Update on pharmacology of antiplatelets, anticoagulants, and thrombolytics

Esteban Cheng-Ching, MD
Edgar A. Samaniego, MD, MS
Bharath Reddy Naravetla, MD
Osama O. Zaidat, MD, MS
Muhammad Shazam Hussain, MD

Correspondence & reprint requests to Dr. Hussain: HUSSAIS4@ccf.org

ABSTRACT

Understanding of the pharmacology of thrombolytics, anticoagulants, and antiplatelets is critical to performing safe and effective endovascular therapy for acute ischemic therapy. This is a basic review of the clinical pharmacologic data on the anticoagulants, antiplatelets, and fibrinolytic agents most commonly used in the treatment of stroke and in the neurointerventional suite. ***Neurology*® 2012;79 (Suppl 1):S68–S76**

GLOSSARY

CYP = cytochrome P450; **FDA** = US Food and Drug Administration; **HIT** = heparin-induced thrombocytopenia; **LMWH** = low-molecular-weight heparin; **Pro-UK** = prourokinase; **rtPA** = recombinant tissue plasminogen activator; **tPA** = tissue plasminogen activator; **UFH** = unfractionated heparin; **VTE** = venous thromboembolism.

Medical manipulation of thrombosis and hemostasis is the cornerstone of ischemic stroke therapy. From acute stroke therapy to secondary prevention of stroke, it is critical that practitioners understand the various drug therapies available and how these act upon the thrombosis cascade. This cascade has been reviewed in a separate publication in this supplement. Here we review the pharmacology of antiplatelet agents, antithrombotic agents, and thrombolytic agents (table 1), as well as platelet function testing (table 2).

SECTION I: ANTIPLATELET AGENTS Because of the central role of platelets in thrombus initiation, antiplatelet agents have been a main focus of secondary stroke prevention. US Food and Drug Administration (FDA)–approved agents for secondary stroke prevention include aspirin, clopidogrel, ticlopidine, and the combination of aspirin and dipyridamole (Aggrenox). Cilostazol is an antiplatelet medication that has been studied mostly in Asia. Each of these agents has specific characteristics and a side effect profile that may impact therapeutic selection.

Aspirin. Aspirin has shown to have substantial net benefit in secondary prevention of vascular events.[1,2] The daily dose of aspirin in clinical trials has ranged from 50 to 1,500 mg. Low doses (50 to 150 mg daily) have benefits similar to those of higher doses (500 to 1,500 mg daily). The most commonly used doses range from 50 to 325 mg daily.

Given its wide availability, low cost, and proven benefit, aspirin is the first-choice antiplatelet agent for the treatment and prevention of cerebrovascular disease. It is also widely used as an adjunctive antiplatelet agent in endovascular procedures, such as in the setting of aneurysmal coiling and after angioplasty and stenting (in the latter, usually in combination with clopidogrel in the acute period).

Mechanism of action. Aspirin irreversibly inhibits cyclo-oxygenase I, which normally acts upon arachidonic acid to produce prostaglandin G2, prostaglandin H2, and subsequently thromboxane A2. Loss of thromboxane A2 synthesis in platelets results in decreased ability for platelet aggregation.[3] Because of the irreversible inhibition of cyclo-oxygenase I and the inability of platelets to produce new cyclo-oxygenase, the aspirin effect is sustained until new platelets are produced, typically 7 to 10 days after a single dose.[4]

Oral aspirin is rapidly absorbed from the stomach and proximal small intestine (peak plasma concentrations within 30 minutes). Enteric coated tablets take longer to be absorbed, with peak concentrations occurring at 3 to 4 hours.[5]

From the Cleveland Clinic Stroke Program (E.C.-C., M.S.H.), Cleveland Clinic, Cleveland, OH; Stanford Stroke Center (E.A.S.), Stanford University, Palo Alto, CA; Neurovascular Service (B.R.N.), University of California, San Francisco; and Neurointerventional Division (O.O.Z.), Vascular and Interventional Neurology, Medical College of Wisconsin, Milwaukee.

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Table 1 Select antiplatelet, anticoagulant, and fibrinolytic agents

Class	Agent	Pharmacokinetics	Dosage
Oral antiplatelet agents	Aspirin	Rapid absorption within 1 h, but this is reduced with food and with enteric-coated formulation; metabolized through liver and kidney	50–325 mg orally daily
	Ticlopidine (Ticlid)	Better, more consistent absorption with food; metabolized mainly through liver; steady-state concentrations are ~2× as high in elderly patients	250 mg orally twice daily
	Clopidogrel (Plavix)	Well absorbed orally; a prodrug converted by liver to active metabolite through cytochrome P450 (CYP) system; genetic polymorphism (CYP 2C19) can result in reduced metabolism of prodrug to active metabolite, resulting in decreased effectiveness of platelet inhibition; proton pump inhibitors also interfere with CYP system and cause decreased effectiveness of drug's platelet inhibition when used in combination	75 mg orally daily; may load with 300–600 mg orally
	Dipyridamole	Peak plasma concentration 2 h post dose; metabolized by liver	Extended-release 200 mg twice daily; Aggrenox, which is combination of 200 mg extended-release dipyridamole plus 25 mg aspirin, is dosed as 1 tablet orally twice daily
	Cilostazol (Pletal)	Metabolized by liver, half-life = 10–13 h; in addition to antiplatelet effects, also causes smooth muscle relaxation and alteration of lipid profile by lower triglycerides and increasing high-density lipoproteins	100 mg orally twice daily
Glycoprotein IIb/IIIa inhibitors	Abciximab (Reopro)	In vitro platelet inhibition of the bound antibody for 18–24 h after infusion is stopped	0.25-mg/kg bolus followed by 0.125 μg/kg/min for 12 hours (in acute coronary syndromes)
		Unbound antibody is cleared from circulation in 10–30 min; after bolus administration, 28% occupation of the IIb/IIIa receptors is maintained for 8 d	Intra-arterial boluses (2–5 mg) have been used for intraoperative thromboembolic complications[a]
	Eptifibatide (Integrilin)	Platelet aggregation is restored within 6–12 h after infusion is stopped; excreted mostly renally	180-μg/kg bolus ×2 with 10 min apart, followed by 2-μg/kg/min infusion (in acute coronary syndrome and percutaneous coronary intervention)
	Tirofiban (Aggrastat)	Minimally hepatic metabolism; half-life elimination of 2 h; excreted mainly through kidneys	0.4-μg/kg/min bolus for 30 min and then 0.1-μg/kg/min infusion (in acute coronary syndromes)
Tissue plasminogen activators	Alteplase (Activase)	Clearance occurs by hepatic metabolism; half-life is 5–10 min	IV: loading dose of 0.09 mg/kg (10% of 0.9-mg/kg dose) as bolus over 1 min, followed by 0.81-mg/kg infusion over 60 min
			Intra-arterial alteplase in small bolus doses can be used, although optimal dose has not been established

[a] Fiorella et al.[39]

Recently, concerns have been raised about relative aspirin resistance as a potential role in recurrent ischemic events in patients on aspirin. Possible contributory factors should be investigated, including poor compliance, inadequate dosing, concurrent use of medications that interact with aspirin's action on cyclo-oxygenase I (nonsteroidal anti-inflammatory drugs), genetic polymorphisms, and increased platelet turnover. Increasing the dose of aspirin to partially overcome the resistance has been suggested; however, the exact best therapeutic approach for this situation is unknown.[6,7]

Side effects. Gastrointestinal effects, particularly ulcers of the upper gastrointestinal tract, are the main concern with aspirin therapy. These can lead to gastrointestinal bleeding, which can be severe and life-threatening. Bleeding at other sites is also possible, including intracranial bleeding. Throm-

Table 2 Platelet functional testing

Assay	Mechanism	Advantage	Disadvantage
Bleeding time	Earlobe or forearm incision; for latter, a sphygmomanometer is inflated to 40 mm Hg to standardize intracapillary pressure	Performed at bedside; low cost	Poorly reproducible, invasive; vWF and fibrinogen dysfunction affect results
Optical aggregometry	Light transmission measurement of agonist-induced platelet aggregation	Considered gold standard: good reproducibility	Complicated sample processing Expert personnel and labor intensive
Whole-blood aggregometry	Measurement of electrical impedance between 2 electrodes immersed in whole blood after addition of a platelet agonist	Less labor intense than optical aggregometry	Restricted to specialized laboratories
Point-of-care rapid platelet function (VerifyNow)	Light transmission measurement of agonist- and fibrinogen-coated beads	Simplified technology; user-friendly processing	Whole blood may affect platelet aggregation; not specific for platelet function, with vWF and fibrinogen dysfunction
Platelet function analyzer (PFA-100)	Measures time required for platelets to adhere to agonist-coated membranes and aggregate under shear stress	Simple; sensitive to hemostatic disorders	Does not measure platelet aggregation directly; not specific for platelet function, with vWF and fibrinogen dysfunction

Abbreviation: vWF = von Willebrand factor.

bocytopenia and pancytopenia have also been reported.

Thienopyridines (ticlopidine, clopidogrel, prasugrel). Ticlopidine was the first FDA-approved thienopyridine, but it is rarely used now, given the risk of significant neutropenia and the availability of clopidogrel, which has a similar mechanism of action but a safer profile.[5] Clopidogrel is used at a dose of 75 mg daily. Whereas several daily doses are required to achieve a steady state, a loading dose of at least 300 mg of clopidogrel produces a rapid onset of pharmacodynamic action.[8] A loading dose up to 600 mg may produce higher levels of the active metabolite and enhanced inhibition of adenosine diphosphate–related platelet aggregation.[9] Clopidogrel is widely used in patients with cerebrovascular ischemic disease, and in combination with aspirin it has been utilized in the acute setting after angioplasty and stenting.

Prasugrel is mostly used in cardiac patients. This medication has been associated with worse clinical outcomes and higher risk of bleeding in patients with history of cerebrovascular disease, leading to a black box warning, and it should not be used in this patient population.[10]

Mechanism of action. These agents act on the $P2Y_{12}$ receptor, irreversibly blocking adenosine diphosphate activation of this receptor, therefore disrupting the downstream signal transduction, with a net result of decreased stability of platelet aggregation.[5]

The most commonly utilized agent, clopidogrel, is administered orally once daily as a prodrug, which is metabolized to an active compound through the liver's cytochrome P450 (CYP) system. Genetic polymorphisms (CYP 2C19)[11] have been implicated in altered metabolism of clopidogrel, resulting in decreased effectiveness of the medication, with clinical consequences.[12] Pharmacokinetic and pharmacodynamic studies suggest that proton pump inhibitors (especially omeprazole) can attenuate the antiplatelet effect of clopidogrel. However, clinical observations and a randomized clinical trial have shown inconsistent evidence. Until further clinical trials better clarify this issue, the concomitant use of proton pump inhibitors and clopidogrel should be based on a detailed assessment of risk and benefits.[13]

Ticlopidine and prasugrel are also oral agents with similar mechanism of action, by inhibiting the $P2Y_{12}$ receptor. Prasugrel has faster peak effectiveness and increased potency in comparison with clopidogrel.[14]

Side effects. These agents can be associated with bleeding.

Ticlopidine has very limited use, mainly because of the potential for severe side effects: neutropenia and thrombotic thrombocytopenic purpura.

Clopidogrel has a superior safety profile, with lower risk of neutropenia and thrombocytopenia. Its main side effect is bleeding.

Prasugrel is associated with a much greater risk of bleeding than clopidogrel and is also associated with worse outcomes in patients with cerebrovascular disease.[10]

Dipyridamole (Aggrenox: extended-release dipyridamole in combination with aspirin). Dipyridamole has a short half-life and, as an immediate-release formulation, requires to be dosed 4 times a day. Therefore, extended-release formulation is preferred and used in combination with aspirin. This combination of extended-release dipyridamole and aspirin is FDA-approved for stroke prevention on the basis of results of the European Stroke Prevention Study 2 (ESPS-2) and European/Australasian Stroke Prevention in Re-

versible Ischaemia Trial (ESPRIT),[15,16] but it has not been shown to be superior to clopidogrel in the prevention of recurrent strokes.[17] The usual dose is 200 mg of extended-release dipyridamole in combination with 25 mg of aspirin, requiring administration twice a day.

Mechanism of action. Dipyridamole inhibits phosphodiesterase, resulting in potentiating and direct release of prostacyclin, as well as inhibition of adenosine release. The net effect is reduced platelet aggregation.[3]

Dipyridamole is metabolized in the liver and conjugated to glucuronide, which is mostly excreted through the bile.

Side effects. In addition to bleeding, dipyridamole can cause dizziness, gastrointestinal disturbances (dyspepsia, diarrhea, nausea), and headache, which limit compliance.[15,16]

Cilostazol. Extensively investigated in Asia, cilostazol has shown beneficial effects in stroke prevention in Asian populations. However, it is not approved for the treatment and prevention of cerebrovascular disease in the United States.[18,19] The usual dose is 100 mg twice a day.

Mechanism of action. Cilostazol acts through inhibition of cyclic nucleotide phosphodiesterase 3, resulting in decreased platelet aggregation. Additionally, it has effects on vascular smooth muscle, promoting vasodilatation. It may also have beneficial effects on lipid profiles, decreasing triglyceride levels while increasing high-density lipoprotein levels.[4]

Cilostazol is metabolized by the liver's CYP system and is excreted in the urine.[18]

Side effects. Cilostazol is contraindicated in patients with heart failure. Side effects include bleeding, headache, diarrhea, palpitations, tachycardia, and dizziness. These side effects are transient, but in a clinical trial, up to 20% of patients discontinued the medication secondary to adverse drug reactions.[19]

Glycoprotein IIb/IIIa inhibitors. These are effective agents when acute inhibition of platelets is required. These parenteral medications (IV or intra-arterial) are mostly used in the treatment of acute coronary syndromes. They are also used as an adjunctive off-label strategy for acute and transient platelet inhibition during the endovascular treatment of patients with cerebrovascular disease.

Mechanism of action. Glycoprotein IIb/IIIa inhibitors block platelet aggregation by preventing fibrinogen and other adhesion molecules, such as von Willebrand factor, from binding to the IIb/IIIa platelet receptor. Inhibition of binding to this receptor blocks platelet aggregation induced by agonists such as thrombin, collagen, or thromboxane A_2. Abciximab (Reopro) is a humanized monoclonal antibody directed against the $\alpha_{IIb}\beta_3$ receptor, and it has an irreversible antagonist effect. Eptifibatide (Integrilin) and tirofiban (Aggrastat) are peptides that mimic the arginine–glycine–aspartic acid sequence that is avidly bound by the IIb/IIIa receptor, and they compete with various coagulation mediators for binding with the arginine–glycine–aspartic acid site functioning as reversible competitive inhibitors of the IIb/IIIa receptor. Both compounds dissociate rapidly from the IIb/IIIa receptor; therefore, platelet function returns to baseline hours after the infusion is stopped.

Side effects. The major side effect is bleeding, with major hemorrhage frequencies between 1% and 10%. Thrombocytopenia has been seen in about 2% of patients and is more frequent with abciximab because of the development of neoepitopes by bound antibody. If bleeding occurs, platelets, cryoprecipitate, and fresh-frozen plasma can be infused to promote hemostasis. Antiplatelet effects of the competitive antagonists abate over a relatively short period if the infusion is discontinued.

SECTION II: ANTICOAGULANTS Anticoagulants such as warfarin and heparin are established agents for therapy in particular subsets of ischemic stroke patients. Novel agents are showing promise for similar efficacy profiles with more consistent therapeutic effect and reduced complication rates.

Warfarin. ***Mechanism of action.*** Warfarin acts by inhibiting vitamin K epoxide reductase, an enzyme that is required for reduction of the oxidized form of vitamin K. Reduced vitamin K is a cofactor in the gamma carboxylation of clotting factors II, VII, IX, and X, a step during which these clotting factors are activated. The effect of warfarin leads to an inability to activate these coagulation factors, without an effect on the activated ones, which eventually become depleted according to their individual half-lives.[20]

Initial effects of warfarin administration occur within 24 hours, but peak anticoagulation effect may take up to 3 to 5 days. A single dose lasts between 2 and 5 days.

Proteins C and S are natural procoagulants, and their activation also requires this pathway dependent on reduced vitamin K. At initiation of therapy with warfarin, a paradoxical procoagulant effect may be seen, given the depletion of proteins C and S and the delayed full anticoagulant effect.

Warfarin is water soluble and nearly completely absorbed after oral administration; it is strongly protein-bound, and only the unbound fraction is biologically active. It is metabolized in the liver primarily by CYP2C9 and is excreted in urine and stool.

Genetic variation of CYP2C9 and VKORC1 (which is related to vitamin K epoxide) determines differences in the response to warfarin.[21] Warfarin also has multiple interactions with many drugs and food products, at several pharmacokinetic and pharmacodynamic levels.[20]

Side effects. Bleeding is the most common and problematic side effect. The procoagulant effect is an important consideration at initiation of therapy, especially in patients with hypercoagulability due to protein S and C deficiency, in whom initiation of warfarin without heparin bridging therapy can lead to thrombotic complications. Other potential side effects of warfarin include skin necrosis and teratogenesis. Treatment of overdose is dependent on the degree of anticoagulation and the urgency of the clinical complication and includes vitamin K, fresh-frozen plasma, and activated factor IX or VII.

Unfractionated heparin. Unfractionated heparin (UFH) is a parenteral anticoagulant used in certain subgroups of patients with cerebrovascular disease and in the treatment and prevention of venous thromboembolism (VTE). It is also used IV during endovascular procedures.

UFH is a glycosaminoglycan, with average weight of 15,000 Da (Daltons) and contains numerous random pentasaccharides.

Mechanism of action. Heparin binds to antithrombin III, enhancing its activity on the inhibition of thrombin and factor Xa.[22] The complex is active only against free thrombin and does not act on clot-bound thrombin, which can stimulate its own generation by activating factors V, VIII, and XI.[22] Hence, thrombin formation continues during and after heparin therapy. Heparin anticoagulant effect is transient.

IV heparin with a continuous infusion is used to achieve full anticoagulation, and this therapy is monitored by the activated partial thromboplastin time. Subcutaneous administration is utilized for prophylaxis of VTE, and no monitoring is required. Heparin is cleared by 2 phases: a rapid saturable phase by binding to endothelial cell receptors and macrophages, and a slower nonsaturable phase dominated mainly by renal clearance.[23] It can also interact with platelets.

Side effects. The major side effect is bleeding. If this occurs, infusion should be stopped, and reversal of anticoagulation can be achieved with IV protamine sulfate. Other side effects include heparin-induced thrombocytopenia (HIT), osteoporosis, and elevation of serum transaminase levels.[23]

Low-molecular-weight heparins. Low-molecular-weight heparins (LMWHs) approved for clinical use in the United States are enoxaparin, dalteparin, tinzaparin, and nadroparin. Derived from UFH, these drugs have an average molecular weight of 4,000 to 6,000 Da.

Mechanism of action. LMWH has one pentasaccharide that interacts with antithrombin, activating it, a mechanism by which it exerts the anticoagulant effect. LMWH does not promote thrombin inhibition but leads to factor Xa inactivation by antithrombin. As compared with UFH, LMWHs have a more predictable dose–response relationship, longer half-life, less interaction with platelets, and therefore less association with HIT. LMWHs are administered subcutaneously and used to achieve full anticoagulation or prophylactic effect for VTE, depending on the dose and interval utilized.

These medications are renally cleared, with half-life prolongation in renal failure.[23]

LMWHs are usually administered on a weight-based fixed dose, and laboratory monitoring is not required. However, an anti–factor Xa assay can be used, especially when treating pregnant women, obese patients, or those with reduced creatinine clearance.

Side effects. The main side effect is bleeding. Even though protamine may neutralize partially the effects of these medications, this effect is incomplete and uncertain. There is no proven method of reversing LMWH.[23]

Danaparoid. Danaparoid is a low-molecular-weight heparinoid, a mixture of heparin sulfate, dermatan sulfate, and chondroitin sulfate. It is a more selective factor Xa inhibitor than LMWH. However, this medication is rarely used. Therapy with danaparoid is monitored by an anti–factor Xa assay.[24]

Factor Xa inhibitors. Parenteral formulations include fondaparinux, idraparinux, and idrabiotaparinux. Oral formulations include rivaroxaban and apixaban.

Fondaparinux is a synthetic analog of the antithrombin-binding pentasaccharide, with a long half-life and high affinity to antithrombin, leading to factor Xa inhibition. It has been used for the treatment and prevention of VTE, and for the treatment of acute coronary syndromes. Laboratory monitoring is not necessary; however, anticoagulant effect can be measured by anti-Xa assays.[25]

Idraparinux is a synthetic form of fondaparinux with strong affinity to antithrombin and a very long half-life (about 80 hours). It is not used secondary to excessive bleeding complications because of its long half-life and the lack of an effective antidote.[25]

Idrabiotaparinux is a biotinylated version of idraparinux, but with the benefit that it can be antagonized with avidin. This agent is currently being investigated.[25]

Rivaroxaban is an orally available direct factor Xa inhibitor, rapidly absorbed, with a bioavailability of approximately 80%. It is dually excreted through the liver and kidneys. It is used for the prevention of VTE and does not require laboratory monitoring.[25,26]

Apixaban is another oral direct factor Xa inhibitor, with a rapid absorption and bioavailability of >50%. It is metabolized by the liver, 75% excreted in the feces and 25% by the kidneys. This medication has shown to be efficacious in stroke prevention in atrial fibrillation. In a recent study, it was demonstrated to be superior to warfarin for stroke prevention in atrial fibrillation, causing less bleeding and being associated with lower mortality.[27]

Direct thrombin inhibitors. These anticoagulants directly bind and inhibit thrombin. Parenteral options include hirudin, lepirudin, desirudin, bivalirudin, and argatroban, and these medications are generally used as alternatives to heparin. Oral medications include Ximelagatran and Dabigatran, of which the latter is approved for stroke prevention in atrial fibrillation.[26,28]

Mechanism of action. Direct thrombin inhibitors adhere to both bound and free thrombin, blocking its interaction with its substrates; they do not bind to plasma proteins and therefore have a more predictable response. The do not interact with platelet factor-4 or von Willebrand factor and remain active in platelet-rich thrombus. These agents are renally excreted, with the exception of bivalirudin, which has partial renal and liver clearance, and argatroban, which is cleared mainly by the liver. Argatroban and recombinant hirudins can be monitored with activated partial thromboplastin time, and bivalirudin can be monitored by the activated clotting time.[28]

Hirudin is a 65–amino acid protein extracted from the saliva of the medicinal leech (*Hirudo medicinalis*), is a bivalent inhibitor of thrombin, and is approved for the treatment of HIT. Lepirudin and desirudin are recombinant hirudins. Lepirudin is approved for HIT and desirudin is approved as prophylaxis for deep vein thrombosis.[28]

Bivalirudin is a synthetic version of hirudin used frequently in percutaneous coronary intervention. It is degraded mostly by proteolysis, and only 20% is renally excreted.[28]

Argatroban is a small synthetic molecule acting by competitive inhibition of thrombin. It is approved for the treatment of HIT.[28]

Ximelagatran is an oral prodrug of megalatran, a direct thrombin inhibitor. This medication was shown to be efficacious for VTE prophylaxis and for stroke prevention in atrial fibrillation, but it was not approved because of hepatotoxicity.[26,28]

Dabigatran etexilate is an oral prodrug converted by serum esterase to dabigatran, a direct competitive thrombin inhibitor. It has shown to be efficacious for stroke prevention in atrial fibrillation and has been approved for this purpose.[29] It has also been shown to be efficacious for VTE prevention after total knee and total hip arthroplasty. The anticoagulation achieved is predictable, and no monitoring is required. It is renally cleared, and it is contraindicated in the setting of severe renal dysfunction. There is no antidote, but hemodialysis may help to remove the drug.[26]

Side effects. The major side effect is bleeding, which can be serious, although rates of major hemorrhage appear to be reduced in comparison with warfarin and heparinoids. Liver dysfunction has been noted with ximelagatran but not with other thrombin inhibitors.[26,28]

SECTION III: FIBRINOLYTICS Fibrinolytics are the mainstay in pharmacologic therapy for acute stroke, and their off-label use in neurointerventional procedures has become routine practice.[4] IV administration of alteplase is the current standard of care for acute ischemic stroke. Intra-arterial delivery of fibrinolytics at the site of occlusion can provide direct administration of the agent with a lower dose and higher concentration, reducing the systemic effects of larger IV doses and decreasing the risk of systemic hemorrhage.[30] Catheter-based thrombolysis also increases the rates of recanalization,[31] especially when used in combination with other mechanical approaches. All currently available agents activate plasminogen to plasmin and ultimately degrade fibrin.

Streptokinase. Streptokinase is derived from group C β-hemolytic streptococci, with low fibrin specificity and a half-life between 60 and 90 minutes. It is not used in acute ischemic stroke treatment, given the high risk of hemorrhage, including intracranially, as well as its association with poor benefit and worse outcomes in patients treated with this drug.[30,32]

Prourokinase and urokinase. Prourokinase (Pro-UK) was utilized for the PROACT (Prolyse in Acute Cerebral Thromboembolism) trials. However, it is no longer available and is of historical interest.

Mechanism of action. Pro-UK is a single-chain precursor molecule that is converted to urokinase. Urokinase is a double-chain protease derived from neonatal kidney cell cultures. Pro-UK and urokinase efficiently activate its natural substrate plasminogen to plasmin,[33] which is a natural thrombolytic. The largest randomized trial of intra-arterial thrombolysis was performed with Pro-UK and had positive results, with 40% of patients in the pro-UK arm achieving a

modified Rankin Scale score of ≤2, vs 25% in the control arm ($p = 0.04$). Mortality was 25% for the pro-UK group and 27% for the control group.[31]

Side effects. There is an overall 2% risk of bleeding. Intracranial hemorrhage with neurologic deterioration within 24 hours occurred in 10% of patients treated with pro-UK in the PROACT II trial.[31]

Recombinant tissue plasminogen activators. The recombinant tissue plasminogen activators (rtPAs) include alteplase, reteplase, tenecteplase, and desmoteplase.

Mechanism of action. The rtPAs are secreted serine proteases responsible for catalyzing the conversion of proenzyme plasminogen into plasmin.

Tissue plasminogen activator is a natural enzyme found in human endothelial cells and is produced by recombinant DNA technology for therapeutic use. The half-life is about 3.5 minutes, and it has high affinity and specificity for fibrin. The activity of alteplase is limited in plasma but increases about 1,000-fold in the presence of fibrin. There is theoretical concern about its inability to penetrate the clot matrix, as well as possible neurotoxic effects. However, it has been demonstrated to be effective in the treatment of acute ischemic stroke, and it is the only agent currently approved by the FDA for acute stroke therapy.[34] Alteplase is administered at a dose of 0.9 mg/kg, with 10% provided as a bolus and the rest given over an hour. Much lower doses are used intra-arterially for thrombolysis in the endovascular treatment of acute stroke.

Reteplase and tenecteplase are modified forms of alteplase, with longer half-life in the range of 15 to 18 minutes.[30] Desmoteplase is a recombinant form of a plasminogen activator originally isolated from the saliva of the vampire bat *Desmodus rotundus*. It converts fibrin-bound plasminogen to the active form plasmin, resulting in fibrinolysis and clot dissolution. Desmoteplase is less neurotoxic than alteplase.[30] These agents are not currently being used in clinical practice.

Side effects. Hemorrhage is the more common and feared complication. In the National Institute of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator (tPA) trial, symptomatic intracranial hemorrhage occurred in 6.4% of patients in the tPA group.[34] Immune hypersensitivity reactions have been described in less than 0.02%. Angioedema of the tongue is a rare but dangerous reaction, causing airway obstruction that can potentially be life-threatening.

SECTION IV: PLATELET FUNCTIONAL TESTING Resistance to antiplatelet agents has been reported in patients with cerebrovascular disease, with wide interindividual variability.[35,36] Even though the exact mechanisms are not well defined, it is likely multifactorial, with clinical, cellular, and genetic mechanisms influencing the variability of platelet function. Clinical mechanisms include compliance, dosing, absorption, and interaction with other medications and with other disease processes. Cellular mechanisms are related to deviations in the action of the antiplatelet in its receptor, substrates, and related pathways. Genetic factors represent the individual polymorphisms of the receptor and associated pathways.[37]

There is wide variability in the definition of antiplatelet resistance, and this is also influenced by the variety of methodology used to evaluate platelet function. Multiple platelet-function assays are available, varying between institutions, and no method of platelet function inhibition has consensually been recommended.[38,39]

Measurement of bleeding time is a simple bedside technique to assess platelet function; however, it is insensitive, nonspecific, inaccurate, and poorly reproducible. Several semiautomated platelet function analyzers have become available for diagnosis or therapeutic monitoring of platelet function. Direct and indirect measurements of platelet function utilize different approaches, such as light transmission through the platelet-formed clot, electrical impedance, and clot formation in agonist-coated membranes (table 2). A variety of agonists, such as arachidonic acid for aspirin, adenosine 5′-diphosphate with clopidogrel, and thrombin receptor agonist peptides for IIb/IIIa antagonists, are used to trigger platelet aggregation and quantify platelet function.[39] These techniques for measuring platelet function represent a biochemical assessment of platelet function. However, clinical implications may be derived from previous meta-analysis, suggesting an association between the biochemical resistance and the recurrence of clinical events.[40]

Given the lack of consensus on the methodology to measure platelet function and the definition of antiplatelet resistance, as well as the lack of randomized controlled trials, measurement of platelet function cannot be widely used in clinical practice at this time, and there is no evidence to suggest a clinical impact on the basis of modifying antiplatelet therapy guided by these techniques. Despite this, their use may become a useful adjunct in the titration and modification of antiplatelet agents, with critical implications in the care of patients with cerebrovascular disease, especially those undergoing endovascular procedures.[39]

AUTHOR CONTRIBUTIONS

Dr. Cheng-Ching: drafting/revising the manuscript. Dr. Samaniego: drafting/revising the manuscript, study concept or design. Dr. Reddy

Naravetla: drafting/revising the manuscript, study concept or design, and writing of a chapter. Dr. Zaidat: study concept or design and study supervision. Dr. Hussain: drafting/revising the manuscript, analysis or interpretation of data.

DISCLOSURE

Dr. Cheng-Ching, Dr. Samaniego, and Dr. Reddy Naravetla report no disclosures. Dr. Zaidat serves on the Scientific Advisory Board for Talecris; served on the adjudication committee for Stryker; received speaker honoraria from Stryker; served on the Editorial Board of *Frontiers in Neurology* (Endovascular & Interventional Neurology Section); serves as Editor of *The Journal of Neurointerventional Surgery*; serves as Associate Editor and is a member of the Editorial Board of *Journal of Stroke & Cerebrovascular Diseases*; served as a consultant for Stryker Neurovascular-Commercial, Codman Neurovascular–Commercial, and Microvention Inc-Commercial; and has received research support from a Society of Vascular & Interventional Neurology (SVIN) Grant for this educational activity. Dr. Hussain reports no disclosures. **Go to Neurology.org for full disclosures.**

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