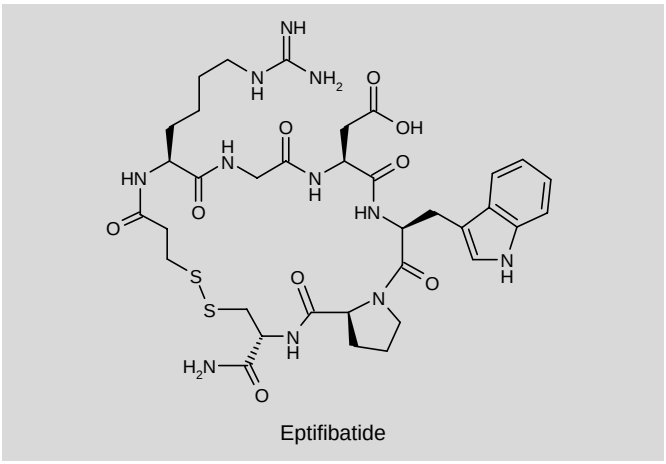
Cilostazol

Although they have been used as antiplatelet agents for some time, the clinical usefulness of PDE inhibitors is debatable. With the advent of evidence-based medicine, the use of these drugs has declined over the years, except in a small subpopulation of patients. Even in these settings, these drugs generally do not show much benefit when used as monotherapy and are combined with ASA. Also, given the efficacy and low cost of ASA monotherapy, the overall utilization of PDE inhibitors has suffered and there have not been many significant advances within this class of antiplatelet agents.

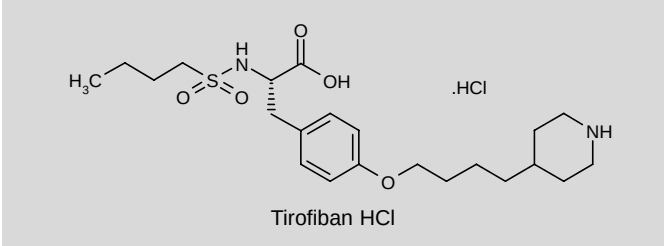
GPIIb/IIIa ANTAGONISTS

Even with successful thromboxane and ADP inhibition, platelets can still be activated by other mechanisms. This has led to the development of an entirely separate class of antiplatelet drugs known as glycoprotein IIb/IIIa (GPIIb/IIIa) receptor antagonists. During the platelet activation process, the surface of the platelet transforms its shape to expose the GPIIb/IIIa receptors. These receptors bind to fibrinogen and von Willebrand factor, resulting in clot formation and clot adherence, respectively (86). GPIIb/IIIa-facilitated binding of fibrinogen to platelets is responsible for securing aggregated platelets to one another. Thus, blocking these receptors prevents platelet aggregation regardless of the precipitant (87, 88). GPIIb/IIIa inhibitors have proven useful in reducing the risk of periprocedural MI and urgent target vessel revascularization during catheterization and have claimed a place in therapy for these indications (89).

As of today, there are three GPIIb/IIIa inhibitors on the market, which can be categorized into two types: small nonpeptide molecules and a large monoclonal antibody (mAb). The small-molecule inhibitors **eptifibatide** and **tirofiban** exhibit reversible binding to the GPIIb/IIIa receptor, whereas the large mAb **abciximab** demonstrates irreversible binding. It has been postulated that additional binding of abciximab to the $\alpha_v\beta_3$ and $\alpha_M\beta_2$ integrin receptors helps to reduce inflammation in the vessels (89, 90). These differences have been responsible for initiating the debate over the issue of superiority between the two subclasses of GPIIb/IIIa inhibitors. The TARGET trial showed significantly better short-term efficacy and safety for abciximab compared with tirofiban (89, 91).



Eptifibatide



Tirofiban HCl

Due to the fact that GPIIb/IIIa receptor binding is the final common pathway in platelet aggregation, its inhibition has proven to be very effective in preventing complications in patients undergoing PCI procedures. An overall benefit can be seen with the use of these drugs; however, increased bleeding continues to be a major concern among physicians, restricting the use of GPIIb/IIIa inhibitors mainly to high-risk patients (89). Because of the known benefits of using GPIIb/IIIa inhibitors in patients with ACS and undergoing PCI, research is being undertaken to investigate the expansion of their use into other disease states. PAD is a painful ischemic condition that can lead to endovascular procedures, placing the patient at risk for clots. Limited options have forced physicians to use high-risk thrombolytics to dissolve these clots. The small clinical trial RELAX and that of the Tübingen group have demonstrated moderate advantages in using low-dose thrombolytics in combination with GPIIb/IIIa inhibitors (90).

Currently there is debate regarding the optimal time for initiation of GPIIb/IIIa inhibition therapy. During PCI procedures, GPIIb/IIIa inhibitors may be given upstream (> 1 h prior to procedure) or periprocedurally (during procedure) (92). The early ADMIRAL study found only marginal benefits when initiating therapy upstream, but these observations were not statistically significant (93). More recently, conclusions drawn from the ACUITY trial have suggested that upstream administration shows a minor reduction in mortality, as well as reduced ischemia, at the expense of increased bleeding when compared to periprocedural administration (94). Investigators continue to debate whether the benefits shown with upstream administration outweigh the heightened risk of overall bleeding. Recently, Hernandez et al. have demonstrated that older individuals are at an increased risk for bleeding compared to the populations studied in other trials, suggesting that extra caution be taken if upstream administration is to be considered in the elderly (95). Currently, the time of administration for GPIIb/IIIa inhibitors is left largely to the preference of individual institutions, although the recently published 2007 ACC/AHA guidelines offer updated recommendations regarding this issue. In summary, these guidelines recommend considering the upstream use of eptifibatide or tirofiban in high-risk patients undergoing invasive therapy, while conserving abciximab for patients receiving periprocedural GPIIb/IIIa inhibitors (96).

Of further concern is the observed association between GPIIb/IIIa receptor antagonists and drug-induced thrombocytopenia (DITP), a potentially life-threatening condition leading to an increased risk of bleeding and also a paradoxical increased risk of clot formation. While DITP is associated with all GPIIb/IIIa inhibitors, it is more commonly seen with abciximab, with a reported incidence of 1% seen upon first drug exposure and up to 4% seen upon second drug exposures (97). Thrombocytopenia seen with first drug exposure is rare and defies traditional explanations of immune antibody-mediated thrombocytopenia. Recent studies have shed light on the mecha-

nism behind DITP, explaining that delayed DITP can be caused by newly formed antibodies or weak preexisting antibodies stimulated to a high titer by GPIIb/IIIa exposure (7). Seiffort et al. have demonstrated that by prescreening for these antibodies, the incidence of GPIIb/IIIa inhibitor-induced DITP can be reduced by tenfold (98).

The current GPIIb/IIIa inhibitors require invasive administration and are relatively short-acting. This has prompted the search for an orally active GPIIb/IIIa inhibitor. **Orbofiban**, **xemilofiban**, **lotrafiban** and **sibrafiban** are four oral GPIIb/IIIa inhibitors that have been tested in phase III clinical trials. Unfortunately, these compounds have not progressed through clinical trials due to high rates of thrombocytopenia, erratic pharmacokinetics, reported prothrombotic activity and increased risk for mortality (99).

THROMBIN INHIBITORS

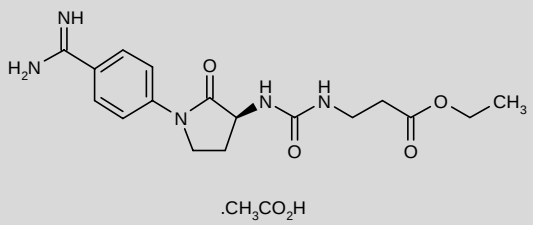
While they are not often immediately thought of as antiplatelet drugs, direct thrombin inhibitors (DTIs) do exert significant platelet-inhibitory effects. The number of drugs in this class is limited but there is much research in this area being undertaken to expand the future use of this mechanism of platelet inhibition. DTIs as a class are traditionally used as anticoagulant medications, but also provide an additional option for stopping platelet activation. DTIs can decrease platelet-induced blockages by two unique mechanisms: by reducing the thrombin-mediated activity of platelets and by inactivating circulating and clot-formed thrombin molecules (100).

The DTIs most commonly used, argatroban, lepirudin and bivalirudin, are all derived from hirudin. These agents have proven effective in the settings of ACS procedures and as alternative to heparin in patients with a history of heparin-induced thrombocytopenia (HIT). It is here that DTIs have claimed a place in therapy (101).

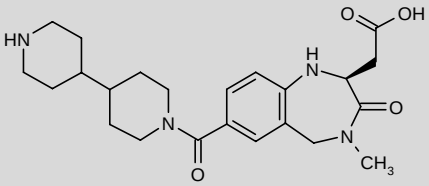
Traditionally, heparin has been used to achieve desired anticoagulant affects; however, due to its erratic pharmacokinetics, unfavorable effects on the kidney, thrombocytopenic events and associated bleeding risks, studies such as REPLACE-2 and ACUITY have investigated the use of DTIs and have demonstrated noninferior efficacy and an improved safety profile for bivalirudin compared to heparin (102). These studies have helped to make DTIs a standard in therapy and it is important to continue to explore and potentially expand the use of DTIs for other indications with similar pathologies, such as stroke prevention and atrial fibrillation. The SPORTIF trial has shown DTIs to be effective for stroke prevention and the treatment of atrial fibrillation. Other results of this study demonstrate a safety profile that may prove superior to that of anticoagulants, which could possibly lead to changes in standard practice in the future (103, 104).

The prospect of developing a stable oral DTI to be used in patients with cardiovascular and clotting disorders has ignited recent excitements; however, this has proven to be a difficult task. **Ximelagatran** is an oral DTI that has been extensively studied, producing favorable results that support its usefulness. The THRIVE study showed ximelagatran to be noninferior to combination treatment with enoxaparin and warfarin for venous thromboembolism. Furthermore, SPORTIF supports the theory that ximelagatran may be associated with a reduced incidence of bleeding compared to traditional therapy. Due to an associated increase in liver enzymes and 3 reported deaths due to liver injury after long-term ximelagatran use, the drug failed to receive FDA approval in the U.S.

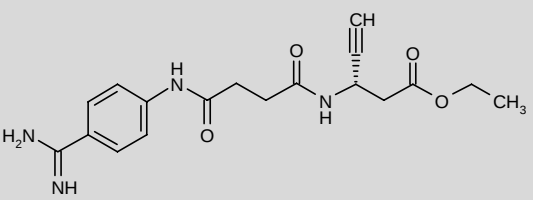
Dabigatran, another novel oral DTI, has remained a promising agent throughout early evaluation. The RENOVATE study has shown dabigatran to be noninferior to enoxaparin in preventing venous thromboembolism in patients with total hip replacement. Interestingly, this study showed a reduced number of liver complications in subjects receiving this oral DTI than those receiving enoxaparin (105). The PETRO study, however, did reveal a small percentage (0.9%) of patients receiving dabigatran to have elevated liver enzymes (106). The potential benefits that could be seen with a safe and effective oral DTI continue to fuel interest and further research in this area; however, judging from the FDA response to past developments, it may be some time before we see one of these drugs reach the market.



Orbofiban acetate

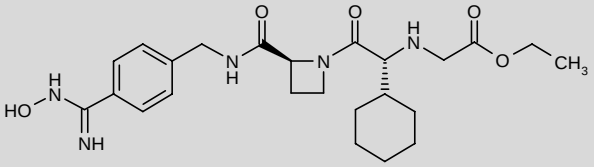


Lotrafiban

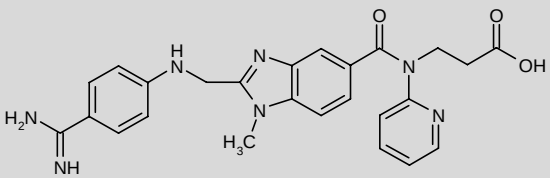


Xemilofiban

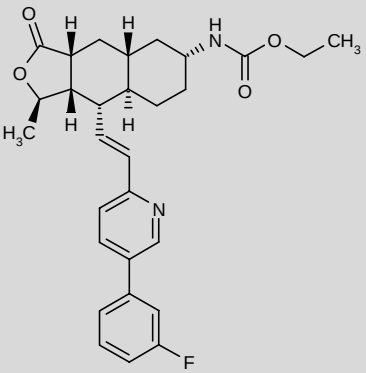
Sibrafiban



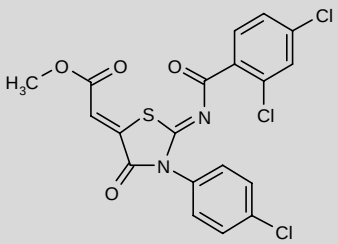
Ximelagatran



Dabigatran



Sch-530348



FR-171113

THROMBIN RECEPTOR ANTAGONISTS

Platelet thrombin receptors, termed protease-activated receptors (PARs), represent one promising target for the development of antiplatelet therapies. The discovery of a potent series of PAR1 antagonists based on the natural product himbacine has been described. Optimization of this series has led to the discovery of **Sch-530348**, a potent oral antiplatelet agent that is currently undergoing phase III clinical trials for ACS (unstable angina/NSTEMI) and secondary prevention of cardiovascular events in high-risk patients (107). Additionally, several other PAR1 antagonists are under preclinical development, such as **FR-171113** (108). This compound inhibits Ser-Phe-Leu-Leu-Arg-Asn-NH_2- (a synthetic PAR1 agonist peptide) or thrombin-induced aggregation of guinea pig platelets in a concentration-dependent manner. S.c. administration of FR-171113 (0.1-3.2 mg/kg) produced a dose-dependent inhibition of platelet aggregation ex vivo. The agent inhibits arterial thrombosis without a prolongation of thrombin time or coagulation time in the $FeCl_3$-induced carotid artery thrombosis model in guinea pigs at 1 mg/kg s.c. Furthermore, FR-171113 did not prolong bleeding time even at 32 mg/kg s.c., which is a much higher dose than that required for activity in the arterial thrombosis model. These observations suggest that FR-171113 or other PAR1 antagonists could have desirable antiplatelet effects associated with a wider therapeutic index (Table I).

COMBINATION OF ANTIPLATELET THERAPY AND THROMBOLYTIC OR ANTICOAGULANT THERAPIES

While platelets represent an important part of thrombus formation, other factors are equally important in the formation of thrombi. Thus, as platelet inhibition represents an effective option for reducing the complications due to hypercoaguable states in several clinical settings, drugs that target the different factors involved in coagulation and clot formation have also been used to provide clinical benefit. These include thrombolytic agents and anticoagulants. It follows that, in some settings, utilizing multiple approaches to manipulating hemostasis can increase clinical benefit.

Thrombolytics and antiplatelet agents

Fibrinolytic therapy is a form of thrombolysis that has demonstrated efficacy in disease states such as MI, stroke and PAD. Fibrinolytic therapy has been shown to reduce mortality in patients with STEMI through restoration of adequate coronary reperfusion (109). Unfortunately, a low proportion of patients treated with fibrinolytic monotherapy will achieve adequate reperfusion. This is most likely due to "fibrinolytic resistance" or increased platelet activation (110). In fact, in the late 1980s a monumental study was published by Fitzgerald et al. which showed increased thromboxane production in patients who were given streptokinase (111). This observed phenomenon fueled the development of trial designs, such as that used in the ISIS-2 study, to successfully demonstrate the superiority of combinations of ASA and fibrinolytics over fibrinolytic monotherapy (112). These results were an important milestone; however, the aforementioned high failure rate with fibrinolytics was also seen with this combination, with only 40-50% reaching adequate reperfusion, suggesting additional antiplatelet use (110).

As previously mentioned, GPIIb/IIIa inhibitors act on the final common pathway for platelet activation and aggregation, making them a logical choice for combination with fibrinolytic agents. This, along with the ability of GPIIb/IIIa inhibitors to aid in "de-thrombosis", has amplified interest in this combination. The Tübingen group, as well as Drescher et al., performed early research to demonstrate the potential benefits of combination of GPIIb/IIIa antagonists and fibrinolytics, such as the ability to lyse clots more efficiently and with lower rates of major bleeding. Because the small populations used in these studies limit the validity of the results, larger trials, such as

the RELAX and APART studies, were performed in order to determine the safety, efficacy and comparisons among combinations of fibrinolytics and GPIIb/IIIa inhibitors (90). These results were comparable to other pilot studies which describe fibrinolytic and GPIIb/IIIa inhibitor combinations as having modest efficacy with a slightly increased rate of overall bleeding (112).

The results observed using GPIIb/IIIa inhibitors in combination with thrombolytics have largely been disappointing, prompting further research on fibrinolytic combination therapy with other antiplatelet drugs. $P2Y_{12}$ receptor antagonists (e.g., ADP inhibitors) have enjoyed general success as antiplatelet drugs, which inspired investigation of the combination of these drugs with fibrinolytics. Sabetine et al. concluded that the combined use of ASA, clopidigrel and a fibrinolytic improves coronary arterial patency in patients with STEMI, without significantly increasing the risk of bleeding (112). The large CLARITY trial, which used a similar combination, demonstrated a lower rate of ischemic complications when compared to traditional therapy. The results from the previously mentioned trials were encouraging and were further validated when the results of the COMMIT trial suggested the benefit of decreased mortality with this type of combination (110). Despite the positive results of these trials, conclusions should be limited, as the study populations largely consisted of low-risk, nonelderly patients. To investigate the use of combinations with antiplatelet and fibrinolytic drugs in high-risk elderly patients, the ASSENT-3 and ASSENT-3 PLUS trials were initiated. A subset of the population in these high-risk patients was treated with a combination of a GPIIb/IIIa inhibitor and a fibrinolytic agent. Unfortunately, the results of these trials did not mirror those of the trials in low-risk, nonelderly populations. In fact, the combination therapy investigated appears to be less beneficial and to carry an increased risk of bleeding in this population (113).

Researchers have uncovered substantial proof that platelet activation plays a major role in the failure of thrombolytic therapy. Many trials have supported the benefits of utilizing combinations with fibrinolytic and antiplatelet therapies, although conflicting results and limited study designs make it difficult to offer a decisive conclusion. While this is so, the proven benefits of combination therapy with fibrinolytics and antiplatelet agents cannot be forgotten and will serve as templates for future trials.

Anticoagulant/antiplatelet combinations

Combinations of anticoagulants and antiplatelet agents have long been used due to the benefits in terms of morbidity and mortality for the treatment of cardiovascular complications. It is well recognized that thrombosis involves both the actions of the coagulation cascade and platelets. Therefore, concomitant anticoagulation and platelet inhibition stands to offer a more efficient method for lysing the clots and treating diseases associated with clotting. In fact, this combination is so effective that profound bleeding can occur due to a shift in the hemodynamic balance toward the inability to clot. Thus, this combination must be used with caution and its use may be prohibited in clinical settings.

Combinations of anticoagulants and antiplatelet agents are frequently used to treat patients presenting with ACS. In fact, the majority of subjects presenting with unstable angina, NSTEMI or STEMI will automatically be placed on some sort of anticoagulation, ASA and clopidogrel combination if the physician rules out the possibility of CABG (96).

Current interest in the area of anticoagulant/antiplatelet combinations involves the addition of a third antiplatelet agent to the established combination. The EPISTENT and ESPRIT trials have evaluated this practice in patients diagnosed with NSTEMI undergoing PCI with stent placement, finding that a combination of unfractionated heparin, a GPIIb/IIIa inhibitor, clopidogrel and ASA reduced ischemic complications at 30 days when compared to the traditional treatment (114). Similar beneficial results emerged from the PRISM-PLUS and PURSUIT trials, which demonstrated a lower rate of ischemic events with this combination when used during early angiography. The ACUITY trial demonstrated that GPIIb/IIIa inhibitors used in combination with anticoagulants provide various benefits (115).

It has been demonstrated that bivalirudin monotherapy is as effective as the combination and also is associated with less bleeding events. This suggests that, in certain clinical settings (low-risk patients), bivalirudin monotherapy is clinically sufficient. Furthermore, REPLACE-2 compared combinations of GPIIb/IIIa inhibitors with unfractionated heparin versus GPIIb/IIIa inhibitors combined with direct thrombin inhibitors. The results suggest that in low-risk patients greater safety is seen when using the combination including a thrombin inhibitor (114). Additional studies are ongoing.

The other investigated use for anticoagulant/antiplatelet combinations is for the secondary prevention of prothrombotic disease states such as stroke and MI. After an initial ischemic event, the literature suggests that the coagulation cascade is stimulated for several months (116). Evidence suggests that combination therapy using warfarin and ASA provides an overall reduction in ischemic events post-MI (117). This important finding, however, is at least partially offset by an associated increased risk of bleeding. Furthermore, the significance of the reduction in the incidence of ischemic events has been questioned, as some experts cannot associate clinical significance with many of the studies on this subject. The CHAMP, CAR and OASIS-2 studies also failed to find a significant benefit for the combination, while reporting an increased incidence of bleeding events (116). The conflicting nature of the available evidence correlates with the lack of conclusive guidelines on the use of anticoagulant/antiplatelet combinations. The decision, therefore, is left to be made by clinicians upon evaluation of the risk factors of individual patients. Many patients with a relatively low risk of bleeding receive anticoagulation and antiplatelet combinations to ensure maximal cardiovascular protection.

Despite drawbacks associated with specific combinations in specific settings, combination therapies using both anticoagulant and antiplatelet agents have largely been shown to improve clinical outcomes. Clinical trials continue to expand the use of anticoagulant/antiplatelet combinations in ACS. Positive results and further research may help to expand the use of this combination in other prothrombotic conditions such as atrial fibrillation and PAD.

CONCLUSIONS

Past antiplatelet therapy largely consisted of the use of ASA based on its known benefit on clinical outcomes. Subsequently, the specific effects of ASA on platelets were discovered, launching the idea of

platelet inhibition as a new therapeutic approach to cardiovascular disease. To this day, ASA remains the benchmark in platelet inhibition, although numerous compounds with various mechanisms of platelet inhibition have been investigated and several have made it into clinical use as antiplatelet agents.

As knowledge accumulated regarding cardiovascular disease states and the effect of platelet inhibition by ASA and subsequently developed agents, insight was gained into the workings of platelets. Various structural and functional characteristics of platelets lend themselves as targets for platelet inhibition and we now have many options available to achieve antiplatelet effects. However, as with any therapy, these options have their own drawbacks. This has encouraged the further development of antiplatelet agents in order to overcome the problems associated with previous options.

As mentioned above, ASA remains the benchmark against which these subsequent antiplatelet agents are evaluated, not only because it has been widely studied and proven to be effective, but also because it is widely available and very inexpensive. The desire to further improve clinical outcomes, as well as controversy surrounding the idea of a variable response to some antiplatelet agents such as ASA and clopidogrel, has fueled the search for new antiplatelet agents with various mechanisms of action.

While new antiplatelet agents are being developed, the tried and true compounds of the past continue to prove themselves and solidify their place in therapy. This has led to a general shift in the attitude taken toward developing antiplatelet therapies. New indications for existing compounds are continually being investigated, as are higher doses and different routes or schedules of administration. Furthermore, while in the past new compounds for potential use as antiplatelet drugs were investigated for their usefulness in place of ASA, today they are almost always evaluated for their effects in combination with ASA. This idea has also taken shape with continued vigorous investigation into the appropriate use of combination therapies based on platelet inhibition by various mechanisms and also of combinations of antiplatelet and thrombolytic or anticoagulant agents. The future of platelet inhibition as a field of study promises to be exciting as new compounds and new uses for existing agents continue to be investigated.

REFERENCES

1. Stevens, M.L. Fundamentals of Clinical Hematology. W.B. Saunders Company, Philadelphia, 1997.
2. Hambleton, J. Drugs Used in Disorders of Coagulation, in Basic & Clinical Pharmacology. B.G. Katzung (Ed.). McGraw-Hill, New York, 2004, 543-60.
3. Cattaneo, M. *Aspirin and clopidogrel: Efficacy, safety, and the issue of drug resistance.* Arterioscler Thromb Vasc Biol 2004, 24(11): 1980-7.
4. Sudlow, C. *What is the role of dipyridamole in long-term secondary prevention after an ischemic stroke or transient ischemic attack?* CMAJ 2005, 173(9): 1024-6.
5. Antithrombotic Trialists' Collaboration. *Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients.* BMJ 2002, 324(7329): 71-86.
6. Fugate, S.E., Cudd, L.A. *Cangrelor for treatment of coronary thrombosis.* Ann Pharmacother 2006, 40(5): 925-30.
7. Eikelboom, J.W., Hirsh, J., Weitz, J.I., Johnston, M., Yi, Q., Yusuf, S. *Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events.* Circulation 2002, 105(14): 1650-5.
8. Husted, S. *New developments in oral antiplatelet therapy.* Eur Heart J Suppl 2007, 9(Suppl. D): D20-7.
9. Gaussem, P., Reny, J.L., Thalamos, C. et al. *The specific thromboxane receptor antagonist S18886: Pharmacokinetic and pharmacodynamic studies.* J Thromb Haemost 2005, 3(7): 1437-45.
10. Osende, J.I., Shimbo, D., Fuster, V., Dubar, M., Badimon, J.J. *Antithrombotic effects of S 18886, a novel orally active thromboxane A2 receptor antagonist.* J Thromb Haemost 2004, 2(3): 492-8.
11. Celestini, A., Violi, F. *A review of picotamide in the reduction of cardiovascular events in diabetic patients.* Vasc Health Risk Manag 2007, 3(1): 93-8.
12. Vezza, R., Spina, D., Tallarida, R.J., Nathan, M., Page, C.P., Gresele, P. *Antivasoconstrictor and antiaggregatory activities of picotamide unrelated to thromboxane A2 antagonism.* Thromb Haemost 1997, 78(5): 1385-91.
13. Balsano, F., Violi, F. *Effect of picotamide on the clinical progression of peripheral vascular disease. A double-blind placebo-controlled study. The ADEP Group.* Circulation 1993, 87(5): 1563-9.
14. Milani, M., Longoni, A., Maderna, M. *Effects of picotamide, an antiplatelet agent, on cardiovascular, events in 438 claudicant patients with diabetes: A retrospective analysis of the ADEP study.* Br J Clin Pharmacol 1996, 42(6): 782-5.
15. Neri Serneri, G.G., Coccheri, S., Marubini, E. et al. *Picotamide, a combined inhibitor of thromboxane A2 synthase and receptor, reduces 2-year mortality in diabetics with peripheral arterial disease: The DAVID study.* Eur Heart J 2004, 25(20): 1845-52.
16. Buccellati, C., Sala, A., Rossoni, G. et al. *Pharmacological characterization of 2NTX-99 [4-methoxy-N1-(4-trans-nitrooxycyclohexyl)-N3-(3-pyridinylmethyl)-1,3-benzenedicarboxamide], a potential antiatherothrombotic agent with antithromboxane and nitric oxide donor activity in platelet and vascular preparations.* J Pharmacol Exp Ther 2006, 317(2): 830-7.
17. Nile Therapeutics, Inc. Pipeline. www.nilethera.com.
18. Jin, Y.R., Han, X.H., Lee, J.J. et al. *Antiplatelet effect of NQ12: A possible mechanism through the arachidonic acid cascade.* J Pharmacol Sci 2007, 105(2): 193-200.
19. Springthorpe, B., Bailey, A., Barton, P. et al. *From ATP to AZD6140: The discovery of an orally active reversible P2Y12 receptor antagonist for the prevention of thrombosis.* Bioorg Med Chem Lett 2007, 17(21): 6013-8.
20. Angiolillo, D.J. *ADP receptor antagonism: What's in the pipeline?* Am J Cardiovasc Drugs 2007, 7(6): 423-32.
21. Cattaneo, M. *Platelet P2 receptors: Old and new targets for antithrombotic drugs.* Expert Rev Cardiovasc Ther 2007, 5(1): 45-55.
22. Chattaraj, S.C. *Cangrelor AstraZeneca.* Curr Opin Investig Drugs 2001, 2(2): 250-5.
23. Kunapuli, S.P., Ding, Z., Dorsam, R.T., Kim, S., Murugappan, S., Quinton, T.M. *ADP receptors — Targets for developing antithrombotic agents.* Curr Pharm Des 2003, 9(28): 2303-16.
24. Storey, R.F. *The P2Y12 receptor as a therapeutic target in cardiovascular disease.* Platelets 2001, 12(4): 197-209.
25. Siller-Matula, J., Schrör, K., Wojta, J., Huber, K. *Thienopyridines in cardiovascular disease: focus on clopidogrel resistance.* Thromb Haemost 2007, 97(3): 385-93.

26. Savi, P., Pereillo, J.M., Uzabiaga, M.F. et al. *Identification and biological activity of the active metabolite of clopidogrel.* Thromb Haemost 2000, 84(5): 891-6.

27. Jakubowski, J.A., Payne, C.D., Weerakkody, G.J. et al. *Dose-dependent inhibition of human platelet aggregation by prasugrel and its interaction with aspirin in healthy subjects.* J Cardiovasc Pharmacol 2007, 49(3): 167-73.

28. Quinn, M.J., Fitzgerald, D.J. *Ticlopidine and clopidogrel.* Circulation 1999, 100(15): 1667-72.

29. Gent, M., Blakely, J.A., Easton, J.D. et al. *The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke.* Lancet 1989, 1(8649): 1215-20.

30. Hass, W.K., Easton, J.D., Adams, H.P. Jr. et al. *A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group.* N Engl J Med 1989, 321(8): 501-7.

31. Balsano, F., Rizzon, P., Violi, F. et al. *Antiplatelet treatment with ticlopidine in unstable angina. A controlled multicenter clinical trial. The Studio della Ticlopidina nell'Angina Instabile Group.* Circulation 1990, 82(1): 17-26.

32. *Collaborative overview of randomised trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration.* BMJ 1994, 308(6921): 81-106.

33. Balsano, F., Coccheri, S., Libretti, A. et al. *Ticlopidine in the treatment of intermittent claudication: A 21-month double-blind trial.* J Lab Clin Med 1989, 114(1): 84-91.

34. Bergqvist, D., Almgren, B., Dickinson, J.P. *Reduction of requirement for leg vascular surgery during long-term treatment of claudicant patients with ticlopidine: Results from the Swedish Ticlopidine Multicentre Study (STIMS).* Eur J Vasc Endovasc Surg 1995, 10(1): 69-76.

35. Becquemin, J.P. *Effect of ticlopidine on the long-term patency of saphenous-vein bypass grafts in the legs. Etude de la Ticlopidine apres Pontage Femoro-Poplite and the Association Universitaire de Recherche en Chirurgie.* N Engl J Med 1997, 337(24): 1726-31.

36. Castelli, P., Basellini, A., Agus, G.B. et al. *Thrombosis prevention with ticlopidine after femoropopliteal thromboendarterectomy.* Int Surg 1986, 71(4): 252-5.

37. Boissel, J.P., Peyrieux, J.C., Destors, J.M. *Is it possible to reduce the risk of cardiovascular events in subjects suffering from intermittent claudication of the lower limbs?* Thromb Haemost 1989, 62(2): 681-5.

38. Janzon, L., Bergqvist, G., Boberg, J. et al. *Prevention of myocardial infarction and stroke in patients with intermittent claudication; effects of ticlopidine. Results from STIMS, the Swedish Ticlopidine Multicentre Study.* J Intern Med 1990, 227(5): 301-8.

39. Janzon, L. *The STIMS trial: The ticlopidine experience and its clinical applications. Swedish Ticlopidine Multicenter Study.* Vasc Med 1996, 1(2): 141-3.

40. Leon, M.B., Baim, D.S., Popma, J.J. et al. *A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators.* N Engl J Med 1998, 339(23): 1665-71.

41. Bertrand, M.E., Legrand, V., Boland, J. et al. *Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The full anticoagulation versus aspirin and ticlopidine (FANTASTIC) study.* Circulation 1998, 98(16): 1597-603.

42. Urban, P., et al., *Randomized evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients: The multicenter aspirin and ticlopidine trial after intracoronary stenting (MATTIS).* Circulation 1998, 98(20): 2126-32.

43. Savi, P., Herbert, J.M. *Clopidogrel and ticlopidine: P2Y12 adenosine diphosphate-receptor antagonists for the prevention of atherothrombosis.* Semin Thromb Hemost 2005, 31(2): 174-83.

44. McTavish, D., Faulds, D., Goa, K.L. *Ticlopidine. An updated review of its pharmacology and therapeutic use in platelet-dependent disorders.* Drugs 1990, 40(2): 238-59.

45. Gill, S., Majumdar, S., Brown, N.E., Armstrong, P.W. *Ticlopidine-associated pancytopenia: Implications of an acetylsalicylic acid alternative.* Can J Cardiol 1997, 13(10): 909-13.

46. Bennett, C.L.,Weinberg, P.D., Rozenberg-Ben-Dror, K., Yarnold, P.R., Kwaan, H.C., Green, D. *Thrombotic thrombocytopenic purpura associated with ticlopidine. A review of 60 cases.* Ann Intern Med 1998, 128(7): 541-4.

47. Kupfer, Y., Tessler, S. *Ticlopidine and thrombotic thrombocytopenic purpura.* N Engl J Med 1997, 337(17): 1245.

48. Page, Y., Tardy, B., Zeni, F., Comtet, C., Terrana, R., Bertrand, J.C. *Thrombotic thrombocytopenic purpura related to ticlopidine.* Lancet 1991, 337(8744): 774-6.

49. Patrono, C., Coller, B., FitzGerald, G.A., Hirsh, J., Roth, G. *Platelet-active drugs: The relationships among dose, effectiveness, and side effects: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.* Chest 2004, 126(3, Suppl.): 234S-64S.

50. Denninger, M.H., Necciari, J., Serre-Lacroix, E., Sissmann, J. *Clopidogrel antiplatelet activity is independent of age and presence of atherosclerosis.* Semin Thromb Hemost 1999, 25(Suppl. 2): 41-5.

51. Fares, R.R., Lansing, L.S., Gallati, C.A., Mousa, S.A. *Antiplatelet therapy with clopidogrel and aspirin in vascular diseases: Clinical evidence for and against the combination.* Expert Opin Pharmacother 2008, 9(3): 377-86.

52. CAPRIE Steering Committee. *A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE).* Lancet 1996, 348(9038): 1329-39.

53. Bhatt, D.L., Hirsch, A.T., Ringleb, P.A., Hacke, W., Topol, E.J. *Reduction in the need for hospitalization for recurrent ischemic events and bleeding with clopidogrel instead of aspirin. CAPRIE investigators.* Am Heart J 2000, 140(1): 67-73.

54. Ringleb, P.A., Bhatt, D.L., Hirsch, A.T. et al. *Benefit of clopidogrel over aspirin is amplified in patients with a history of ischemic events.* Stroke 2004, 35(2): 528-32.

55. Mehta, S.R., Yusuf, S., Peters, R.J. et al. *Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: The PCI-CURE study.* Lancet 2001, 358(9281): 527-33.

56. Cannon, C.P., Husted, S., Harrington, R.A. et al. *Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: Primary results of the DISPERSE-2 trial.* J Am Coll Cardiol 2007, 50(19): 1844-51.

57. Braunwald, E., Antman, E.M., Beasley, J.W. et al. *ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—summary article: A report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina).* J Am Coll Cardiol 2002, 40(7): 1366-74.

58. Kapetanakis, E.I., Medlam, D.A., Petro, K.R. et al. *Effect of clopidogrel premedication in off-pump cardiac surgery: Are we forfeiting the benefits of reduced hemorrhagic sequelae?* Circulation 2006, 113(13): 1667-74.

59. Fares, R.R., Lansing, L.S., Gallati, C.A., Mousa, S.A. *Antiplatelet therapy with clopidogrel and aspirin in vascular diseases: Clinical evidence for and against the combination.* Expert Opin Pharmacother 2008, 9(3): 377-86.

60. Tantry, U.S., Bliden, K.P., Gurbel, P.A. *Azd6140.* Expert Opin Investig Drugs 2007, 16(2): 225-9.

61. Gurbel, P.A., Bliden, K.P., Hiatt, B.L., O'Connor, C.M. *Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity.* Circulation 2003, 107(23): 2908-13.

62. Gurbel, P.A., Bliden, K.P., Hayes, K.M., Yoho, J.A., Herzog, W.R., Tantry, U.S. *The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting.* J Am Coll Cardiol 2005, 45(9): 1392-6.

63. Angiolillo, D.J., Fernandez-Ortiz, A., Bernardo, E., Alfonso, F., Macaya, C., Bass, T.A., Costa, M.A. *Variability in individual responsiveness to clopidogrel: Clinical implications, management, and future perspectives.* J Am Coll Cardiol 2007, 49(14): 1505-16.

64. Angiolillo, D.J., Shoemaker, S.B., Desai, B. et al. *Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: Results of the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) study.* Circulation 2007, 115(6): 708-16.

65. Storey, R.F., Husted, S., Harrington, R.A. et al. *Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes.* J Am Coll Cardiol 2007, 50(19): 1852-6.

66. Muller, I. et al. *Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement.* Heart 2001, 85(1): 92-3.

67. Wiviott, S.D., Trenk, D., Frelinger, A.L. et al. *Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial.* Circulation 2007, 116(25): 2923-32.

68. Niitsu, Y., Jakubowski, J.A., Sugidachi, A., Asai, F. *Pharmacology of CS-747 (prasugrel, LY640315), a novel, potent antiplatelet agent with in vivo P2Y12 receptor antagonist activity.* Semin Thromb Hemost 2005, 31(2): 184-94.

69. Farid, N.A., Payne, C.D., Small, D.S. et al. *Cytochrome P450 3A inhibition by ketoconazole affects prasugrel and clopidogrel pharmacokinetics and pharmacodynamics differently.* Clin Pharmacol Ther 2007, 81(5): 735-41.

70. Jernberg, T., Payne, C.D., Winters, K.J. et al. *Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease.* Eur Heart J 2006, 27(10): 1166-73.

71. Wiviott, S.D., Braunwald, E., McCabe, C.H. et al. *Prasugrel versus clopidogrel in patients with acute coronary syndromes.* N Engl J Med 2007, 357(20): 2001-15.

72. van Giezen, J.J., Humphries, R.G. *Preclinical and clinical studies with selective reversible direct P2Y12 antagonists.* Semin Thromb Hemost 2005, 31(2): 195-204.

73. Greenbaum, A.B., Grines, C.L., Bittl, J.A. et al. *Initial experience with an intravenous P2Y12 platelet receptor antagonist in patients undergoing percutaneous coronary intervention: Results from a 2-part, phase II, multicenter, randomized, placebo- and active-controlled trial.* Am Heart J 2006, 151(3): 689 e1-689 e10.

74. Storey, R.F., Oldroyd, K.G., Wilcox, R.G. *Open multicentre study of the P2T receptor antagonist AR-C69931MX assessing safety, tolerability and activity in patients with acute coronary syndromes.* Thromb Haemost 2001, 85(3): 401-7.

75. Steinhubl, S.R., Oh, J.J., Oestreich, J.H., Ferraris, S., Charnigo, R., Akers, W.S. *Transitioning patients from cangrelor to clopidogrel: Pharmacodynamic evidence of a competitive effect.* Thromb Res 2008, 121(4): 527-34.

76. Husted, S., Emanuelsson, H., Heptinstall, S., Sandset, P.M.,Wickens, M., Peters, G. *Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: A double-blind comparison to clopidogrel with aspirin.* Eur Heart J 2006, 27(9): 1038-47.

77. Jones, L., Griffin, S., Palme, S. et al. *Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: A systematic review and economic evaluation.* Health Technol Assess 2004, 8(38): iii-iv, 1-196.

78. Diener, H.C., Cunha, L., Forbes, C., Sivenius, J., Smet, P., Lowenthal, A. *European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke.* J Neurol Sci 1996, 143(1-2): 1-13.

79. Bennett, J.S., Mousa, S. *Platelet function inhibitors in the year 2000.* Thromb Haemost 2001, 85(3): 395-400.

80. Min, P.K., Jung, J.H., Ko, Y.G., Choi, D., Jang, Y., Shim, W.H. *Effect of cilostazol on in-stent neointimal hyperplasia after coronary artery stenting: A quantitative coronary angiography and volumetric intravascular ultrasound study.* Circ J 2007, 71(11): 1685-90.

81. Money, S.R., Herd, J.A., Isaacsohn, J.L., Davidson, M., Cutler, B., Heckman, J., Forbes, W.P. *Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease.* J Vasc Surg 1998, 27(2): 267-74; discussion 274-5.

82. Beebe, H.G., Dawson, D.L., Cutler, B.S., Herd, J.A., Strandness, D.E. Jr., Bortey, E.B., Forbes, W.P. *A new pharmacological treatment for intermittent claudication: Results of a randomized, multicenter trial.* Arch Intern Med 1999, 159(17): 2041-50.

83. Park, S.W., Lee, C.W., Kim, H.S. et al. *Comparison of cilostazol versus ticlopidine therapy after stent implantation.* Am J Cardiol 1999, 84(5): 511-4.

84. Tsuchikane, E., Fukuhara, A., Kobayashi, T. et al. *Impact of cilostazol on restenosis after percutaneous coronary balloon angioplasty.* Circulation 1999, 100(1): 21-6.

85. Yoon, Y., Shim, W.H., Lee, D.H., Pyun, W.B., Kim, I.J., Jang, Y., Cho, S.Y. *Usefulness of cilostazol versus ticlopidine in coronary artery stenting.* Am J Cardiol 1999, 84(12): 1375-80.

86. Wang, X., Dorsam, R.T., Lauver, A. et al. *Comparative analysis of various platelet glycoprotein IIb/IIIa antagonists on shear-induced platelet activation and adhesion.* J Pharmacol Exp Ther 2002, 303(3): 1114-20.

87. Clappers, N., Brouwer, M.A., Verheugt, F.W. *Antiplatelet treatment for coronary heart disease.* Heart 2007, 93(2): 258-65.

88. Freson, K., Thys, C., Wittevrongel, C., Van Geet, C. *Mechanisms of action and targets for actual and future antiplatelet drugs.* Mini Rev Med Chem 2006, 6(6): 719-26.

89. Antoniucci, D. *Differences among GP IIb/IIIa inhibitors: Different clinical benefits in non-ST-segment elevation acute coronary syndrome percutaneous coronary intervention patients.* Eur Heart J Suppl 2007, 9(Suppl. A): A32-6.

90. Tepe, G., Wiskirchen, J., Pereira, P., Claussen, C.D., Miller, S., Duda, S.H. *GP IIb/IIIa blockade during peripheral artery interventions.* Cardiovasc Intervent Radiol 2008, 31(1): 8-13.

91. Topol, E.J., Moliterno, D.J., Herrmann, H.C. et al. *Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization.* N Engl J Med 2001, 344(25): 1888-94.

92. Tricoci, P., Peterson, D.E., Chen, A. et al. *Timing of glycoprotein IIb/IIIa inhibitor use and outcomes among patients with non-ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention (results from CRUSADE).* Am J Cardiol 2007, 99(10): 1389-93.

93. Montalescot, G., Borentain, M., Payot, L., Collet, J.P., Thomas, D. *Early vs late administration of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction: A meta-analysis.* JAMA 2004, 292(3): 362-6.

94. Stone, G.W., Bertrand, M.E., Moses, J.W. et al. *Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: The ACUITY Timing trial.* JAMA 2007, 297(6): 591-602.

95. Hernandez, A.V. et al. *Effects of platelet glycoprotein IIb/IIIa receptor blockers in non-ST segment elevation acute coronary syndromes: Benefit and harm in different age subgroups.* Heart 2007, 93(4): 450-5.

96. Cohen, M., Diez, J.E., Levine, G.N. et al. *Pharmacoinvasive management of acute coronary syndrome: Incorporating the 2007 ACC/AHA guidelines: the CATH (cardiac catheterization and antithrombotic therapy in the hospital) Clinical Consensus Panel Report—III.* J Invasive Cardiol 2007, 19(12): 525-38; quiz 539-40.

97. Aster, R.H. *Immune thrombocytopenia caused by glycoprotein IIb/IIIa inhibitors.* Chest 2005, 127(2, Suppl.): 53S-59S.

98. Seiffert, D., Stern, A.M., Ebling, W. et al. *Prospective testing for drug-dependent antibodies reduces the incidence of thrombocytopenia observed with the small molecule glycoprotein IIb/IIIa antagonist roxifiban: Implications for the etiology of thrombocytopenia.* Blood 2003, 101(1): 58-63.

99. Mousa, S.A., Giugliano, R. *Antiplatelet therapies: Platelet GPIIb/IIIa antagonists and beyond*. In: New Therapeutic Agents in Thrombosis. Sasahara, A.A. (Ed.). Marcel Dekker, New York, 2003, 341-7.

100. Lehman, S.J., Chew, D.P. *Bivalirudin in percutaneous coronary intervention.* Vasc Health Risk Manag 2006, 2(4): 357-63.

101. Bauer, K.A. *New anticoagulants.* Hematology Am Soc Hematol Educ Program 2006, 450-6.

102. Speredelozzi, N., Baroletti, S., Fanikos, J. *A review of antithrombotic therapies in acute coronary syndrome.* Formulary 2007, 42(3): 150-62.

103. Flaker, G.C., Gruber, M., Connolly, S.J. et al. *Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: An exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) trials.* Am Heart J 2006, 152(5): 967-73.

104. Kaul, S., Diamond, G.A., Weintraub, W.S. *Trials and tribulations of non-inferiority: The ximelagatran experience.* J Am Coll Cardiol 2005, 46(11): 1986-95.

105. Eriksson, B.I., Dahl, O.E., Rosencher, N. et al. *Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: A randomised, double-blind, non-inferiority trial.* Lancet 2007, 370(9591): 949-56.

106. Ezekowitz, M.D., Reilly, P.A., Nehmiz, G. et al. *Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study).* Am J Cardiol 2007, 100(9): 1419-26.

107. Chackalamannil, S., Wang, Y., Greenlee, W.J. et al. *Discovery of a novel, orally active himbacine-based thrombin receptor antagonist (SCH 530348) with potent antiplatelet activity.* J Med Chem 2008, 51(11): 3061-4.

108. Kato, Y., Kita, Y., Hirasawa-Taniyama, Y. et al. *Inhibition of arterial thrombosis by a protease-activated receptor 1 antagonist, FR171113, in the guinea pig.* Eur J Pharmacol 2003, 473(2-3): 163-9.

109. Greenbaum, A.B., Ohman, E.M., Gibson, C.M. et al. *Preliminary experience with intravenous P2Y12 platelet receptor inhibition as an adjunct to reduced-dose alteplase during acute myocardial infarction: Results of the Safety, Tolerability and Effect on Patency in Acute Myocardial Infarction (STEP-AMI) angiographic trial.* Am Heart J 2007, 154(4): 702-9.

110. Emmons, K.L., Taylor, N.R. *Contemporary issues in clopidogrel therapy: New evidence shaping clinical practice.* Pharmacotherapy 2007, 27(4): 553-63.

111. Fitzgerald, D.J. et al. *Marked platelet activation in vivo after intravenous streptokinase in patients with acute myocardial infarction.* Circulation 1988, 77(1): 142-50.

112. Lange, R.A., Hillis, L.D. *Concurrent antiplatelet and fibrinolytic therapy.* N Engl J Med 2005, 352(12): 1248-50.

113. Sinnaeve, P.R., Huang, Y., Bogaerts, K. et al. *Age, outcomes, and treatment effects of fibrinolytic and antithrombotic combinations: Findings from Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-3 and ASSENT-3 PLUS.* Am Heart J 2006, 152(4): 684 e1-9.

114. Fanikos, J., Seybert, A., Spinler, S. *Anticoagulation in non-ST-segment elevation acute coronary syndromes (NSTE ACS): Emerging therapeutic options*. 2007, NSTAR.

115. Stone, G.W., Ware, J.H., Bertrand, M.E. et al. *Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: One-year results from the ACUITY trial.* JAMA 2007, 298(21): 2497-506.

116. van Es, R.F., Jonker, J.J., Verheugt, F.W. et al. *Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): A randomised controlled trial.* Lancet 2002, 360(9327): 109-13.

117. Hurlen, M., Abdelnoor, M., Smith, P., Erikssen, J., Arnesen, H. *Warfarin, aspirin, or both after myocardial infarction.* N Engl J Med 2002, 347(13): 969-74.