Chapter 44
Neuroendovascular Surgery Medications

Ron Neyens

Antithrombotics

In order to minimize periprocedural thromboembolic complications, clinicians must understand the hematological system and targeted treatment strategies. The current physiology of hemostasis has evolved into a cell-based model with the platelet serving an integral role along all phases from clot initiation, amplification, and propagation [1, 2] (Fig. 44.1). In a traditional sense, endothelial injury/irritation occurs (plaque rupture, trauma, or catheter/balloon/stent interface), and the platelet immediately interacts with subendothelial proteins (tissue factor, von Willebrand factor, collagen matrix) *initiating* platelet adhesion and activation. It is followed by a thrombin-mediated *amplification* and release of soluble agonists (adenosine diphosphate, thromboxane A_2, serotonin) inducing recruitment, aggregation, and, finally, fibrinogen cross-linking with the glycoprotein (GP) IIb/IIIa receptor. Concomitantly, coagulation factors assemble on the surface of platelets, monocytes, and macrophages, *propagating* a tissue factor-initiated and thrombin-activated burst within both the prothrombinase complex and the intrinsic tenase. The magnitude of response and the strength of the formed clot depend upon the degree of endothelial injury as well as the concentration and activity of platelet/coagulation factors. In the absence of specific endothelial damage, endovascular-specific factors (composition of implants/tools, surface charge, contrast, and sheer stress) may initiate an inflammatory response to the "foreign body" and serve as the *initiating* phase of platelet activation and aggregation [3].

Therefore, the goal of pharmacological therapy is to prevent/minimize thrombus formation by decreasing platelet activity (via inhibiting adhesion/aggregation) and/

R. Neyens (✉)
Department of Pharmacy Services, Medical University of South Carolina, Charleston, SC, USA
e-mail: neyens@musc.edu

A. M. Spiotta et al. (eds.), *Management of Cerebrovascular Disorders*,
https://doi.org/10.1007/978-3-319-99016-3_44

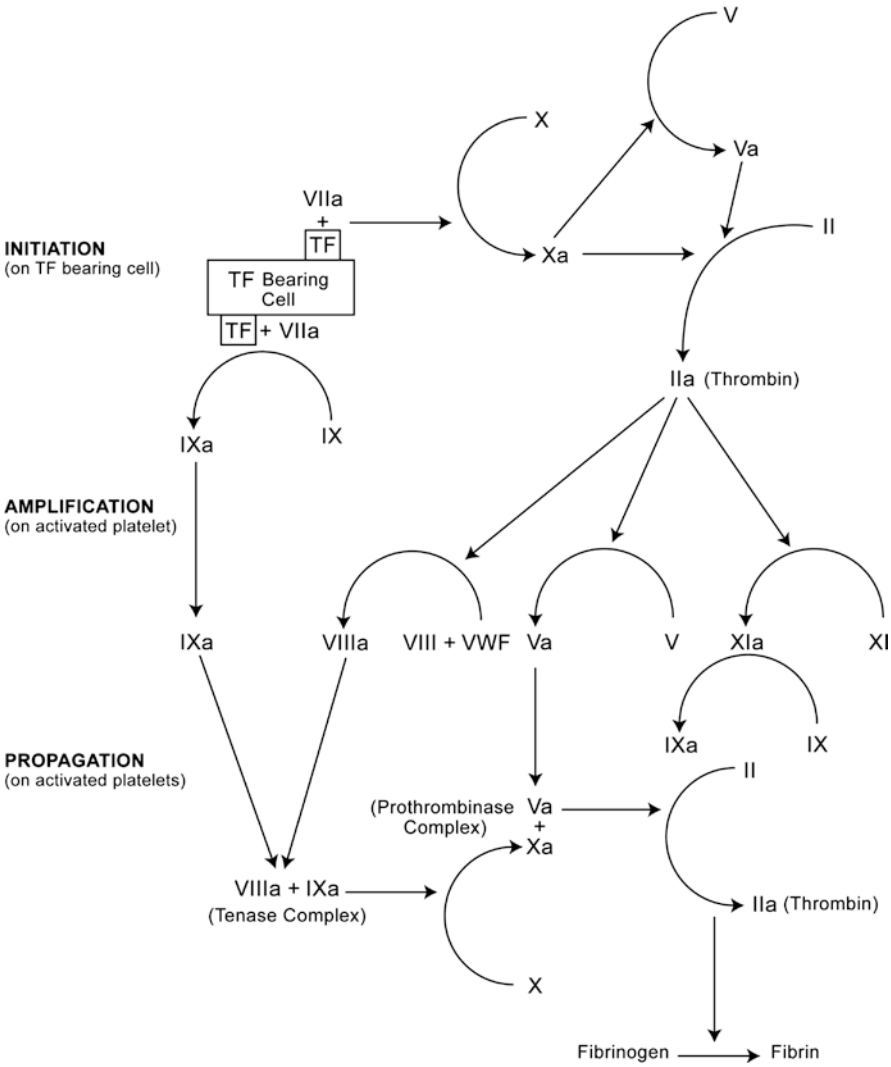

Fig. 44.1 Diagrammatic representation of cell-based model of hemostasis comprising initiation, amplification, and propagation. TF, tissue factor; a, activated [1]. (From Vine [1], with permission)

or thrombin-mediated propagation of fibrin formation. The greatest thrombosis risk ensues acutely over the initial 24 h following the NES procedure and/or endothelial injury and may maximally persist for up to 72 h until the local concentration of tissue factor and thrombin slowly dissipates [4]. If an implant is deployed, the thrombosis risk is extended into the subacute (within 30 days), late (within 1 year), and possibly the very late (greater than 1 year) phases [5]. It at least extends until neointimal endothelialization occurs, with the risk being device and location dependent, lasting at least a few weeks to several months.

Anticoagulation

Unfractionated Heparin (UFH)

Unfractionated heparin is the predominant anticoagulant utilized in the majority of neuroendovascular cases (Table 44.1). It carries a long history in interventional cardiology for the management of acute coronary syndrome (ACS) with clinical application extending to the management of NES cases. Of all current intravenous anticoagulants, it presently remains the most ideal given its vast clinical experience, ease of monitoring, and reversibility. It binds and forms an UFH-antithrombin III (AT-III) complex facilitating the inactivation of factors IIa, IX, Xa, XI, and XII [6]. By inhibiting factor IIa, it prevents the conversion of fibrinogen to fibrin, thus preventing clot propagation. In addition, it may inhibit thrombin-induced activation of platelets and factors V and VIII [10]. However, the clinical utility remains to be defined, and it must be carefully balanced with an observed UFH dose-dependent aggregation of platelets.

The dose of UFH for neuroendovascular procedures is not standardized and can be highly variable depending upon the amount of circulating AT-III, neutralizing acute-phase reactant proteins, degree of heparin clearance, and procedural hemorrhagic risk [7]. There is a myriad of reported doses, fixed at 3000–10,000 units, as

Table 44.1 Characteristics of anticoagulants and fibrinolytics for neuroendovascular procedures

Drug	Dose	Pharmacokinetics/ Pharmacodynamics	Considerations
Unfractionated heparin	IV: 3000–5000 units, titrate to ACT goal ACT: 1.5–2.5x baseline (200–350 s)	Onset: immediate T 1/2: 30–60 min (dose dependent)	Thrombocytopenia HIT (type I): little clinical significance HIT (type II): 1–2%, onset 4–10 days, prothrombotic Antidote Protamine: 1 mg/100 units UFH
Bivalirudin	IV: 0.6 mg/kg bolus and then 1.25 mg/kg/h (ACT 300–350 s) IV: 0.5 mg/kg bolus and then 0.8 mg/kg/h (ACT 200–300 s)	Onset: immediate T 1/2: 25 min (longer if renal impairment)	HIT history (preferred anticoagulant) Antidote None, may consider PCC in severe cases
Alteplase	IA: 2–5 mg aliquots up to max of 25 mg (total) IV: 1–2 mg/h (local catheter directed)	Onset: immediate T 1/2: 5 min 80% cleared within 10 min Lytic activity persists for ~1 h	Hypofibrinogenemia Lytic infusion: fibrinogen goal of 150–200 mg/dL Angioedema: <1% ACE-I increases risk

Data from Refs. [6–9]

well as weight-based doses ranging from 50 to 100 units/kg. The goal activated clotting time (ACT) is based on expert opinion, limited literature in carotid stenting, and often extrapolated from cardiac literature, which doesn't account for the technical difficulties encountered in NES procedures as well as the risk of dissections, thromboembolism, and vessel rupture. It is suggested to use a lower goal (ACT 200–300 s) for embolization of aneurysms and arteriovenous malformations (AVMs), whereas a higher goal (ACT 300–350 s) may be warranted for angioplasty and stenting [7]. It may be best to start with an UFH dose of 3000–5000 units (depending upon the procedural risk and patient weight) and then supplement to achieve the desired ACT. However, it is encouraged that each neuroendovascular group develop an appropriate UFH dose based on the utilized point-of-care ACT machine, reagent sensitivity, and desired ACT goal.

Direct Thrombin Inhibitors (DTIs)

There are currently two intravenous (IV) DTIs (bivalirudin and argatroban) in clinical use. In comparison with bivalirudin, argatroban has a longer half-life, which may not be an ideal agent for neuroendovascular procedures given the risk of hemorrhagic complications and the lack of a reversal antidote. In addition, argatroban dosing is often much less predictable provided its clearance is highly dependent upon hepatic blood flow and metabolic function. Bivalirudin has the majority of literature in both interventional cardiology and neuroendovascular procedures. In fact, it had gained traction as the preferred anticoagulant over UFH for percutaneous coronary intervention (PCI) given more predictable titration, the absence of platelet aggregation, and fewer periprocedural complications. However, most recent evidence for PCI stent deployment with the use of improved techniques, newer generation stents, and lower UFH doses now reveal that periprocedural complications are similar, which will possibly drive change back to UFH given the ease of reversibility and a much improved pharmacoeconomic profile [11]. Bivalirudin inhibits both free and clot-bound factor IIa, whereas UFH only inhibits free factor IIa; however, the clinical relevance of this is lacking in endovascular procedures. At present, given bivalirudin's similar efficacy/safety, high cost, and lack of reversibility, its clinical role is confined to cases of immune-mediated heparin-induced thrombocytopenia (HIT) or heparin resistance with the inability to reliably achieve targeted anticoagulation with UFH [12].

The dose of bivalirudin for neuroendovascular procedures is limited, but it is often lower than interventional cardiology procedures given the differing ACT goals. It is suggested that a dose of 0.6 mg/kg followed by a continuous infusion of 1.25 mg/kg/h is effective at maintaining an ACT of 300–350 s [8]. The bolus/maintenance dose would require incremental adjustments depending upon the procedural risk and the desired ACT. It does have some renal elimination (~10–20%) and will require dose adjustment in patients manifesting severe renal impairment (creatinine clearance <30 mL/min).

Fibrinolytics

Intra-arterial thrombolytics have been used for several years in the acute management of coronary and cerebrovascular ischemic disease (Table 44.2). Multiple agents are approved; however, only alteplase (tPA) is currently utilized clinically during neuroendovascular procedures. All serve as plasminogen activators, converting it into plasmin, which lyses fibrin-based clots into soluble degradation products. Pro-urokinase (first-generation thrombolytic) improved recanalization rates and functional outcome, but it also increased rates of intracranial hemorrhage [16]. Alteplase, being a newer-generation agent, is more clot/fibrin specific, targeting its dynamic action to the site of interest, thus improving the rates of clot dissolution with a theoretical lower risk of hemorrhage. It is currently utilized intra-procedurally for the management of ischemic stroke and for thromboembolic rescue treatment. However, its endovascular use in ischemic stroke has declined significantly as mechanical clot disruption techniques have advanced and rescue treatment is often considered to be inferior to glycoprotein (GP) IIB/IIIa inhibitors secondary to lower recanalization rates and higher hemorrhagic complications [9]. This is conceivable as acute, periprocedural clots tend to be very platelet rich with limited amounts of fibrin, thus mechanistically supporting a superior role for platelet inhibitors.

Antiplatelets

Cyclooxygenase Inhibitor

Aspirin has a long-standing history in interventional cardiology and was routinely utilized as mono-antiplatelet therapy alongside anticoagulation until the mid-1990s to early 1990s when it was discovered that local platelet deposition and activation were major periprocedural risk factors in thrombosis (Table 44.2 and Fig. 44.2) [13]. It was then delineated that dual antiplatelet therapy (DAPT) following PCI stent deployment is superior to aspirin/anticoagulation for preventing stent thrombosis, ischemic events, and hemorrhagic complications. This same finding has also been replicated in carotid artery stenting [18]. Initially, aspirin was combined with ticlopidine but later transitioned to combine with newer-generation P2Y12 inhibitors given the lower incidence of life-threatening hematological disorders. Aspirin irreversibly inhibits cyclooxygenase (COX), blocking the conversion of arachidonic acid to prostaglandins and thromboxane A_2, thereby inhibiting platelet aggregation [14].

P2Y12 Inhibitors

There are currently three oral P2Y12 inhibitors in clinical use (clopidogrel, prasugrel, and ticagrelor). Again, the majority of the literature is in interventional cardiology with extrapolated application to neuroendovascular procedures.

Table 44.2 Characteristics of antiplatelets for neuroendovascular procedures

Drug	Dose	Pharmacokinetics/ pharmacodynamics	Considerations
Aspirin	Oral Load: 325–650 mg Maintenance: 81–325 mg daily Rectal Load: 300–600 mg	Onset: 20–60 min (immediate release) T 1/2: 15–20 min (parent); 3–4 h (salicylate) Duration: 5–7 days	Resistance: 6–27% Hypersensitivity Urticaria-angioedema: 2–4% Bronchospastic: 10–15% of asthmatics
Clopidogrel	Oral Load: 300–600 mg Maintenance: 75 mg daily	Onset (time to 40–50% inhibition) 300 mg (6–10 h) 600 mg (2–6 h) T 1/2: 6 h (parent), 30 min (active) Duration: 5–10 days	Resistance: 10–48% ADRs: Hematological (rare) Hypersensitivity Anaphylaxis (rare) Rash: 3–5%, can attempt desensitization or substitute ticagrelor
Ticagrelor	Oral Load: 180 mg Maintenance: 90 mg BID	Onset (time to 70–80% inhibition) 180 mg (45–60 min) T 1/2: 7 h (parent), 9 h (active) Duration: 3–5 days	Resistance: n/a ADRs: Hematological (rare); dyspnea, 10–15%; hyperuricemia, 15–20%
Prasugrel	Oral Load: 60 mg Maintenance: 10 mg daily 5 mg (<60 kg)	Onset (time to 70–80% inhibition) 60 mg (45–60 min) T 1/2: 7–15 h (parent), 4–7 h (active) Duration: 5–10 days	Resistance: n/a ADRs: Hematological (rare) Black box: prior TIA or stroke
Abciximab	IV: 0.25 mg/kg bolus and then 0.125 mcg/kg/min IA: Variable 2–5 mg aliquots, up to max of 20–25 mg (total) 0.25 mg/kg	Onset (time to 70–80% inhibition) 0.25 mg/kg (10 min) T 1/2: 30 min Duration: variable ~75% platelet recovery at 48 h	Thrombocytopenia Actual: 0.5–5% Pseudo-(lab artifact): 1–2%, rule out by sending EDTA, citrate, and heparin tubes Hypersensitivity (rare) Immunogenicity Antibodies: ~5–7% with risk of infusion reactions and thrombocytopenia upon reexposure
Eptifibatide	IV: 180 mcg/kg bolus and then 0.5–2 mcg/kg/min IA: Variable 2 mg aliquots, up to max of 22 mg (total) 0.2 mg/kg	Onset (time to 70–80% inhibition) 180 mcg/kg (5–10 min) T 1/2: 2.5 h Duration: 4–8 h	Thrombocytopenia (rare)
Tirofiban	IV: 8–25 mcg/kg bolus and then 0.1–0.15 mcg/kg/min IA: Variable 0.2 mg aliquots, up to max of 1 mg (total) 0.3 mg aliquots, up to max of 1.2 mg (total)	Onset (time to 70–80% inhibition): 25 mcg/kg (5–10 min) T 1/2: 2 h Duration: 4–8 h	Thrombocytopenia (rare)

Data from Refs. [13–15]

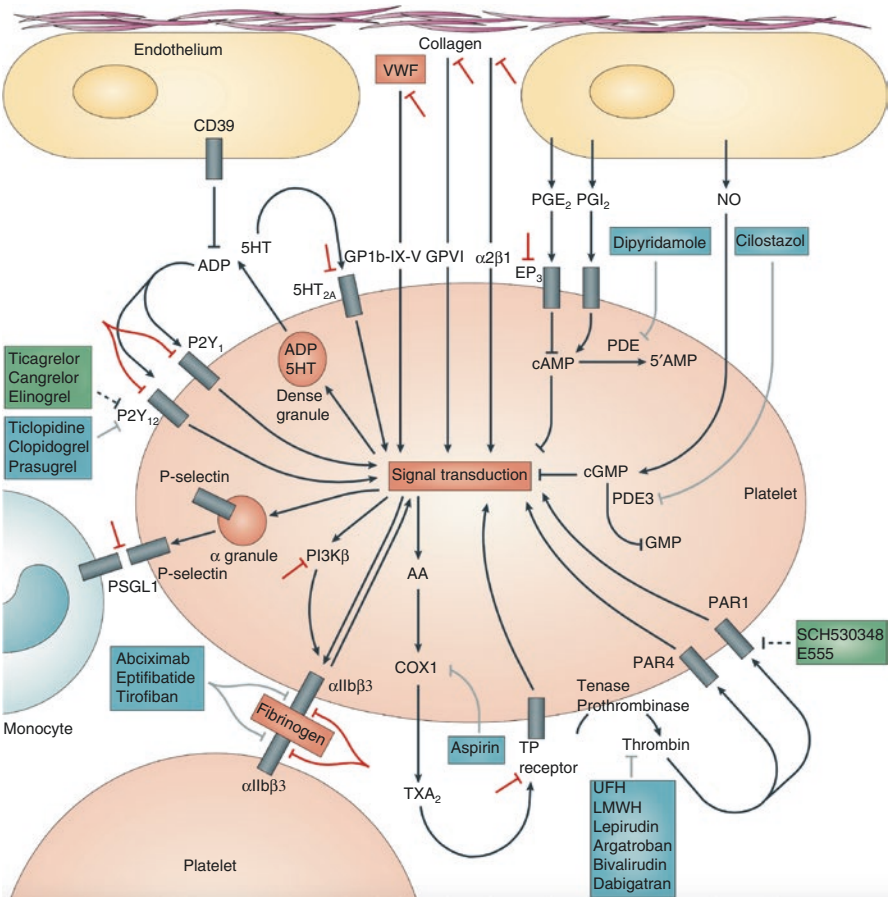

Fig. 44.2 Platelet function and molecular targets of antiplatelet agents. Initial platelet adhesion to damage vessel walls is mediated by the finding of exposed collagen to platelet surface glycoprotein Vl (GPVI) and integrin alpha2beta1 and the binding of von Willebrand factor (VWF) to the platelet surface glycoprotein 1b (GP1b)-IX-V complex. (From Michelson [17], with permission)

Clopidogrel was the first ticlopidine replacement and has been used for several years. Recently, newer-generation agents (prasugrel and ticagrelor) are being established as preferred therapy in acute coronary syndromes (ACS) following PCI stent deployment, especially in high-risk patients (large stent burden, diabetics) and those with high on-treatment platelet reactivity with clopidogrel [14]. The literature for novel antiplatelet agents in NES procedures is limited with the majority of case reports/series involving those expressing high on-treatment platelet reactivity with clopidogrel. All the P2Y12 inhibitors block ADP binding to the P2Y12 receptor, thereby inhibiting platelet aggregation [13]. However, they all have differing PK/PD, specifically in regard to the activation, onset, and/or potency of platelet inhibition. Clopidogrel and prasugrel are both irreversible

thienopyridine prodrugs requiring metabolic cytochrome P450 hepatic activation. Clopidogrel requires two-step activation and is more susceptible to drug-drug interactions (CYP2C19 inhibitors) and genetic polymorphisms exposing patients to a greater risk of hypo- or hyperresponse. Ticagrelor is an irreversible, (this should state, Ticagrelor is a reversible), direct-acting non-thienopyridine that does not require metabolic activation. Ticagrelor and prasugrel are both more potent than clopidogrel and superior in preventing coronary stent thrombosis and ischemic events. However, the trade-off is more hemorrhagic complications. Of importance to NES procedures, prasugrel carries an FDA black box warning for intracranial hemorrhage risk in patients with a prior transient ischemic attack (TIA) or stroke. It also requires weight-based dose adjustments adding to its dosing complexity. These specific factors have driven a shift toward the use of ticagrelor in situations requiring the use of a newer-generation P2Y12 inhibitor.

GP IIb/IIIa

There are currently three GP IIb/IIIa inhibitors in clinical use (abciximab, eptifibatide, and tirofiban). There are several years of experience with all three agents in interventional cardiology. Initially, abciximab was felt to be a superior agent theorized to be driven by its unique ability to inhibit endothelial and smooth muscle receptors preventing platelet adhesion and limiting inflammation [15]. Following dose optimization, evidence now suggests that the GP IIb/IIIa inhibitors have similar efficacy and safety outcomes after coronary revascularization. Abciximab has the majority of literature for neuroendovascular procedures; however, evidence for eptifibatide and tirofiban are accumulating. In fact, a recent meta-analysis suggested an improved recanalization rate with eptifibatide or tirofiban following aneurysm coil thrombosis rescue strategies [9]. The GP IIb/IIIa inhibitors block the final common pathway of fibrinogen cross-linking of platelets, thereby inhibiting platelet aggregation; however, they have different PK/PD. Abciximab is a large-molecule, monoclonal antibody that displays a long half-life and irreversibly binds the GP IIb/IIIa receptor [15]. Intermittent abciximab intravenous (IV)/intra-arterial (IA) bolus dosing strategies display a theoretical advantage in stent or flow-diverter deployment given the longer half-life and its potential to provide a longer duration of platelet inhibition while awaiting the onset of DAPT. However, the clinical application remains undefined but may be of relevance in emergent cases in which planned initiation of DAPT is not feasible. In comparison, eptifibatide and tirofiban are small-molecule, reversible inhibitors. The shorter half-lives may be attractive as bridge therapy post-procedural, before committing to DAPT, until the clinician is sure no open intracranial procedure or intracranial device is required. The relevance of each situation depends upon the case complexity, dose, route (IA vs IV), and mode of administration (bolus vs continuous) of the GP IIb/IIIa inhibitor.

Antiplatelet Monitoring

Antiplatelet monitoring started in interventional cardiology with "resistance" or high on-treatment platelet reactivity to aspirin and/or clopidogrel being associated with increased rates of stent thrombosis and recurrent ischemic events [13]. Point-of-care platelet inhibition assays were then utilized to identify an optimal target to direct dose individualization. Despite all these efforts, clopidogrel dose individualization in large randomized studies didn't result in improved cardiac outcomes. The new P2Y12 inhibitors were then found to be more clinically effective in PCI stent deployment, halting further studies for point-of-care-directed clopidogrel dose individualization. However, the increased hemorrhage risk with the more potent, newer-generation P2Y12 inhibitors has created some trepidation to use as standard of care in all high-risk neuroendovascular procedures requiring DAPT. Therefore, the NES realm still faces the difficult questions regarding the utility of antiplatelet monitoring, the most appropriate assay, the goal inhibition targets, and the dosing strategy.

The rates of actual "resistance" are variable and dependent upon the patient population, exposure time, methodology, assay, and interpretative criteria [19]. The reported rates for aspirin and clopidogrel are between 6–27% and 10–48%, respectively. It appears to be dose related, with higher doses able to achieve a greater degree of platelet inhibition, and susceptible to comorbidities (diabetes, atherosclerosis, myeloproliferative syndromes, etc.). It is clearly associated with clinical ischemic and thrombotic complications in interventional cardiology with accumulating evidence for associated thrombotic complications in neuroendovascular procedures [13].

There are several monitoring assays available, light transmission aggregometry (LTA), whole blood aggregometry (WBA), and various point-of-care tests: PFA-100, thromboelastography (TEG) platelet mapping, flow cytometry (VASP), and VerifyNow [20]. Each test has unique limitations regarding individual covariance and sensitivity/specificity. LTA is considered the "gold standard" and serves as the correlative comparator for alternative methods. The ideal assay would be readily available, rapidly performed with good sensitivity and specificity, with clearly defined targets to direct clinical decisions. LTA is very labor intensive (~3–4 h) and not logistically feasible in most NES procedures. WBA (multiplate) is not routinely available in the United States and is poorly correlated to LTA. PFA-100 also has poor correlation to LTA and is deemed not suitable for detection of platelet "resistance." TEG platelet mapping appears to have good correlation to LTA but presently has limited data for interpretive criteria and clinical application to interventional procedures. VASP is unique in its ability to isolate the effects of clopidogrel in the presence of GP IIb/IIIa inhibitors, which is an advantage over other point-of-care assays. However, it is not routinely available and is technically challenging to perform. VerifyNow is specifically designed to rapidly detect antiplatelet drug "resistance" at the bedside, allowing for rapid clinical decisions. It has been the most studied assay, with more well-established interpretive criteria (aspirin reaction units (ARU) for aspirin and P2Y12 reaction units (PRU) for P2Y12 inhibitors) for clinical

application in both interventional cardiology and neuroendovascular procedures. However, it is important to note that the ARU and PRU results are affected by certain factors: patient comorbidities, timing and dose of loading strategies, and the presence of circulating GP IIb/IIIa inhibitors.

As mentioned, there are no well-defined inhibition targets, specifically PRU, when utilizing VerifyNow to direct clopidogrel dose response during neuroendovascular procedures. The cardiology literature suggests a targeted PRU window between 95 and 208 to balance both safety and efficacy [21]. In general, much of the neuroendovascular literature replicates efforts in interventional cardiology. The exception is for more thrombotic implants (pipeline embolization devices) where the target PRU range may ideally fall between a range of 70 and 150 [22]. However, some suggest a PRU < 200 is not necessary for anterior circulation pipeline embolization devices [23]. The most optimal treatment strategy to overcome hyporesponsiveness (PRU > upper limit target) of clopidogrel lacks supported literature; however, one may consider reloading and increasing the maintenance dose (150 mg/day) or switch to an alternative P2Y12 inhibitor (ticagrelor). In a similar fashion, those expressing hyperresponsiveness (PRU < lower limit target) may benefit from a clopidogrel dose reduction (75 mg QOD) or switch to an alternative P2Y12 inhibitor [24]. It is the author's opinion given the known risk of thrombotic and hemorrhagic complications with higher and lower than target PRUs, respectively, to consider an alternative P2Y12 inhibitor, preferably ticagrelor, which is not a prodrug requiring metabolic activation.

Cerebrovascular Vasodilators

Intra-arterial vasodilating agents are predominantly utilized for the treatment of arterial vasospasm as a complication of aneurysmal subarachnoid hemorrhage (Table 44.3) [25]. In addition, they may be utilized to dilate vessels and assist with catheter/device advancement during endovascular procedures. Historically, papaverine, an opium-based phosphodiesterase inhibitor, had been utilized. It has fallen out of favor provided concerns for drug-induced intracranial hypertension, seizures, and neurotoxicity. There are currently three pharmacological agents in clinical use (verapamil, nicardipine, and milrinone). The first two agents are calcium-channel blockers (CCBs), while the latter is a phosphodiesterase inhibitor (PDE3-I). Nicardipine is a more vascular-selective agent in comparison with verapamil. It does appear to provide effective angiographic vasodilation with documented reductions in cerebral blood flow (CBF) velocities and associated neurologic improvement. The greatest concern is hypotension, which may be profound and potentially prolonged leading to a reduction in cerebral perfusion pressures. Verapamil is less selective for the cerebral vasculature yet has been shown to provide effective angiographic vasodilation and associated neurologic improvement. Although hypotension may occur, it may be less common than nicardipine given its lower degree of vascular selectivity. Milrinone has more limited literature but appears to quickly

Table 44.3 Characteristics of vasodilators for neuroendovascular procedures

Drug	Dose	Pharmacokinetics/ pharmacodynamics	Considerations
Nicardipine	IA: total dose (variable), 5–40 mg Dilute with NS to concentration of 1 mg/mL, administer 0.5–1 mL in an aliquot dosing strategy	Onset: 30–60 s Duration: 1–3 h	Hypotension (dose related)
Verapamil	IA: total dose (variable), 1–40 mg Dilute with NS to concentration of 1 mg/mL, administer 1–5 mL in an aliquot dosing strategy	Onset: 1–5 min Duration: 20–40 min	Hypotension/ bradycardia (dose related)
Milrinone	IA: total dose (variable), 4–15 mg Dilute with NS to concentration of 0.1 mg/mL, administer 2–4 mL in an aliquot dosing strategy	Onset: 1–5 min Duration: 2–4 h	Hypotension/ tachycardia (dose related)

Data from Refs. [25, 26]

improve angiographic vasodilation [26]. There is no comparative evidence documenting superiority; therefore, agent selection is largely based on clinician comfort and experience.

References

1. Vine AK. Recent advances in haemostasis and thrombosis. Retina. 2009;29:1–7.
2. Ferreira CN, Sousa MO, Sant'Ana Dusse LM, et al. A cell-based model of coagulation and its implications. Rev Bras Hematol Hemoter. 2010;32:416–21.
3. Palmaz JC. Intravascular stenting: from basic science to clinical application. Cardiovasc Intervent Radiol. 1992;15:279–84.
4. Ferns GA, Stewart-Lee AL, Anggard EE. Arterial response to mechanical injury: balloon catheter de-endothelialization. Atherosclerosis. 1992;92:89–104.
5. Klisch J, Turk A, Turner R, et al. Very late thrombosis of flow-diverting constructs after the treatment of large fusiform posterior circulation aneurysms. AJNR Am J Neuroradiol. 2011;32:627–32.
6. Hirsh J. Heparin. N Engl J Med. 1991;324:1565–74.
7. Hussein HM, Georgiadis AL, Qureshi AI. Point-of-care testing for anticoagulation monitoring in neuroendovascular procedures. Am J Neuroradiol. 2012;33:1211–20.
8. Georgiadis AK, Shah Q, Suri FK, et al. Adjunct bivalirudin dosing protocol for neuro-endovascular procedures. J Vasc Interv Neurol. 2008;1:50–3.
9. Brinjikji W, Morales-Valero SF, Murad MH, et al. Rescue treatment of thromboembolic complications during endovascular treatment of cerebral aneurysms: a meta-analysis. AJNR Am J Neuroradiol. 2015;36:121–5.
10. Mascelli MA, Kleiman NS, Marciniak SJ, et al. Therapeutic heparin concentrations augment platelet reactivity: implications for the pharmacologic assessment of the glycoprotein IIb/IIIa antagonist abciximab. Am Heart J. 2000;139:696–703.
11. Valgimigli M, Frigoli E, Leonardi S, et al. Bivalirudin or unfractionated heparin in acute coronary syndromes. N Engl J Med. 2015;373:997–1009.
12. Hassan AE, Merron MZ, Georgiadis AL, et al. Safety and tolerability of high-intensity anticoagulation with bivalirudin during neurovascular procedures. Neurocrit Care. 2011; 15(1):96–100.

13. Gandhi CD, Bulsara KR, Fifi J, et al. Platelet function inhibitors and platelet function testing in neurointerventional procedures. J Neurointerv Surg. 2014;6:567–77.
14. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. Nat Rev Cardiol. 2015;12:30–47.
15. 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. 2007;9(Supp A):A32–6.
16. Del Zoppo GJ, Higashida RT, Furlan AJ, et al. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. Stroke. 1998;29:4–11.
17. Michelson AD. Antiplatelet therapies for the treatment of cardiovascular disease. Nat Rev. 2010;9:154–69.
18. Enomoto Y, Yoshimura S. Antiplatelet therapy for carotid artery stenting. Interv Neurol. 2013;1:151–63.
19. Oxley TJ, Dowling RJ, Mitchell PJ, et al. Antiplatelet resistance and thromboembolic complications in neurointerventional procedures. Front Neurol. 2011;2:1–9.
20. Le Quellec S, Bordet JC, Negrier C, et al. Comparision of current platelet functional tests for the assessment of aspirin and clopidogrel response. Thromb Haemost. 2016;116:638–50.
21. Stone GW, Witzenbichler B, Weisz G, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicenter registry study. Lancet. 2013;382:614–23.
22. Daou B, Starke RM, Chalouhi N, et al. P2Y12 reaction units: effect on hemorrhagic and thromboembolic complications in patients with cerebral aneurysms treated with the pipeline embolization device. Neurosurgery. 2016;78:27–33.
23. Bender MT, Lin L, Colby GP, et al. (2016) P2Y12 hyporesponse (PRU > 200) is not associated with increased thromboembolic complications in anterior circulation pipeline. J Neurointerv Surg. 2017;9(10):978–81.
24. Goh C, Churilov L, Mitchell P, et al. Clopidogrel hyper-response and bleeding risk in neurointerventional procedures. AJNR Am J Neuroradiol. 2013;34:721–6.
25. Weant KA, Ramsey CN, Cook AM. Role of intraarterial therapy for cerebral vasospasm secondary to aneurysmal subarachnoid hemorrhage. Pharmacotherapy. 2010;30:405–17.
26. Shankar JS, dos Santos MP, Deus-Silva L, et al. Angiographic evaluation of the effect of intraarterial milrinone therapy in patients with vasospasm from aneurysmal subarachnoid hemorrhage. Neuroradiology. 2011;53:123–8.