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Neurosurg Clin N Am 16 (2005) 517–540

NEUROSURGERY
CLINICS
OF NORTH AMERICA

Antiplatelet Therapy in Neuroendovascular Therapeutics

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The rapid proliferation of catheter-based devices and neuroendovascular techniques has resulted in an exponential growth in the spectrum of neurologic disease processes that are amenable to percutaneous endovascular therapy. As the scope of pathologic conditions treated by the endovascular neuroradiologist and neurosurgeon broadens, so does the required knowledge base that forms the foundation for rationale decision making and optimal patient management.

Antithrombotic pharmacotherapy currently represents a critical component of this evolving neuroendovascular knowledge base. The importance of optimal antithrombotic therapy should continue to increase in the coming years as carotid stenting emerges as an alternative to endarterectomy, as flexible self-expandable stents for the treatment of intracranial atherosclerotic disease are introduced, and as continued progress is made with respect to the development of intracranial stents to treat cerebral aneurysms.

Agents from all the major classes of antithrombotic drugs, including (1) anticoagulants (heparinoids, warfarin, and related compounds), (2) antiplatelet agents (aspirin, thiopyridines, and IIb/IIIa inhibitors), and (3) fibrinolytics, are used routinely during neuroendovascular procedures. In addition, new agents and new classes of agents with different mechanisms of action (eg, direct thrombin inhibitors like hirudin and bivalirudin) are being continuously added to the armamentarium. Correspondingly, antithrombotic pharmacotherapy represents a perpetually evolving and increasingly complex field.

The myriad of neurologic disease processes that may be addressed endovascularly (eg, aneurysms, arteriovenous malformations [AVMs], and fistulae) are relatively uncommon (in comparison to coronary atheromatous disease), and each category comprises a broad, complex, and heterogeneous collection of lesions. For these reasons, large multicenter trials designed to examine different antithrombotic regimens in neuroendovascular intervention are much more difficult to orchestrate. For this reason, the rationale behind the application of antithrombotic agents in neuroendovascular procedures is based almost exclusively on extrapolations of existing data derived from preventative and interventional cardiology and stroke trials. Although these studies can provide some guidance, fundamental differences with respect to the nature of the disease processes treated and the clinical context in which intervention is undertaken often limit direct translation and application.

In many ways, achieving an optimal level of anticoagulation and platelet inhibition in the context of neuroendovascular intervention is considerably more complex. The brain is an unforgiving end organ, and even relatively minor thromboembolic events may have disastrous clinical implications. The most common disease processes addressed involve acutely hemorrhagic or potentially hemorrhagic vascular lesions that require the

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doi:10.1016/j.nec.2005.03.003

operator to negotiate a precarious balance between the prevention of thrombosis and the provocation of hemorrhage. Often, the most demanding decisions regarding antithrombotic therapy must be made emergently on a case by case basis (eg, the management of an acute thromboembolic complication arising in the setting of the embolization of a ruptured aneurysm). For these reasons, a complete understanding of the pharmacology of the existing agents as well as the data available regarding the applications of these agents in different clinical scenarios is required to develop a rational antithrombotic strategy for any given situation.

Platelets represent the predominant component of arterial thrombi and form in response to stimuli like endothelial injury, turbulent blood flow with associated high wall shear stress, or the introduction of an intravascular foreign body. Correspondingly, it follows that platelet inhibition represents the cornerstone of antithrombotic therapy in neuroendovascular intervention.

Mechanisms of platelet aggregation

Adhesion-activation-secretion-aggregation sequence

Platelets are anucleate blood cells with a tremendous capacity for interaction with their surrounding vascular environment. Platelets contain storage granules that hold multiple chemokines, cytokines, and growth factors. In addition, platelets can synthesize bioactive prostaglandins from membrane phospholipids.

In the resting state, the intact endothelium releases inhibitory factors, such as prostacyclin (PGI_2) and nitric oxide (NO), which function to maintain platelets in a nonactivated state (Fig. 1A). After the introduction of a stimulus, a cascade of events begins, which ultimately results in thrombus formation. This cascade consists of platelet adhesion, activation, secretion, and, finally, aggregation (see Fig. 1). The most common and well-understood stimulus is endothelial injury. High wall shear stress or the introduction of an intravascular foreign body represents additional stimuli that can also activate the process of platelet aggregation.

When an endothelial injury exposes thrombogenic collagen and subendothelial matrix, platelets adhere to the injured surface primarily via the interactions between the platelet surface Ib receptor with von Willebrand's factor (vWF) bound to the exposed collagen (see Fig. 1B). These adherent platelets spread to form a monolayer along the surface of the injured endothelium. The adherent platelets become activated after adhesion. Endothelial injury also exposes tissue factor (TF) to the bloodstream. TF is expressed exclusively by cells (eg, fibroblasts) that are not in contact with the blood under normal circumstances. Exposed TF binds factor VIIa, leading to activation of the intrinsic and extrinsic coagulation pathways that ultimately results in thrombin formation. Thrombin, in addition to converting fibrinogen to fibrin monomers, functions as a potent platelet agonist, resulting in further platelet activation. The activated platelets secrete additional soluble agonists that are prepackaged in storage granules (including ADP, calcium, and serotonin [5-HT]) and synthesize and secrete thromboxane A_2 (TXA_2). These substances all result in the further amplification of platelet activation (see Fig. 1C). Platelet activation by this myriad of agonists results in the stimulation of multiple different intracellular signaling pathways. These pathways all ultimately converge to induce a conformational change in the platelet surface glycoprotein (GP) IIb/IIIa receptor. This conformational change converts the IIb/IIIa receptor from a quiescent low-affinity state to an activated high-affinity binding site for fibrinogen and vWF. The stronger platelet agonists (ie, thrombin, collagen) also recruit additional GP IIb/IIIa receptors from the intracellular storage pool to the platelet surface.

The binding of the active platelet IIb/IIIa receptor to fibrinogen (and vWF) results in the formation of platelet-platelet and platelet-matrix adhesive interactions and the formation of a stable, larger platelet aggregate at the site of injury (see Fig. 1E). Although there is a significant level of redundancy built into the cascade of platelet activation, the binding of the IIb/IIIa receptor to fibrinogen (or vWF) represents the final common pathway to platelet aggregation, and thus the formation of stable thrombus. As this stable platelet aggregate forms, insoluble fibrin monomers begin precipitating around the aggregated platelets and eventually become cross-linked to form a more permanent thrombus.

Interaction of blood with intravascular foreign bodies: catheters, coils, and stents

The response of flowing arterial blood to an intravascular foreign body is incompletely understood. Within seconds after introduction, plasma proteins, predominantly fibrinogen, adhere

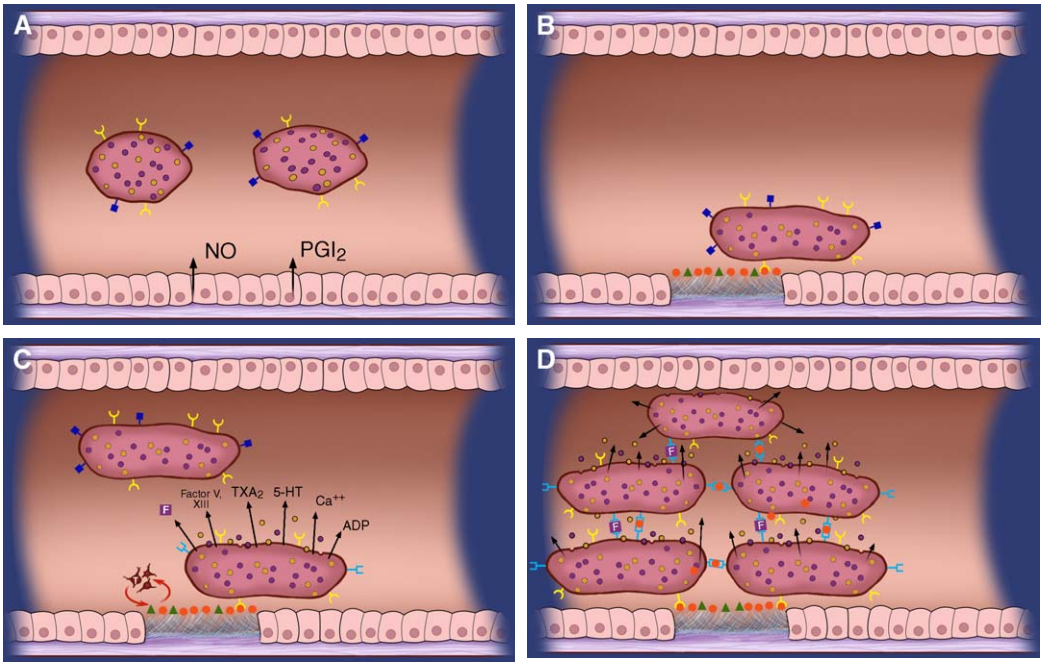

Fig. 1. (*A*) In the resting state, intact endothelial cells release factors like NO and PGI_2 to maintain platelets in their inactive state. (*B*) When the endothelium is injured, the breech exposes thrombogenic collagen and subendothelial matrix, which binds vWF (orange circles). (*C*) The platelet surface Ib receptor (yellow receptor) then binds vWF. These adherent platelets spread to form a monolayer along the surface of the injured endothelium. Endothelial injury also exposes TF (green triangles) to the bloodstream. Exposed TF binds factor VIIa, leading to activation of the intrinsic and extrinsic coagulation pathways that ultimately results in thrombin formation. Thrombin, in addition to converting fibrinogen to fibrin monomers, functions as a potent platelet agonist, resulting in further platelet activation. The activated platelets secrete additional soluble agonists that are prepackaged in storage granules (including ADP, calcium, and 5-HT) and synthesize and secrete TXA_2. (*D*) These substances all result in the further amplification of platelet activation. Platelet activation by this myriad of agonists results in the stimulation of multiple different intracellular signaling pathways. These pathways all ultimately converge to induce a conformational change in the platelet surface GP IIb/IIIa receptor. This conformational change converts the IIb/IIIa receptor from a quiescent low-affinity state (dark blue receptor) to an activated high-affinity binding site (light blue receptor) for fibrinogen (purple squares) and vWF. The stronger platelet agonists (ie, thrombin, collagen) also recruit additional GP IIb/IIIa receptors from the intracellular storage pool to the platelet surface. The binding of the active platelet IIb/IIIa receptor to fibrinogen (and vWF) results in the formation of platelet-platelet and platelet-matrix adhesive interactions and the formation of stable larger platelet aggregate at the site of injury.

to the surface of the foreign body [1]. These adsorbed proteins, probably in concert with turbulent flow and/or shear stress at the interface between the foreign body and bloodstream, result in platelet adhesion and varying degrees of platelet activation, secretion, and aggregation. Platelet adhesion begins within minutes, forming a layer over the implant during the initial 15 to 90 minutes of contact. Platelet activation may progress, resulting in the formation of platelet aggregates, the activation of blood coagulation, and thrombosis. Alternatively, the implant may undergo a process termed *passivation* and become resistant to further platelet attachment.

The degree of platelet aggregation and thrombosis depends on the characteristics of the implant, including its chemical composition, surface charge, and topography, as well as the local hemodynamic environment, specifically, the associated level of shear stress.

The mechanism of introduction also contributes to this process. During the electrolytic detachment of Guglielmi detachable coils (GDCs), negatively charged blood constituents, particularly platelets and red blood cells, are attracted by the positive charge induced within the platinum coil during detachment. This process of electrothrombosis is theorized to provide

a significant contribution to acute occlusion of aneurysms during GDC embolization. Coils detached by other mechanisms would not be expected to induce this effect. A similar disparity is recognized with respect to stenting. The deployment of a balloon-expandable stent for the treatment of atheromatous stenosis is expected to induce significant endothelial injury and subsequent platelet activation. Conversely, the deployment of a low radial force self-expanding intracranial stent (eg, Neuroform; Boston Scientific, Freemont, California) for aneurysm treatment should leave the underlying endothelium relatively intact. Although the introduction of a stent in either scenario could result in in situ thrombosis, this would be expected to occur much more frequently in the context of an endothelial injury induced by a high radial force stent. The consequences of introducing a low radial force self-expanding stent into the cerebral vasculature are largely uncharacterized at this point.

Pharmacology of antiplatelet agents

Aspirin

Mechanism of action

The initial activation of platelets results in the activation of phospholipase A_2, leading to the liberation of arachidonic acid (AA) from membrane phospholipids. AA is immediately converted by cyclo-oxygenase (COX-1) to prostaglandin G_2 (PGG_2) and PGH_2 and then to TXA_2 by thromboxane synthase (TS). TXA_2 is then released from the platelet to participate in a platelet receptor–mediated positive feedback loop, which plays a critical role in the further amplification of regional platelet activation. TXA_2 also functions to recruit additional platelets to the site of thrombus formation and induces local vasoconstriction. Aspirin irreversibly inactivates COX-1 through the acetylation of a serine residue at position 529, thus blocking the conversion of AA to PGG_2 and PGH_2 and, ultimately, the production of TXA_2 (Fig. 2). Platelets lack the synthetic machinery to generate new COX-1. Therefore, this inhibition of TXA_2 synthesis persists for the lifetime of the platelet [2].

Aspirin also has effects on vascular endothelial cells, in which the blockade of COX activity inhibits the synthesis of prostacyclin, a prostaglandin that functions to decrease platelet activation. These effects are typically seen only at higher aspirin doses at which the activity of COX-1 and COX-2 are inhibited. This phenomenon has been termed the *aspirin dilemma* and has led to the hypothesis that an optimal aspirin dose could provide maximal inhibition of TXA_2 synthesis with minimal disruption of the production of PGI_2. In addition, this phenomenon may explain the relatively decreased efficacy of aspirin administered in higher doses [3]. Unlike platelets, vascular endothelial cells have the synthetic machinery to generate new COX enzyme; thus, the inhibition of PGI_2 synthesis is likely to be fully recovered within the interval between the once-daily doses of aspirin administered for platelet inhibition [4].

Pharmacokinetics

The onset of antiplatelet activity after an oral dose of aspirin is remarkably fast. Serum thromboxane B_2 levels (a marker of TXA_2 production) are significantly reduced as early as 5 minutes after oral administration, with the maximum effect occurring within 30 to 60 minutes and remaining stable for 24 hours. The rapid rate of onset has been attributed to the acetylation of COX-1 in platelets within the presystemic portal circulation [4,5].

Dose

Aspirin has a myriad of different effects in addition to its antiplatelet activity, functioning as an analgesic, antipyretic, and anti-inflammatory agent. These effects all exhibit different dose-response relations with the lowest doses required to achieve platelet inhibition. Ex vivo studies of platelet inhibition have demonstrated that similar levels of inhibition can be achieved with daily aspirin doses ranging from 30 to 325 mg [4,5]. In a large meta-analysis, the Antithrombotic Trialists Collaboration found no evidence to support high-dose aspirin therapy. The meta-analysis demonstrated that doses of 75 to 150 mg (32% reduction), 160 to 325 mg (26% reduction), and 500 to 1500 mg (19% reduction) produced similar reductions in vascular events. In this same meta-analysis, doses of less than 75 mg (13% reduction) demonstrated a significantly smaller beneficial effect. In the Aspirin and Carotid Endarterectomy Trial, lower doses of aspirin (81 or 325 mg) resulted in lower rates of stroke, death, and myocardial infarction (MI) than higher (625–1300 mg) dosing regimens at 3 months [3].

Taken together, the available data would suggest that an aspirin dose between 81 and 325 mg would provide an optimal risk profile. If the lower range is to be used (ie, 81 mg/d), the operator should consider the administration of a 162- to

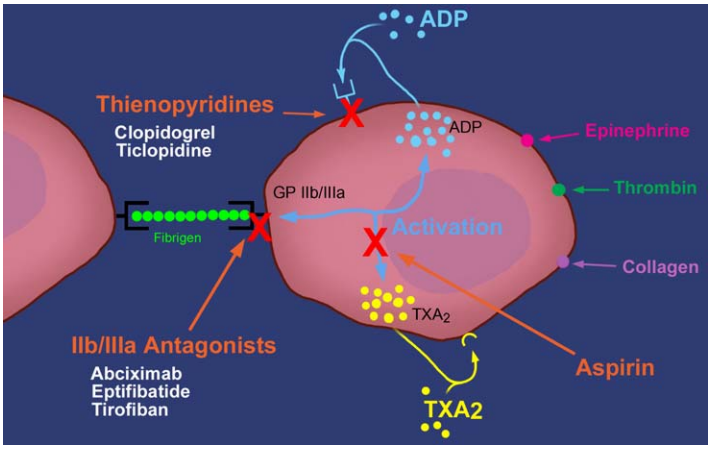

Fig. 2. Mechanisms of action of antiplatelet agents. Aspirin functions to acetylate the COX-1 enzyme irreversibly, thereby blocking the synthesis of TXA_2. Clopidogrel functions to irreversibly block the P2Y12 receptor (light blue). ADP and TXA_2 represent only two of multiple soluble agonists that function to activate platelets. Although the soluble agonist pathways that lead to platelet activation are highly redundant, IIb/IIIa receptor activation represents the final common pathway on which all these pathways converge to enable platelet aggregation and the formation of a stable platelet thrombus. The IIb/IIIa receptor antagonists function irreversibly (abciximab) or reversibly (eptifibatide, tirofiban) to block this component of the platelet aggregation cascade. (Adapted from Steinhubl SR. Aspirin and thienopyridines, transcatheter cardiovascular therapeutics, expert presentations pool. 2004; with permission.)

325-mg loading dose so that a therapeutic level of antiplatelet activity can be achieved immediately.

Resistance

Aspirin resistance is a significant problem that has been recognized recently as tests for the adequacy of platelet blockade have become more available. Between 5% and 40% of patients are resistant to the antiplatelet effects of standard doses of aspirin [6,7]. The incidence of aspirin resistance has been found to be related to aspirin dose. In a study of patients with previous ischemic stroke on aspirin therapy, platelet function testing with a platelet function analyzer (PFA)-100 system demonstrated 56% resistance at an 81 mg daily dose and 28% resistance at a 325 mg dose [8]. These same authors reported that 65% of patients taking enteric coated aspirin had normal platelet function test results. In addition, aspirin resistance may progressively develop over time with long-term therapy. Pulcinelli et al [9] observed a significant reduction in platelet sensitivity to aspirin therapy over a 24-month period.

A growing volume of data suggests that aspirin resistance has significant clinical implications. Gum et al [6] reported a three times higher risk of death, MI, and cerebrovascular accident (CVA) in stable cardiovascular patients over an approximately 2-year period. Chen et al [7] found aspirin-resistant patients to have a three times greater risk of having creatine kinase (CK)-MB elevations after nonemergent percutaneous coronary intervention (PCI). In patients with a prior stroke, those with aspirin resistance were 89% more likely to have a recurrent cerebrovascular accident within 2 years [10]. After peripheral intervention, an increase in arterial reocclusion has been observed in a cohort of aspirin nonresponders [11].

Although no studies currently exist, similar implications should be anticipated for neuroendovascular patients undergoing procedures requiring stent deployment or angioplasty. A priori knowledge of aspirin resistance could significantly influence the treatment plan, particularly in those cases in which other reasonable therapeutic options exist (eg, carotid endarterectomy versus carotid stenting, balloon-assisted versus stent-assisted aneurysm embolization).

Thienopyridines: clopidogrel and ticlopidine

Mechanism of action

Clopidogrel (Plavix) and ticlopidine (Ticlid) are the two available thienopyridines that have been routinely applied for use as antiplatelet agents. Both agents have no activity in vitro because they require hepatic transformation to active metabolites that mediate the antiplatelet

effect. The active metabolites irreversibly inhibit ADP from binding to its platelet surface P2Y12 receptor (see Fig. 2). This blockade prevents the soluble platelet agonist ADP from stimulating activation of the intracellular second-messenger (adenylate cyclase) system, which functions to amplify regional platelet activation by stimulating secretion and ultimately modulates the conversion of the GP IIb/IIIa receptor to its high-affinity state.

Ticlopidine use has declined substantially over the past decade because of the associated side effect of bone marrow depression, with neutropenia occurring in 2.4% of patients, and the emergence of clopidogrel as an adequate substitute [12]. In the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS), a direct comparison of ticlopidine and clopidogrel administered in combination with aspirin, clopidogrel demonstrated a superior safety profile and comparable efficacy in preventing thrombotic complications after coronary stenting [13]. Studies of the pharmacokinetics of both agents indicate that clopidogrel also demonstrates a more prompt onset of maximal platelet inhibition in comparison to ticlopidine [14]. Currently, the use of ticlopidine is largely restricted to patients who are intolerant of clopidogrel. For this reason, the remainder of this section focuses on the pharmacology of clopidogrel.

Pharmacokinetics and dosing: clopidogrel

Clopidogrel is rapidly absorbed and quickly metabolized, with extremely low plasma concentrations of the drug measured in patients on daily therapy [15]. The active metabolite(s) produce an irreversible alteration of the ADP binding site, and, subsequently, the effect persists for the duration of the platelet's lifespan, with 7 days required for the return of normal platelet function after therapeutic levels are attained.

The time required to establish maximally therapeutic levels of platelet inhibition with clopidogrel is dependent on the dosing regimen used [16]. If a standard daily dose of 75 mg is administered without a loading dose, significant levels of platelet inhibition can be measured at 12 to 24 hours. Daily doses of 75 mg produce only 25% to 30% inhibition at 48 hours, however. An average of 5 days (range: 3–7 days) is required to achieve maximal steady-state levels (50%–60%) of platelet inhibition at this dose [17,18]. If a loading dose (300–600 mg) is administered, however, maximal levels of inhibition are achieved within 2 to 6 hours and remain relatively stable for up to 48 hours [17,19,20]. In the CREDO study, patients who received the 300-mg clopidogrel loading dose 6 hours or more before the procedure had a 38.6% reduction in death, MI, or urgent target vessel revascularization at 1 month, whereas no benefit was observed in patients receiving the loading dose before the 6-hour time point [21].

Resistance

The efficacy of clopidogrel differs between patients with a significant incidence of resistance. Unlike aspirin, clopidogrel resistance has been classified as a binary as well as a graded phenomenon by different investigators. Resistance is measured by determining the degree of reduction in ADP-induced platelet aggregation. Gurbel et al [22] observed resistance in 31% of patients at 24 hours and 5 days, decreasing to 15% at 30 days after a 300 mg loading dose of clopidogrel and a dose of 75 mg/d after that. When divided into subcategories, Muller et al [23] reported that 5% to 11% were nonresponders and 9% to 26% were semiresponders, depending on the dose of ADP used to stimulate platelet aggregation. Lau et al [24] reported rates of clopidogrel resistance in 22% of patients and 16% of volunteers, with an additional 23% of patients and 12% of volunteers categorized as "low" responders.

Similar to aspirin, clopidogrel resistance has been demonstrated to have significant clinical implications. For example, individual variability in response to clopidogrel in the setting of PCI after MI was found to predict an increased risk of recurrent cardiovascular events [25].

Unlike aspirin, clopidogrel resistance does not seem to develop with time. Thus, if a patient is confirmed to be responsive initially, a durable antiplatelet effect can be anticipated with long-term administration [26]. This durability may account for the added benefit observed when clopidogrel is added to supplement long-term aspirin therapy.

The mechanisms of clopidogrel resistance are incompletely understood. The leading hypothesis is that individual differences in hepatic metabolism result in variable rates of conversion of the clopidogrel to its active metabolite [24].

Reversal

As with aspirin, platelet inhibition by the thienopyridines is durable for the lifetime of the platelet. Platelet function gradually returns to

normal, via platelet turnover, over a period of 7 days after the last dose of clopidogrel is administered. Correspondingly, immediate reversal can only be achieved with a platelet transfusion.

Dipyridamole

Mechanism of action

The mechanism by which dipyridamole inhibits platelet activity is poorly understood. Hypotheses include increases in intracellular cyclic AMP levels via the inhibition of phosphodiesterase or the blockade of adenosine uptake, direct stimulation of PGI_2 synthesis or inhibition of PGI_2 degradation, and the potentiation of the effects of NO. The concentrations of the agent required to achieve these effects are far greater than those achieved at conventional dosing regimens, however [27].

Pharmacokinetics and dosing

The pharmacokinetics of dipyridamole are also complex. The conventional formulations of the agent result in poor systemic bioavailability. As such, an extended-release formulation (200 mg) has been introduced and is available in combination with low-dose aspirin (25 mg). The half-life of the dipyridamole is 10 hours, which forms the basis for a twice-daily dosing regimen in the existing clinical studies [28]. Because of its vasodilatory effects and potential to provoke a coronary steal phenomenon when used as a pharmacologic stress agent, there has been some concern about the routine use of dipyridamole in patients with coronary artery disease (CAD) [29].

Resistance

We are aware of no studies that have evaluated patients for dipyridamole resistance.

IIb/IIIa inhibitors

Mechanism of action

The IIb/IIIA inhibitors block platelet aggregation by preventing fibrinogen and other adhesion molecules (vWF) from binding to the IIb/IIIa integrin on platelets. There are two general classes of antagonists: the irreversible antagonist abciximab (Reopro) and the reversible antagonists eptifibatide and tirofiban. Abciximab is a monoclonal antibody that binds irreversibly to the IIb/IIIa receptor at the β-chain of the integrin. Eptifibatide (Integrilin) and tirofiban (Aggrastat) are peptides that mimic the naturally occurring arginine-glycine-aspartic acid (RGD) sequence that is avidly bound by the IIb/IIIa receptor. This RGD binding site mediates the binding of vWF, vitronectin, fibronectin, and fibrinogen to platelets. Eptifibatide and tirofiban compete with these factors for binding at the RGD site, functioning as reversible competitive inhibitors of the IIb/IIIa receptor. By eliminating the function of the IIb/IIIa receptor, these agents block the final common pathway of platelet function—platelet aggregation. At approximately 80% IIb/IIIa receptor blockade, platelet aggregation is nearly completely abolished, and at levels greater than 90%, platelet function is ablated to the point that bleeding times become markedly elevated [30].

In addition to its effects at the platelet IIb/IIIa receptor, abciximab binds to the vitronectin receptor (vascular smooth muscle and endothelial cells) and the integrin Mac-1 (activated neutrophils and monocytes). The consequences of these additional receptor interactions remain to be elucidated; however, some have hypothesized that these interactions may play a role in decreasing the inflammatory reaction that follows angioplasty or stenting, thus limiting subsequent intimal hyperplasia.

Side effects

All three IIb/IIIa inhibitors have the potential to induce thrombocytopenia. This occurs at a slightly higher rate with abciximab (up to 6.5%) in comparison to the competitive antagonists [31]. Thrombocytopenia induced by IIb/IIIa inhibitors is usually quickly reversed by stopping the drug. Typically, complete recovery evolves over several days.

Pharmacokinetics and dose: abciximab

Abciximab, a monoclonal antibody, is a large molecule with extremely high affinity for platelet IIb/IIIa receptors. Correspondingly, the plasma half-life of the free drug is short, approximately 10 minutes, because the agent binds immediately to circulating platelets. The agent not bound to platelet receptors is quickly cleared from the circulation. Once bound to platelets, the dissociation time is long and the molecule remains biologically active on the surface of platelets for 12 to 14 hours. These characteristics result in a rapid onset of action and a slow reversal of activity after cessation of administration. After the administration of a bolus and infusion of abciximab, 28% occupation of the IIb/IIIa receptors is sustained at 8 days, declining to 13% at 15 days.

Abciximab is typically administered as a loading dose of 0.25 mg/kg, followed by an infusion at 0.125 μg/kg/min (maximum of 10 μg/min) for 12 hours. If the bolus is given alone, bleeding times recover to near-normal values by 12 hours, with platelet aggregation returning to greater than 50% of baseline within 24 to 48 hours in almost all patients. If the infusion is administered, platelet inactivation is maintained throughout the duration of the infusion.

Pharmacokinetics and dose: eptifibatide and tirofiban

Eptifibatide, a synthetic peptide, is a structural analogue of barbourin, a snake venom disintegrin polypeptide. Tirofiban is a nonpeptide tyrosin derivative also based on the structure of a known disintegrin polypeptide. These agents have less affinity than abciximab for the IIb/IIIa receptor, and their binding to the receptor is reversible. Eptifibatide, in particular, is a low-affinity agonist for the IIb/IIIa receptor. Both compounds demonstrate a rapid dissociation from the receptor (seconds). Correspondingly, after cessation of administration, platelet function returns rapidly to normal. Both agents are cleared through the kidneys, and as such, the effects of these agents may persist longer in patients with renal failure. The plasma half-time of both agents is approximately 1.5 hours in patients with normal renal function. Bleeding times begin to return toward normal shortly (within 15 minutes) after the discontinuation of eptifibatide, with a return to greater than half of the normal platelet aggregation response within 4 hours. Bleeding times also return to normal within approximately 4 hours after discontinuation of the tirofiban infusion, with platelet aggregation inhibition declining to levels less than 50% at this time point.

The Platelet Aggregation and Receptor Occupancy with Integrilin (PRIDE) study demonstrated that a 180 μg/kg bolus of eptifibatide followed by a 2.0 μg/kg/min infusion for 12 hours consistently resulted in greater than 90% platelet inhibition within 5 minutes. This effect was decreased at 1 hour, however, and did not return to the targeted therapeutic level until a steady state was reached at 8 to 24 hours. For this reason, it is currently recommended that two boluses (180 μg/kg) be administered 10 minutes apart, followed by a continuous 2.0 μg/kg/min infusion to achieve a more stable therapeutic effect [32,33]. Tirofiban is administered as a 10-μg/kg bolus, followed by an infusion of 0.15 μg/kg/min for 12 hours. This regimen results in a mean inhibition of platelet aggregation (ADP, 5 μmol/L) of 96% at 5 minutes, 100% at 2 hours, and 95% at the end of the infusion [34].

When IIb/IIIa receptor inhibitors are used in conjunction with heparin, the dose of heparin should be decreased (50–70 U/kg) slightly, because existing literature indicates an increased risk of bleeding without significantly increased efficacy [35,36].

Resistance

The therapeutic window for these agents is narrow, because the occupation of approximately 80% of IIb/IIIa receptors is required for clinically effective inhibition of platelet aggregation; however, greater than 90% inhibition may result in excessive bleeding complications [37]. The number of platelet receptors available for binding varies with the relative state of platelet activation [38]. In addition, the actual platelet counts and, subsequently, the number of receptors vary quite substantially across patients [39]. As such, determining a universal dose of IIb/IIIa inhibitors for any given patient is challenging.

In a study directly comparing the efficacy of all three agents in the setting of high-risk PCI, it was determined that only 52% of patients achieved targeted levels of platelet inhibition after administration of the recommended bolus dose of IIb/IIIa inhibitor (41%, 66%, and 49% with tirofiban, eptifibatide, and abciximab, respectively). The remaining 48% of patients required a second half-bolus to achieve the target levels [40]. In the GOLD [41] study, 25% of all patients administered the recommended bolus doses of IIb/IIIa inhibitors did not achieve adequate platelet inhibition and experienced a significantly higher incidence of adverse cardiac events.

Thus, as with aspirin and the thienopyridines, there is substantial variability in the level of platelet function inhibition achieved with standard regimens of GP IIb/IIIa antagonist therapy, and the level of platelet function inhibition is an independent predictor for the risk of complications during PCI.

Reversal of activity

Abciximab has a protracted duration of action, and reversal requires platelet transfusion. The antiplatelet effects of the competitive antagonists abate over a relatively short period if the infusion is discontinued. Although platelet transfusions hasten the return of normal function, they

are less effective in this setting, because the competitive antagonists have a short dissociation time and maintain higher plasma concentrations. Fibrinogen supplementation in the form of cryoprecipitate or fresh-frozen plasma represents a useful means by which to achieve reversal of these agents. The increasing concentration of fibrinogen tips the balance of competition at the IIb/IIIa receptor in favor of fibrinogen, counteracting the effects of the circulating IIb/IIIa inhibitors [42].

Comparative clinical efficacy

In a direct comparison, abciximab was superior to tirofiban for the prevention of ischemic events after percutaneous transluminal coronary angioplasty (PTCA) [43]. In a comparison of all three agents in high-risk patients undergoing PTCA, however, no difference in major cardiac events was detected at 30 days [40].

Measurement of antiplatelet activity

In neuroendovascular therapeutics, the ability to assess the status of platelet function rapidly and accurately is critical. Not infrequently, antiplatelet agents must be reversed immediately and completely to accommodate a required surgical intervention (eg, ventriculostomy catheter placement or craniotomy) or in response to a procedural hemorrhagic complication. Alternatively, given the frequency, and associated clinical implications, of antiplatelet agent resistance, adequate platelet inhibition is prerequisite to the safe execution of endovascular procedures requiring the deployment of a device within the parent vessel or when performing angioplasty.

Although several assays are currently available, they have not yet emerged as a routine component in the practice of peripheral, coronary, or endovascular therapeutics at most institutions. In addition, the existing assays have significant limitations. As such, the means by which to achieve accurate and accessible measurements of platelet function continue to evolve.

Bleeding time

The measurement of bleeding time is a universally available and relatively simple technique by which to measure platelet function at the bedside. Although the means of assay differ, all methods require a skin incision, usually made on the earlobe or forearm, of a depth that results in the disruption of capillary loops and small vessels. The normal ranges for bleeding time vary significantly with the type of assay used. The measurement of bleeding time has been criticized as an insensitive, inaccurate, nonspecific, and poorly reproducible measure of platelet function. The irreproducibility of the test result also arises because the measurements are dependent on multiple variables in addition to platelet function, including platelet count, red blood cell count and function, and vessel wall integrity [44].

Optical aggregometry

The current "gold standard" assay for platelet function is agonist-induced aggregation measured by optical aggregometry (turbidometric) in citrated blood samples. This assay measures the increased transmission of light through platelet samples that occurs as platelets aggregate in response to the addition of various soluble agonists and precipitate from the suspension. Different agonists are available to assess the activity of different antiplatelet agents. "Resistance" to a given agent is defined as failure of the agent to inhibit agonist-induced platelet aggregation sufficiently, which is expressed as a percentage of mean aggregation. It is important to note that these are specialized laboratory tests requiring unique expertise; as such, they are not universally available.

Aspirin therapy is typically monitored with the agonists ADP (5–20 μmol/L), AA, or collagen. Aspirin resistance is defined at our institution as a mean aggregation of greater than 70% with ADP (10 μmol/L) and greater than 20% with AA (0.5 mg/mL) [6]. Clopidogrel resistance is typically measured by assessing the platelet response to the agonist ADP (20 μmol/L). Clopidogrel nonresponders, low responders, and responders were defined by a mean aggregation of greater than 90%, 90% to 71%, and less than 70% compared with a preclopidogrel administration baseline, respectively, by Lau et al [24]. IIb/IIIa antagonist resistance is measured by the response of platelets to ADP (5–20 μmol/L) and other agonists (eg, thrombin receptor agonist peptides [TRAPs]). Different studies have used variable criteria to define resistance attributable to methodologic differences in the assays (anticoagulants used in the collected samples and doses of ADP used for the stimulation of platelet aggregation), however [45]. Having said this, initial dose-finding studies used a targeted level of platelet inhibition to 20%

of baseline ADP (20 μmol/L)-induced platelet aggregation [46].

Point-of-care rapid platelet function assay

The Verify Now (Ultegra Rapid Platelet Function Assay) system (Accumetrics, San Diego, California) provides a means by which to measure aspirin, clopidogrel, and IIb/IIIa inhibitor function rapidly, using a citrated whole blood sample, at the bedside (point-of-care monitoring). A Vacutainer containing citrate-anticoagulated blood is inserted in a fully self-contained assay device that contains fibrinogen-coated beads and platelet agonists. If platelet function is impaired in response to a given antiplatelet agent, the fibrinogen-coated beads do not agglutinate and light transmission through the sample does not increase. Different assay devices containing different agonists are available for the assessment of each of the different antiplatelet agents.

For the aspirin test, AA is used as the agonist and the results are reported as aspirin reaction units (ARUs). Aspirin induces a dose-related decrease in ARU using this method. An ARU greater than 550 indicates aspirin nonresponsiveness (the absence of aspirin-induced platelet dysfunction). Correlation with light transmission aggregometry with AA indicated a sensitivity of 100% and a specificity of 91.4% for the determination of aspirin resistance. Assessments of patient reproducibility indicated coefficients of variation of 2.5% (within the same patient) and 12.5% to 15% (between patients), respectively [47]. If the patient is being given a GP IIb/IIIa inhibitor or clopidogrel, the results of the aspirin test reflect not only the effects of aspirin but those of these agents. A patient resistant to aspirin but well treated with clopidogrel and aspirin may have an ARU measurement of less than 550.

The VerifyNow P2Y12 assay is currently available for research use only. This system uses ADP as the platelet agonist in combination with an additional antagonist to confer specificity for the measurement of ADP-induced platelet aggregation occurring through the P2Y12 receptor (the receptor that is blocked by clopidogrel). As such, the result of this assay specifically reflects the efficacy of clopidogrel.

The VerifyNow IIb/IIIa assay device uses TRAP as the platelet agonist. TRAP is the most potent agonist of platelet aggregation and is not affected by aspirin and minimally affected by clopidogrel. The assay reports results in platelet activating units (PAUs), with normal predrug levels ranging between 125 and 330 and therapeutic postdrug levels of less than 44. Results may also be reported as percent inhibition based on the differences between the baseline and postdrug results, with a target level of greater than 90% inhibition used in some studies for PCI [40].

Relevant data from clinical antiplatelet trials

Anti-Thrombotic Trialists Collaboration

The most comprehensive summary of available data regarding the clinical efficacy of antiplatelet therapy comes from the Anti-Thrombotic Trialists Collaboration [48]. This study incorporated data from 287 studies (comprehensive through September 1997) involving 135,000 ''high-risk'' patients in comparisons of antiplatelet therapy versus controls. High-risk patients were those with acute or previous vascular disease or with significant risk factors for vascular disease. In these patients, allocation to antiplatelet therapy resulted in an overall 22% reduction in the odds ratio of serious vascular events in comparison to controls (17.8% versus 21.4%; $P < 0.001$). They observed a 17% reduction in all vascular mortality, a 33% decrease in nonfatal MI, and a 25% decrease in the rate of stroke. Clopidogrel and ticlopidine were more effective than aspirin, decreasing events by 10% and 12% in comparison to aspirin therapy, respectively. The addition of dipyridamole to aspirin was not found to be beneficial in comparison to aspirin therapy alone. In patients with a history of stroke or transient ischemic attack (TIA), antiplatelet therapy resulted in 36 fewer significant vascular events per 1000, primarily accounted for by a decreased rate of nonfatal stroke (25 of 1000 patients). In these patients, vascular and all-cause mortality were significantly reduced. In patients with acute stroke, antiplatelet therapy reduced vascular events by 11%. This included a reduction in ischemic stroke of 6.9 per 1000 patients, the benefit of which is slightly attenuated by an increased risk of hemorrhagic stroke of 1.9 per 1000 patients.

Clopidogrel Versus Aspirin in Individuals at Risk of Ischemic Events study

With the emergence of clopidogrel as an adequate substitute for ticlopidine, interest arose in determining the relative efficacy of clopidogrel in

comparison to aspirin. The Clopidogrel Versus Aspirin in Individuals at Risk of Ischemic Events (CAPRIE) study was a large prospective, randomized, blind, level I comparison of clopidogrel (75 mg, n = 9577) versus aspirin (325, n = 9566) in patients with thrombotic disease (stroke, MI, 35 days old, and symptomatic atherosclerotic peripheral artery disease [PAD]) who were followed for 1 to 3 years for the end points of stroke, MI, and vascular death. These observers reported an 8.7% relative risk reduction (RRR) in favor of clopidogrel, with the number of patients needed to be treated (NNT) over 1 year of 196. The overall benefit can be attributed to the disproportionate benefit observed in patients with PAD (RRR = 23.8, range: 8.9–36.2). No significant differences were observed for patients in the stroke group (RRR = 7.3, range: −5.7–18.7) or MI group (RRR = −3.7, range: −22.1–12.0). More significant benefits were observed in some particularly high-risk subgroups, such as patients with previous coronary artery bypass grafting (RRR = 28.9%, NNT = 16), multiple ischemic events (NNT = 50), multiple vascular beds involved (NNT = 41), diabetes mellitus (NNT = 48 [26.3 if on insulin]), and increased cholesterol (NNT = 77). In addition to the significant reductions in primary end points, there were significant reductions in hospitalization for ischemic events and bleeding events (including gastrointestinal bleeding) for patients on Clopidogrel [49].

Clopidogrel in Unstable Angina to Prevent Recurrent Events and Clopidogrel for the Reduction of Events during Observation studies

The antiplatelet effects of clopidogrel and aspirin are mediated by two different receptors. Correspondingly, it is expected that the two agents together could potentially have a synergistic effect. This was first demonstrated in ex vivo experiments [50] and later evaluated clinically in two large cardiology studies: Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and Clopidogrel for the Reduction of Events during Observation (CREDO).

In the CURE study, patients with acute coronary syndrome were treated with aspirin (75–325 mg/d) and placebo (n = 6303) or clopidogrel (75 mg/d, n = 6259) for 3 to 12 months (average of 9 months). Patients treated with both agents demonstrated lower risks of the combined end points of cardiovascular death, MI, and stroke (9.3% versus 11.4%; $P < 0.0001$; RRR = 20%, NNT = 48) with an increased risk of major bleeding (3.7% versus 2.7%). The beneficial effect of clopidogrel was observed across all doses of aspirin. Bleeding risks increased with increasing doses of aspirin despite the lack of any benefit of increased doses on the combined end points measured [51].

When the subset of CURE patients undergoing PCI were selectively evaluated, the beneficial effects of dual-agent therapy were even more evident, with a 31% reduction ($P = 0.002$) in stroke, death, and MI. This beneficial effect was evident before PCI, 1 month after PCI, and at the end of follow-up (average of 8 months) [52].

In the CREDO study, a randomized placebo-controlled trial, patients who were designated to be at a high likelihood of needing PCI were treated with placebo or a 300 mg clopidogrel loading dose before the anticipated interventional procedure. After the procedure, all patients were maintained on clopidogrel at a dose of 75 mg/d. Patients who received the loading dose of clopidogrel before the procedure were maintained on clopidogrel for 1 year. Patients who received the 300 mg clopidogrel loading dose 6 hours or more before the procedure had a 38.6% reduction in death, MI, or urgent target vessel revascularization at 1 month. No benefit was observed in patients receiving the loading dose before the 6-hour time point. In the group treated with clopidogrel for 1 year, a 27% reduction in the combined end points was observed in comparison to those who were treated for only 1 month.

The PCI CURE and CREDO investigators concluded that the continuation of clopidogrel therapy (in addition to aspirin) for up to 1 year resulted in a significant improvement in patient outcomes [21]. In both studies, however, those patients randomized to long-term clopidogrel therapy were the same as those initially randomized to receive a clopidogrel loading dose before PCI. Correspondingly, it is impossible to determine for certain whether the long-term benefits of dual-agent therapy are attributable to the prevention of complications incurred during the initial intervention or to the prevention of new events by sustained dual-agent antiplatelet inhibition, or both [53]. Currently, this remains a somewhat contentious point in cardiology, although most have gravitated to long-term dual-antiplatelet therapy. This is particularly true in patients receiving drug-eluting coronary stents (DES), because a DES requires a longer period to complete endothelialization. In neuroendovascular therapeutics, the issues

surrounding the optimal duration of dual-antiplatelet therapy are further complicated by the results of the MATCH trial.

Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients

In the prospective, randomized, placebo-controlled, double-blind MATCH trial, patients (n = 7599) at high risk for cerebral ischemia (recent ischemic stroke or TIA and at least one additional vascular risk factor) were treated with clopidogrel (75 mg/d) and aspirin (75 mg/d) or placebo for up to 18 months. A nonsignificant decrease in the primary end points (15.7% and 16.7% for the aspirin and placebo groups, respectively [RRR = −4.6% and −16.3%; $P = 0.244$]) of stroke, MI, vascular death, or rehospitalization for acute ischemia (central nervous system, coronary, or peripheral) was observed with the addition of aspirin to clopidogrel. A 1.3% increase in the rate of life-threatening bleeding was observed in the aspirin group. Thus, although aspirin was ineffective in preventing ischemic events, the addition of aspirin to clopidogrel therapy did result in increased bleeding [54].

Although useful, the results of this trial must be viewed in the context of the population studied. Because of the requirement of a secondary vascular risk factor, 70% of the patients included were diabetic and 54% of patients presented with a lacunar infarct as the qualifying ischemic event. In addition, the subset of patients with CAD were largely excluded from the study given that their cardiologists were hesitant to include patients in a trial that might result in randomization to single-agent antiplatelet therapy. Thus, although the results indicate no significant advantage of adding aspirin to clopidogrel, one must first consider that the results suggested a trend toward a benefit from adding aspirin and then consider that the study population was not composed of the typical patients seen by the neuroendovascular interventionist, who is more frequently consulted for the evaluation of angiographically evident large-vessel disease rather than small-vessel ischemic disease.

A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel

In a prospective (2159 patients) randomized trial of abciximab versus placebo in low-risk patients undergoing elective PCI (pretreated with clopidogrel and aspirin), no significant differences in outcomes were observed at 30 days [55]. This trial contradicts the results of multiple other trials that observed a benefit of adding IIb/IIIa inhibitors in patients undergoing PCI.

The initial studies establishing the beneficial effects of IIb/IIIa inhibitors were conducted in high-risk patients. The EPIC study [56] demonstrated a significant reduction (30% RRR) in all adverse ischemic events when an abciximab bolus and infusion were added to conventional heparin and aspirin therapy in high-risk patients (acute MI, recent MI, unstable angina, or high-risk lesions) undergoing PCI. Similarly, the CAPTURE [57] trial demonstrated the efficacy (47% RRR) of abciximab before treatment in patients with unstable angina refractory to conventional therapy undergoing PCI.

These results were then evaluated in a broader group of patients. In the EPISTENT trial [58], an abciximab bolus and infusion significantly (52.9% RRR) reduced adverse ischemic events (death, MI, or urgent revascularization) at 30 days in a less selected group of patients (pretreated with aspirin, ticlopidine, and heparin) undergoing elective or urgent PTCA or stenting. These early benefits were also manifest at 1 year of follow-up as a significant reduction in mortality in patients undergoing stenting with an abciximab bolus and infusion [59]. The IMPACT II [60] and Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) [61] trials demonstrated similar trends toward improved outcomes after PCI performed with eptifibatide and tirofiban; however, neither study reached significance with respect to a reduction in adverse ischemic events at 30 days. In the European-Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) [33], a new dosing regimen of eptifibatide using two boluses followed by an infusion markedly reduced adverse ischemic events at 48 hours in unselected patients (pretreated with aspirin, heparin, and a thienopyridine) undergoing PCI.

Thus, before the Kastrati et al [55] study, the question was not whether to use a IIb/IIIa receptor antagonist as an adjunct to PCI but which one to use. The lack of an additive benefit of abciximab observed by Kastrati et al [55] is most likely attributable to the high clopidogrel loading dose (600 mg) used in this series. It is likely that this aggressive loading dose resulted in a high proportion of patients with therapeutic levels of clopidogrel-induced platelet inhibition at the time of PCI. Correspondingly, these results

suggest that if adequate pretreatment with dual-antiplatelet agents is established, the addition of a IIb/IIIa antagonist is likely not beneficial and may expose the patient to an unnecessary risk of a hemorrhagic complication.

Applications of antiplatelet agents in interventional neuroradiology

There are no widely accepted antiplatelet regimens for application in common neuroendovascular scenarios. The agents selected and doses reported vary widely. Frequently, these decisions are based on individual operator experience and practice patterns rather than on an extrapolation of the existing data.

Stent placement

Neuroendovascular stent placement differs from coronary stenting in several important ways. First, a significant percentage of stents are placed not to restore patency to a narrowed artery but to support aneurysm embolization. In these cases, self-expanding stents with low radial force are used, resulting in little, if any, endothelial injury. In all likelihood, much of what is currently understood about the biology of balloon-expandable coronary stents is not applicable in this setting. Second, when stenting is undertaken to augment or re-establish blood flow, the neurovascular end organ (unlike the heart) is susceptible to reperfusion hemorrhage or hemorrhage as a sequela of ischemic injury that occurred before or during the procedure. These differences must be taken into account when designing antiplatelet regimens for these two subsets of patients.

Despite the differences between stenting for atheromatous disease and stenting for aneurysm therapy, the pretreatment and intraprocedural antiplatelet strategies are similar. Both are geared toward preventing acute stent thrombosis and distal thromboembolic complications related to stent deployment. When performed on an elective basis, the existing literature supports pretreatment with aspirin (162–325-mg loading dose at least 2 hours before the procedure, with continued administration of 81 mg/d up to and including the morning of the procedure) and clopidogrel (300–600 mg bolus administered greater than 6 hours before the procedure, with continued administration of 75 mg/d up to and including the morning of the procedure). Although not routinely available at many institutions, optimal practice would include verification of adequate platelet inhibition before initiation of the procedure.

Some investigators have explored the utility of IIb/IIIa inhibitors as adjunctive agents to lower the risk of the thromboembolic complications associated with carotid stenting. In two small patient series reporting experiences using abciximab in the setting of carotid stenting, a significant risk of intracerebral hemorrhage was observed [62,63]. In a later series of studies, these same investigators found eptifibatide to be a safe adjunct to carotid stenting [64,65]. Whether safe or not, the recent data of Kastrati et al [55] regarding the utility of IIb/IIIa inhibitors in coronary stenting would suggest that the application of such agents is not necessary if adequate platelet inhibition is established with aspirin and clopidogrel before treatment. In all likelihood, the routine addition of a IIb/IIIa inhibitor to an effective regimen of dual-antiplatelet therapy poses minimal benefit and may carry with it a significant risk.

For these reasons, we do not routinely use IIb/IIIa inhibitors in conjunction with aspirin and clopidogrel during elective stenting procedures. We reserve the use of these agents for patients with angiographically evident intraprocedural thromboembolic events and for those patients stented without aspirin and clopidogrel pretreatment (Fig. 3). This is often performed emergently in the context of a bailout and/or salvage maneuver or to restore flow to a threatened vascular distribution on an emergent basis (Fig. 4). In these cases, we have administered a 0.25 mg/kg loading bolus of abciximab to establish immediate platelet inhibition. In some cases, we have administered 50% to 100% of the initial bolus intra-arterially, with the remainder of the bolus dose given intravenously. The intra-arterial administration of a portion of the abciximab bolus is intended to achieve a high local concentration of the agent rapidly in the immediate vicinity of the recently deployed stent. If the treatment was undertaken in the setting of an underlying acutely hemorrhagic lesion (eg, a ruptured aneurysm), the patient is administered a loading dose of aspirin (162–325 mg) and clopidogrel (300–600 mg) immediately after the procedure in lieu of a 12-hour abciximab infusion. If the underlying lesion is not acutely hemorrhagic, the abciximab infusion is administered, with the loading doses of aspirin and clopidogrel given immediately after the procedure. Abciximab therapy is best monitored using point-of-care testing to verify adequate levels of platelet inhibition. In this setting, this monitoring

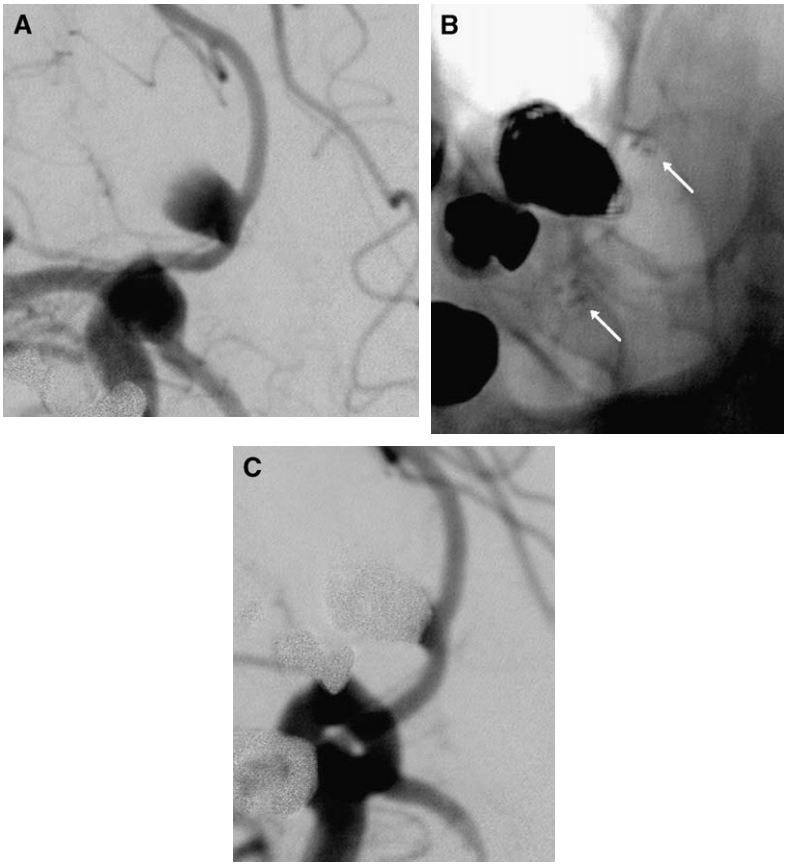

Fig. 3. (*A*) A 76-year-old woman with an unruptured anterior communicating artery complex aneurysm presented for coil embolization. The patient was not pretreated with antiplatelet agents. (*B*) Because of the width of the aneurysm neck, a 2.5-mm × 15-mm Neuroform stent was placed to support coil embolization (white arrows indicate the radiopaque markers delineating the ends of the stent). Immediately preceding deployment of the stent, the patient was administered an intravenous bolus of abciximab (0.25 mg/kg). After the intravenous bolus, the stent was successfully deployed and intravenous abciximab infusion (0.125 μg/kg/min) was initiated. (*C*) The aneurysm was then coiled to near-complete occlusion. The patient emerged from general anesthesia neurologically intact and was administered loading doses of aspirin and clopidogrel.

represents a critical component of therapy, because up to 50% of subjects exhibit subtherapeutic platelet inhibition after a weight-based dose of a IIb/IIIa inhibitor [40].

Some have argued for a continuous heparin drip after neuroendovascular stenting procedures. All investigations of this strategy in the coronary literature have indicated little efficacy in preventing thrombotic complications with significant cost with respect to incidence of hemorrhagic events, however [66,67].

After a stent has been placed, dual-antiplatelet therapy is required for a minimum of 4 to 6 weeks. When a stent has been placed for aneurysm embolization in a large (>3.5 mm) intracranial vessel, we typically maintain patients on aspirin (162–325 mg) and clopidogrel (75 mg) for 6 weeks, with aspirin to be continued indefinitely thereafter. If a stent (carotid or intracranial) is placed for atherostenosis, the existing literature suggests that continued treatment with aspirin (162–325 mg/d) and clopidogrel (75 mg/d) may be beneficial for as long as 1 year [21].

Management of intraprocedural thromboembolic complications

Thromboembolic events account for most of the complications related to the endovascular treatment of intracranial lesions. Advancing the

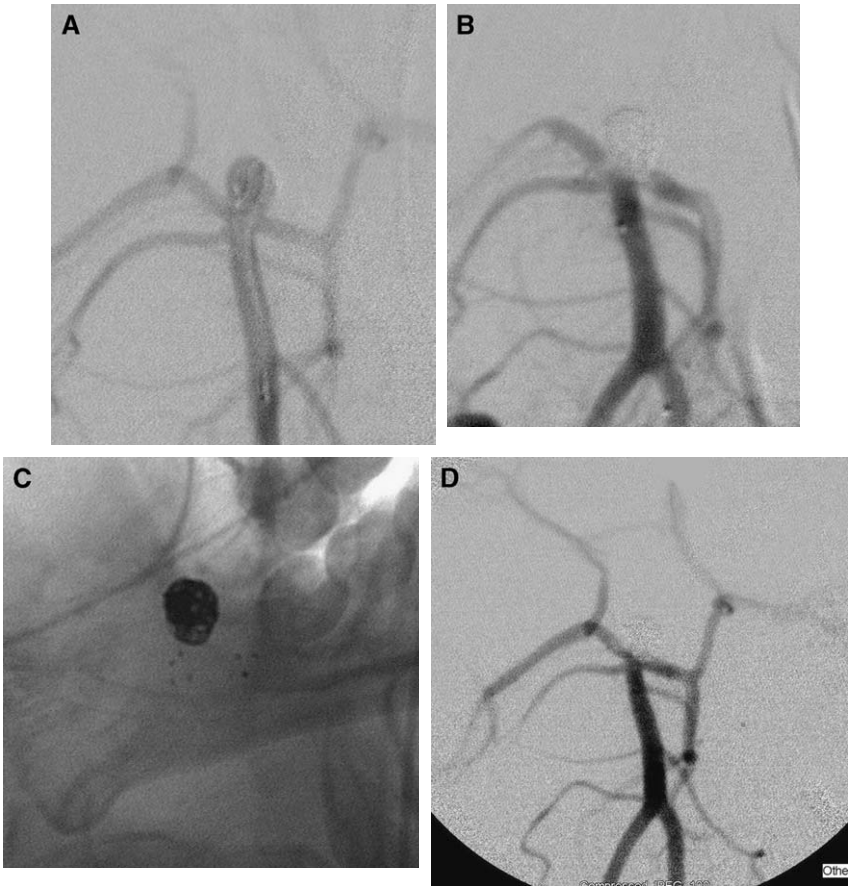

Fig. 4. A 22-year-old woman with an unruptured basilar artery apex aneurysm presented for elective coil embolization. (*A*) A three-dimensional coil produced adequate framing of the aneurysm. Subsequent coil embolization was performed with increasing occlusion of the aneurysm. (*B*) As additional coils were introduced into the aneurysm, however, the three-dimensional coil began to protrude slightly into the basilar apex and thrombus began to accumulate within the basilar apex and extend into the proximal posterior cerebral arteries. Abciximab (10 mg) was administered intra-arterially through a microcatheter positioned just proximal to the basilar apex. (*C*) Subsequently, a 4.5-mm × 15-mm Neuroform stent was placed, extending from the P1 segment of the posterior cerebral artery (PCA) proximally into the distal third of the basilar artery. Follow-up angiography demonstrated complete resolution of the thrombus and restoration of patency to the basilar apex and PCA. The remainder of the abciximab bolus was administered through a peripheral intravenous line. Because the aneurysm was unruptured, 12-hour abciximab infusion was administered. The patient emerged from general anesthesia neurologically intact and was loaded with aspirin and clopidogrel.

ability to prevent, identify, and manage such complications is one of the most efficacious ways by which to optimize the risk-benefit ratio of endovascular therapy.

Most operators fully heparinize patients during endovascular intervention to reduce the incidence of thromboembolic complications. In the setting of an acutely hemorrhagic index lesion, some operators delay full intraprocedural anticoagulation until the lesion is partially secured. Workman et al [68] proposed the strategy of pretreating patients with antiplatelet agents (aspirin alone or aspirin with clopidogrel) to reduce the risk of thromboembolism during the treatment of unruptured aneurysms even further. Despite these preventative measures, angiographically perceptible thromboembolic complications have been reported to occur with a frequency of 6.7% [68].

Thromboembolic complications encountered during the endovascular treatment of hemorrhagic or potentially hemorrhagic vascular lesions represent a particularly challenging problem. The operator must determine the most effective means

by which to achieve clot dissolution without provoking hemorrhage from the target lesion.

Two classes of pharmacologic agents have been applied in this situation—thrombolytic agents (eg, tissue plasminogen activator [tPA] and urokinase) and GP IIb/IIIa inhibitors. Recombinant tissue plasminogen activator (rtPA; eg, alteplase) acts by converting plasminogen to plasmin. Plasmin is also an active serine protease that acts primarily to lyse fibrin and thereby produce thrombolysis. The efficiency of tPA-mediated plasminogen activation is markedly enhanced in the presence of fibrin, which provides a surface for the sequential binding of tPA and plasminogen. By acting primarily on fibrin-entrapped plasminogen, tPA has a more specific localized thrombolytic effect, with less of an associated systemic fibrinolytic action. Cronqvist et al [69] reported the use of urokinase to manage intra- and periprocedural thromboembolic complications encountered during GDC embolization in 19 patients. The investigators reported excellent angiographic results, with partial or complete recanalization achieved in all cases, as well as a good clinical outcome in 74% of patients. Only 6 patients in the series had acutely ruptured aneurysms, however, and in this subset, 3 patients experienced significant hemorrhagic complications after thrombolysis. Koebbe et al [70] used thrombolytic agents to manage thromboembolic complications in a series of 5 patients undergoing embolization of aneurysms. Two of the 5 experienced fatal subarachnoid hemorrhage after thrombolysis. One of these patients had a previously unruptured aneurysm. Taken together, the available data indicate that thrombolytic agents, although effective in achieving dissolution of intraprocedural thrombi, are probably associated with an approximately 50% rate of symptomatic and, in many cases, fatal intracranial hemorrhage when used in the setting of an acutely hemorrhagic aneurysm.

Hyperacute thromboemboli identified during the course of neuroendovascular procedures likely represent primarily aggregates of activated platelets that are not yet stabilized by fibrin cross-linking. For this reason, the GP IIb/IIIa inhibitors, which block the final common pathway of platelet aggregation, are uniquely suited to prevent propagation of hyperacute thrombi without disrupting more subacute fibrin-stabilized thrombi, which stabilize acutely or subacutely hemorrhagic vascular lesions. To date, the use of GP IIb/IIIa inhibitors for the management of intraprocedural thromboembolic events has been documented in 54 patients (22 intravenous and 32 intra-arterial, with 52 patients with hemorrhagic or potentially hemorrhagic vascular lesions), with complete or partial resolution of thrombus in 52 of 54 cases and no documented cases of new or increased intracranial hemorrhage related to the index lesion (Table 1).

In our experience, intra-arterial and intravenous abciximab are effective. The intra-arterial route of administration has two major advantages: the instantaneous achievement of high local concentrations of the drug with a rapid onset of action and the fact that adequate thrombolysis may be achieved at a lower total dose. In our experience [71], the intra-arterial route of administration results in a faster rate of clot dissolution (<5 minutes), whereas the intravenous route of administration requires more time (>10 minutes). We have administered abciximab intra-arterially at up to 0.25 mg/kg (the recommended loading dose). We administer the intra-arterial dose in

Table 1
Summary of available case series reporting the administration of glycoprotein IIb/IIIa inhibitors for the management of thromboembolic complications encountered during endovascular procedures

Study (reference number)	Number of patients	IIB/IIIA agent (route of administration, number of patients)
Wallace et al, 1997 [93]	1	Abciximab (IV)
Lempert et al, 1999 [94]	1	Abciximab (IV)
Tong et al, 2000 [95]	1	Abciximab (IV)
Cloft et al, 2001 [96]	4	Abciximab (IV)
Ng et al, 2001 [97]	1	Abciximab (IV)
Duncan et al, 2002 [98]	5	Abciximab (IA)
Kwon et al, 2002 [99]	2	Abciximab (IA)
Alexander et al, 2002 [100]	1	Abciximab (IV)
Workman et al, 2002 [68]	5	Abciximab (IV, 4); Eptifibatide (IV, 1)
Fiorella et al, 2004 [71]	13	Abciximab (IV, 8; IA, 5)
Mounayer et al, 2003 [101]	13	Abciximab (IA 13) 4 ruptured
Song et al, 2004 [102]	7	Abciximab (IA 7) 4 ruptured

Abbreviations: IA, intra-arterial; IV, intravenous.

2- to 5-mg aliquots through a microcatheter positioned in the vicinity of the thrombus and perform control angiography periodically through the guiding catheter to document the status of the clot. Additional doses are administered intra-arterially as needed to achieve adequate thrombolysis. Adequate lysis is sometimes achieved after the first or second aliquot administered (see Fig. 4). Correspondingly, the intra-arterial administration of abciximab using this methodology results in a lower total dose of abciximab than that administered by the intravenous route, in which the entire dose (0.25 mg/kg) is administered as a bolus. The lower dose of abciximab used with this technique of intra-arterial administration should be associated with a shorter and less intense inhibition of systemic platelet function. Correspondingly, intra-arterial administration would be expected to involve a lower risk of intra- and extracranial hemorrhagic complications.

If the thromboembolic complication occurred as a sequela of a permanent thrombogenic foreign body (eg, a coil pack with some extension into the parent vessel) implanted in the setting of an acutely hemorrhagic lesion (eg, ruptured aneurysm or AVM), the patient is started on aspirin (162–325 mg) immediately after the procedure, provided that no hemorrhagic complication is identified on postprocedural CT imaging. In these cases, antiplatelet therapy (aspirin at a dose of 81 mg/d) is continued indefinitely unless discontinuation is required for another interventional procedure (eg, ventriculoperitoneal shunt placement). Because most thromboembolic complications related to aneurysm embolization occur within the first 24 to 48 hours, it is best if such procedures can be delayed for at least 2 days after the initial procedure [72].

The intravenous route of administration as a bolus and infusion provides a longer duration of platelet blockade and does not require the superselective positioning of a microcatheter. If a thromboembolic complication occurs as the result of a fixed intravascular thrombogenic focus implanted during the treatment of a lesion that has not recently hemorrhaged, a longer acting platelet blockade may be advantageous. In these situations, the thrombus is also frequently small (seen as a filling defect adherent to the coil pack) and does not compromise flow within the parent vessel. Correspondingly, the slightly slower onset of action observed with the intravenous route of abciximab administration is also usually acceptable in these situations. The intravenous route of administration is technically easier and may also be optimal for thromboembolic complications observed during diagnostic angiography, in which the introduction and selective positioning of a microcatheter would entail a significant delay in therapy.

Acute stroke intervention

At the time of percutaneous intervention, most thromboembolic occlusions are caused primarily by relatively organized clot containing platelets, thrombin, and fibrin mesh. After successful fibrinolysis with an agent like rtPA, thrombin and other soluble agonists are released locally in high concentrations, resulting in local platelet activation and aggregation. Aggregation of these activated platelets may obstruct the distal microcirculation and frequently result in reocclusion at the point of the initial obstruction [73–75]. In addition, the new thrombus generated is predominantly composed of platelets and is thus relatively resistant to the effects of the fibrinolytic agents. This phenomenon is observed not only in the cerebrovasculature but in the coronary circulation. For this reason, interventional cardiologists began to use abciximab in concert with fibrinolytic agents to facilitate recanalization of occluded coronary arteries. In the Thrombolysis in Myocardial Infarction (TIMI) [76] 14 study (888 patients), the addition of abciximab augmented the rate and extent of thrombolysis with reduced doses of alteplase. TIMI grade 3 flow at 60 minutes increased from 43% with alteplase alone to 72% using a 50 mg regimen of alteplase over 60 minutes combined with abciximab—a 67% relative increase and a 29% absolute difference in TIMI grade 3 flow rates. Ohman et al [77] observed a similar benefit when eptifibatide was combined with alteplase in patients undergoing acute MI with more complete reperfusion (TIMI grade 3 flow, 66% versus 39%) and a shorter median time to ST-segment recovery in those patients receiving eptifibatide.

Little data exist describing the efficacy of IIb/IIIa inhibitors for the treatment of acute stroke. The combination of IIb/IIIa inhibitors with rtPA significantly reduced infarct size and improved neurologic outcome in a rat model of embolic stroke [78]. In a rabbit stroke model, animals given IIb/IIIa inhibitor with rtPA also paradoxically showed significantly fewer intracerebral hemorrhages than those given rtPA alone [79].

The investigators theorized that the increased rate of hemorrhage in the rtPA-only group may have been attributable to increased reocclusion of cerebral vessels after initial thrombolysis.

In an acute ischemic stroke study, abciximab was administered parenterally to 54 stroke patients up to 24 hours (median of 12 hours) after the onset of symptoms. Although this therapy resulted in 10 asymptomatic cerebral hemorrhages in the abciximab group compared with only 1 in the placebo group, the number of symptomatic hemorrhages did not increase and the abciximab group trended toward a higher rate of excellent recovery at 3 months compared with the placebo group [80]. Seitz et al [81] compared intravenous rtPA with intravenous rtPA plus tirofiban. The patients who received rtPA and IIb/IIIa inhibitors had no higher incidence of hemorrhagic conversion and also had a better modified Rankin Scale (mRS) score at discharge compared with controls. Eckert et al [82] treated 3 patients with vertebrobasilar occlusion with local intra-arterial rtPA in combination with abciximab. Recanalization with clinical improvement occurred in 2 of the 3 patients, and there were no hemorrhagic complications. Junghans et al [83] treated 18 patients with progressive acute ischemic stroke with intravenous tirofiban. None of the patients suffered a major intracranial hemorrhage, and 6 patients sustained asymptomatic hemorrhagic conversion of their stroke.

Although the application of IIb/IIIa inhibitors to achieve acute revascularization likely represents a safe and efficacious strategy, caution must be exercised in those patients already treated with antiplatelet agents. Cheung and Ho [84] reported massive hemorrhagic transformation of an ischemic cerebral infarction in a patient given intravenous abciximab who had been on aspirin and Ticlid therapy. Qureshi et al [62] reported seven patients who developed fatal intracerebral hemorrhages after receiving abciximab during neurointerventional procedures. In all seven patients, abciximab was used in combination with heparin and clopidogrel.

We have recently completed a study designed to examine the safety of the combined administration of intra-arterial rtPA and IIb/IIIa inhibitors in the setting of acute stroke [85]. In our case series, we sought to use primarily rtPA and mechanical thrombolysis with compliant balloon angioplasty to achieve flow restoration. Subsequent intra-arterial IIb/IIIa administration was undertaken only in cases in which attempted rtPA and/or mechanical thrombolysis primarily failed or in the setting of acute reocclusion after initially successful thrombolysis. Of the 21 patients who received combined therapy, 3 patients had asymptomatic postprocedural hemorrhages on CT. No symptomatic or fatal hemorrhagic complications were observed. Partial or complete recanalization occurred in 17 of 21 patients (81%) despite the selection of failed cases. After thrombolysis, 62% of patients were functionally independent (mRS score of 0–3), including half of those patients who presented with basilar thrombosis. These results compare favorably with those of the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) study [86], which documented a recanalization rate of 66% and a rate of intracerebral hemorrhage associated with neurologic deterioration of 10% within 24 hours. A more relevant comparison can be made to case series in which salvage angioplasty was pursued in the patients resistant to thrombolytic infusion. Ringer et al [87] reported a recanalization rate of 56% in 9 patients with inadequate recanalization after initial thrombolytic infusion. Ueda et al [88] performed balloon angioplasty in acute stroke patients with more than 70% stenosis of the offending vessel after thrombolysis. Their recanalization rate was 84% in 13 patients; however, not all the patients had an occlusion refractory to local thrombolytics.

On the basis of these results, we have started to incorporate abciximab into our routine armamentarium for the treatment of acute stroke in those cases in which the US Food and Drug Administration–approved mechanisms for clot retrieval are not possible or do not yield sufficient recanalization. In these instances, we administer alternating doses of rtPA and abciximab in concert with compliant balloon angioplasty to achieve primary recanalization. On the basis of our previous experience, we limit our doses of abciximab to 0.125 mg/kg (one half of the recommended intravenous loading bolus). In these cases, we are not attempting to achieve a systemic level of therapeutic inhibition of platelet activity; as such, we do not routinely verify platelet inhibition with platelet function testing.

Stroke prevention

With increasing frequency, the interventional neuroradiologist and endovascular neurosurgeon are involved in determining appropriate treatment regimens for stroke prevention in patients with symptomatic carotid and intracranial atheromatous disease. As such, the question arises as to the

optimal preventative therapy for acute stroke in these patients. This topic remains the subject of avid contention, and no widely accepted conclusion has been reached at this point.

When evaluating the available data, it is important to consider that most patients evaluated by the neurointerventionist represent only a fraction of the overall cohort of patients requiring pharmacotherapy for secondary prevention for stroke. Only 20% of ischemic stroke is accounted for by patients with atherosclerotic cerebrovascular disease, whereas the remainder is composed of patients with penetrating artery disease and/or small-vessel ischemic disease (25%), cardiogenic embolic disease (20%), cryptogenic causes (30%), and other more rare causes (5%; hypercoagulable states, dissection, vasculitis, vasospasm, and drug related). The heterogeneity of this disease process is particularly relevant in the acute postinfarct period, in which patients with large-artery atheromatous disease are at a much greater risk of clinical deterioration and recurrent stroke. The 30-day risk of recurrent stroke has been reported to be approximately 8% for these patients, which is six times greater than that observed in patients with nonatheromatous stroke [89,90].

As such, much of the available data from the preventative neurology literature (which groups all patients together) is not directly applicable to neuroendovascular patients. Arguably, the subset of the disease process treated by the neuroendovascular interventionist (intra- and extracranial large-vessel atheromatous disease) is more analogous to symptomatic CAD than it is to the remainder of the ischemic stroke population. Correspondingly, it is probably prudent to take guidance from the preventative cardiology literature as well as from the "all-inclusive" preventative stroke literature.

For symptomatic patients who have not been previously treated with an antiplatelet agent, single antiplatelet therapy is probably adequate, consisting of aspirin (50–325 mg/d) or clopidogrel (75 mg/d). Data from the CAPRIE trial [15] and the Ticlopidine Aspirin Stroke Study Group [91] would suggest that there may be a small benefit in choosing a thienopyridine over aspirin as a single agent from the standpoint of the prevention of vascular events as well as from that of a lower risk of a bleeding complication. The only compelling reasons to choose clopidogrel as a first-line agent are aspirin intolerance or aspirin resistance as demonstrated by platelet aggregation studies. Whether there is a beneficial effect of adding clopidogrel to aspirin for stroke prevention is not currently known. Although the CURE study [51] suggests a benefit of dual therapy for the prevention of vascular events, the MATCH study results argue against this.

A recent meta-analysis (merged data from 7 trials involving 11,459 patients) supported the utility of extended-release dipyridamole in addition to aspirin for secondary stroke prevention, with the combination of agents yielding a significant benefit when compared with aspirin therapy alone in patients with previous ischemic stroke or TIA (22% RRR when compared with aspirin alone and 39% RRR in comparison to placebo). Although much of the data supporting the utility of dipyridamole was derived from a single study, ESPS-II, a significant benefit was still observed when these data were excluded from the meta-analysis [92]. Significantly less data exist supporting the utility of dipyridamole in comparison to the other antiplatelet agents, however, and further study is warranted. Two large trials are now underway that should provide further insight into this issue: the ESPRIT (anticoagulation versus aspirin at a dose of 30–325 mg/d versus aspirin at a dose of 20 mg) with extended-release dipyridamole (200 mg administered twice a day), and the Prevention Regimen for Effectively Avoiding Secondary Strokes (PRoFESS) (aspirin with extended-release dipyridamole versus clopidogrel). Given the relative paucity of data directly evaluating the efficacy of dipyridamole in the population of patients with large-vessel atheromatous disease and the theoretic risk of exacerbating coronary artery ischemia in patients with significant CAD, we prefer aspirin or clopidogrel as a primary agent for stroke prevention pending the results of the trials that are currently underway.

Regardless of the agent selected, as they become more widely available, platelet function tests should provide a useful means by which to verify the efficacy of the chosen therapy. If a given regimen produces inadequate levels of platelet inhibition, the dosing regimens or agents used should be changed. Also, if aspirin is used as the agent of choice, periodic platelet function tests may be indicated, because previous studies have demonstrated that resistance to aspirin therapy may develop over time [9]. Platelet function should always be assessed with any evidence of treatment failure so as to verify the continued efficacy of the agent used and to evaluate patient compliance.

If a patient fails single-agent therapy with aspirin as indicated by a neurologic or nonneurologic vascular event (MI or peripheral vascular event), the patient should be changed to clopidogrel or clopidogrel should be added to the aspirin therapy [29]. If the patient fails adequate dual-antiplatelet therapy, neuroendovascular intervention or cerebrovascular bypass options should be strongly considered. If revascularization procedures are not feasible, the addition of coumadin should be considered.

Summary

Our understanding of the pharmacology of antiplatelet therapy continues to evolve rapidly. Although the existing data are primarily generated in the setting of interventional and preventative cardiology studies, these data may be extrapolated to guide the rational application of these agents in neuroendovascular procedures. Platelet function testing represents an increasingly available and practical method by which to verify the adequacy of therapy and guide clinical decision making. The optimal application of these agents will undoubtedly improve the risk profile of neuroendovascular procedures, increase the success rate of acute stroke intervention, and facilitate more effective secondary stroke prevention.

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