Stroke: Vascular and Interventional Neurology

REVIEW

Antiplatelet Resistance: A Review of Concepts, Mechanisms, and Implications for Management in Acute Ischemic Stroke and Transient Ischemic Attack

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Acute ischemic stroke is a leading cause of death and major disability worldwide. Approximately 50% of ischemic strokes are caused by atherothrombotic occlusion of the cerebral arteries, and antiplatelets are the mainstay of secondary stroke preventative treatment. Aspirin is beneficial if given early, and short-term treatment using aspirin and clopidogrel is increasingly used for patients with intracranial atherosclerotic disease, minor stroke, and or transient ischemic attack. However, up to 50% of patients continue to have recurrent stroke and major vascular events, which may be partly attributable to resistance to aspirin and or clopidogrel. Although the precise mechanisms are unknown, clinical and genetic factors associated with bioavailability and binding to target receptors are implicated. This narrative review begins with the concept of aspirin and clopidogrel resistance in ischemic stroke and transient ischemic attack, potential mechanisms including genetic polymorphisms, and an overview of platelet function measures and limitations. We conclude by highlighting practical issues in the management of patients with aspirin andclopidogrel resistance including the emerging interest in ticagrelor, prasugrel, and cilostazol as well as directions for future trials in transient ischemic attack and acute ischemic stroke.

Key Words: aspirin ■ clopidogrel ■ genetics ■ ischemic stroke ■ platelet function test ■ resistance ■ transient ischemic attack

Acute stroke affects >7 million patients worldwide each year and remains a leading cause of adult death and disability.[1] Approximately 85% of strokes are ischemic, and an estimated 50% are caused by atherothrombotic occlusion of the cerebral arteries.[2] Antiplatelet therapy is the mainstay of treatment of non-cardioembolic acute stroke, transient ischemic attack (TIA), and intracranial atherosclerotic disease. Aspirin and clopidogrel are the 2 agents most widely used.[3,4] However, 15% to 50% of patients have recurrent stroke and major vascular events despite treatment,[5] with the majority of events occurring within the first week.[6] One study reported that treatment with clopidogrel after TIA or ischemic stroke did not prevent progression

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of cerebral small-vessel disease, a known cause of lacunar stroke.[7] In the Secondary Prevention of Small Subcortical Strokes trial, clopidogrel plus aspirin did not reduce the risk of recurrent stroke compared with aspirin alone.[8] The investigators also found higher mortality in patients treated with the combination, and this was not related to major bleeding.[8] More recently, 2 studies reported that ≈60% of patients developed new brain infarcts detected by diffusion weighted magnetic resonance imaging within 24 hours of carotid artery stenting for symptomatic stenosis despite treatment with aspirin or clopidogrel.[9,10] The precise reasons of such observations are unclear, but pharmacodynamics/pharmacokinetics and genetic polymorphisms associated with absorption, drug metabolism, and receptor binding, collectively termed as treatment resistance or high-platelet reactivity, are thought to contribute.[11]

Aspirin reduces platelet activation and aggregation by irreversibly inhibiting the enzyme cyclooxygenase 1 (COX-1), which in turn inhibits the release of thromboxane A2.[11] Clopidogrel works by irreversible binding of its active metabolite to the $P2Y_{12}$ class of adenosine diphosphate (ADP) receptors on platelets.[12] Resistance to aspirin andr clopidogrel has been known for >3 decades and in the brain is associated with endothelial dysfunction and blood–brain barrier disruption, which in turn leads to increased platelet aggregation and thrombus formation.[7] Platelet function tests are increasingly available to monitor platelet reactivity in vitro. Tests can be performed in the laboratory (eg, light transmission aggregometry [LTA]) or via point of care (eg, VerifyNow). This could be relevant, as rapid testing in emergency or outpatient settings could identify high-risk patients and guide choice of treatment and duration of therapy.

This narrative review focuses on the concept of resistance to aspirin and clopidogrel, potential underlying mechanisms including genetic polymorphisms, and the implications for treatment in acute ischemic stroke and TIA.

We also discuss platelet function tests, highlighting limitations; current management of resistance to aspirin and clopidogrel; the emerging interest in ticagrelor, prasugrel, and cilostazol; and future directions, which could inform clinical practice and future secondary stroke prevention trials.

Nonstandard Abbreviations and Acronyms

CHANCE	Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events
CYP	cytochrome P450
LOF	loss-of-function
LTA	light transmission aggregometry
PFA	platelet function analyzer
POINT	Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke Trial
TARDIS	Triple Antiplatelets for Reducing Dependency After Ischemic Stroke trial
vWF	von Willebrand factor

CLINICAL PERSPECTIVE

- This narrative review will focus on the concept of resistance to aspirin and clopidogrel; potential underlying mechanisms, including genetic polymorphisms; and the implications for treatment in acute ischemic stroke and transient ischemic attack, including patients undergoing neurointervention.
- This review gives an overview of platelet function tests, highlighting limitations and practical considerations in management of aspirin and clopidogrel resistance.
- This review also highlights the emerging interest in antiplatelets including ticagrelor, prasugrel, and cilostazol, as well as future directions, which could inform clinical practice and future secondary stroke prevention trials.

METHODS

For this narrative review, a search of MEDLINE, PubMed, Embase, and Cochrane Collaboration was performed in 2021. The searches were limited to the English language. Search words (Appendix) were used to identify relevant studies. Abstracts were then reviewed, and the relevant full-text articles were extracted. Reference lists of identified publications were checked for additional studies. We checked reviews, systematic reviews or meta-analyses, cohort studies, and case–control studies. We included studies that addressed antiplatelet resistance and its cause, measurement, or associated resistance to major cardiovascular events. For the genetic aspects, because of its complexity, we excluded studies that had no relevance for functionality and focused on single polymorphism influence on clopidogrel function. We excluded case reports and studies that primarily used bleeding

time as a measure of platelet function. The reason for excluding bleeding time is that it varies widely, has poor sensitivity and specificity, and does not correlate with other indicators of platelet activation. Bleeding time should not be used to quantify platelet function in platelets with thrombocytopenia.[11]

We reviewed guidelines from the United States and Europe. When presenting data of an antiplatelet, we focused on randomized controlled trials or systematic reviews.

The Concept of Antiplatelet Resistance: Laboratory and Clinical

Clinical antiplatelet resistance or failure is operationally defined as the inability to prevent ischemic stroke or major vascular events despite optimal use of antiplatelet medications. It is important to highlight that clinical resistance or failure does not imply laboratory resistance, as aspirin and clopidogrel do not inhibit all pathways of platelet activation.[13] Laboratory resistance to aspirin is defined as failure to reduce thromboxane A2 in platelets after inhibition of the COX-1 enzyme.[11] Similarly, laboratory resistance to thienopyridines such as clopidogrel indicates the inability to induce ADP-mediated platelet aggregation following $P2Y_{12}$ receptor inhibition.[11] Moreover, the mechanisms of ischemic stroke are heterogeneous, and therefore the extent to which platelets aggregate and lead to thrombus formation depends on the etiology of stroke itself and the contributing vascular risk factors.[14] It is estimated that the prevalence of resistance to aspirin and clopidogrel in patients with ischemic stroke and/or TIA ranges from 5% to 65% and 28% to 44%, respectively.[11,15]

Potential Mechanisms

Table 1 lists the potential mechanisms of poor response to aspirin and clopidogrel, including resistance, and they are discussed as follows.

Reduced Compliance or Noncompliance With Treatment

One of the most common causes of reduced bioavailability is patient noncompliance or nonadherence to treatment. One large review (over 140 000 patients) reported that up to 50% of patients who were prescribed antiplatelets had stopped taking or were not regularly taking treatment at 1 year.[16] Predictors of poor compliance or discontinuation included smoking, depression, diabetes, low level of education, and female sex.[16] Another factor to consider in the United States is treatment cost, patient affordability, and lack of availability of certain drug types on insurance plans. In the United Kingdom, some drugs are not available in regional formularies and can be prescribed only by hospitals.

One way to assess compliance is by seeking direct verbal assurance from the patient, but studies have shown that this is not always reliable.[17] Another method is to measure plasma levels of aspirin, clopidogrel, or urinary metabolites, but this may not be feasible when a patient presents in an emergency, and result interpretation is dependent on the timing of sample collection.[18] Alternatively, testing for platelet inhibition after a period of supervised drug intake could be useful, as a shift toward a laboratory therapeutic response would indicate that poor compliance or treatment discontinuation was the reason for poor response to earlier treatment.[14]

Reduced Bioavailability

In regards to aspirin, another key factor that affects bioavailability is absorption. In acute stroke, aspirin is prescribed in different formulations: plain, enteric-coated, soluble, suppository (dysphagic patients), mouth dispersible, and intravenous for patients undergoing mechanical thrombectomy where indicated (angioplasty/stent). Both enteric-coated and slow-release aspirin are absorbed in the small intestine, and here the higher pH of 6 to 7 affects its absorption and reduces the platelet inhibitory effect.[19] By comparison, plain aspirin is stable at the lower pH in the stomach and is absorbed quickly. The soluble and dispersible versions are comparable in terms of the rate of absorption, onset of action, and magnitude of effects of plain aspirin.[20]

It is important to highlight that ≈50% of patients with acute stroke have dysphagia[21] at the time of presentation and may require a nasogastric feeding tube for nutrition and medications. Clopidogrel has no parenteral formulation, which means that the tablet must be crushed and administered with a liquid. Even if the administration is performed correctly, the method of crushing the drug can affect its bioavailability.[22] To overcome this limitation, a microemulsion of clopidogrel is available, but the effects on platelet aggregation need to be validated.[23]

Considerations During Management in Critical Care

Patients with severe stroke may need general anesthesia for intervention or surgery and further treatment in critical care. Drugs including morphine and its derivatives along with other sedatives are known to reduce gastrointestinal motility and emptying. As enteric-coated aspirin and clopidogrel are mainly absorbed in the duodenum, impaired gastric motility may reduce bioavailability.[20] It is also known that patients in critical care are more likely to develop hypoalbuminemia,

Table 1. Potential Mechanisms of Antiplatelet Resistance to Aspirin and Clopidogrel

General
Reduced bioavailability: age, increased weight, poor compliance; reduced absorption (enteric-coated aspirin), metabolism, or excretion; inadequate dosing; smoking (aspirin), exercise, stress, hypercholesterolemia
Affecting binding to COX-1 or $P2Y_{12}$
Alternative pathways of platelet activation: increased epinephrine-mediated platelet activation; increased sensitivity to ADP and collagen; increased release of ADP (eg, infection, inflammation, atherosclerosis)
Increased platelet turnover (eg, myocardial infarction, coronary artery bypass graft, surgical procedures, acute or chronic infection, and inflammation)
Tachyphylaxis with long-term administration (aspirin)
Treatment failure because of nonatherosclerotic ischemic event (eg, vasculitis)
Individual variation in response to treatment
Variation in platelet response to treatment
Aspirin
Concurrent administration with nonsteroidal antiinflammatory drugs (eg, ibuprofen, indometacin, naproxen)
Incomplete suppression of thromboxane A2
Stress-induced COX-2 in platelets
Clopidogrel
Other sources of thromboxane A2: monocytes, macrophages, and endothelial cells
CYP2C19 substrate and competitive inhibition, for example, proton-pump inhibitors (omeprazole, esomeprazole)
CYP3A4 : competing with isoenzyme for metabolism, for example, statins (simvastatin, atorvastatin, fluvastatin); inhibition, for example, dihydropyridine calcium-channel blockers (amlodipine)
Gene polymorphisms
Enzyme: COX-1 and COX-2; uridine diphosphate glucuronyltransferase gene (UGTIA6∗2); thromboxane A2 synthase, *ADRA2A*, *TXBA2R*, *PLA2G7* (aspirin); *CYP3A4*, *CYP1A2*, *CYP2C19*, *ABCB1*, carboxylesterase-1, P-glycoprotein gene (C3435ST subtype), paraoxonase-1 (clopidogrel)
Receptor: P1 A1/A2 (aspirin); $P2Y_1$, $P2Y_{12}$ H2 haplotype (clopidogrel); glycoprotein Ia/IIa, glycoprotein Ib a, glycoprotein IIb/IIIa, glycoprotein IIIa, collagen; von Willebrand factor; thromboxane receptor

ADP indicates adenosine diphosphate; COX, cyclooxygenase; and *CYP*, *cytochrome P450*.

and this in turn can affect the level of the active form of antiplatelets such as clopidogrel.[24] Moreover, managing fluid balance in patients with acute stroke can be complex because of the known risk of cerebral edema,[25] which can make it difficult to assess the volume of distribution of aspirin and clopidogrel irrespective of dosage.[25] Furthermore, treatment with medications of various classes, for example, antibiotics, antiarrhythmics, and antiepileptics, can affect bioavailability and lead to treatment failure.[20]

Neurointervention in Acute Stroke

Up to 12% of the acute ischemic stroke population may be eligible for mechanical thrombectomy to treat large-vessel occlusion (usually involving the middle cerebral artery ± the terminal internal carotid artery). Adjunctive use of angioplasty ± an extracranial or intracranial stent may be required to treat underlying or proximal (tandem) severe vessel stenosis, or may be used as a rescue measure after failed recanalization following attempted thrombectomy.

In patients with tandem proximal vessel stenosis, intravenous thrombolysis may be less effective and access to the intracranial thrombus requires navigation through the vessel stenosis.[26,27] In the event of severe extracranial internal carotid artery stenosis or acute occlusion, balloon angioplasty may be required before crossing the stenosis to access the intracranial vessels for thrombectomy. Angioplasty alone may not be definitive, as there is risk of recoil, residual restenosis, or occlusion of the treated vessel. However, if the vessel remains patent after a period of observation following angioplasty, there may be no need to administer dual antiplatelet agents in the acute setting.

In patients with tandem occlusion or tandem severe carotid stenosis, it is unclear whether acute carotid stenting should be performed before or after thrombectomy of the intracranial occlusion.[26] In the absence of acute carotid reocclusion, it is unknown if a carotid stent should be performed in the acute setting.[26,28] After reperfusion, patients are at risk of hemorrhagic transformation of infarct, and the timing, intensity, and duration of antiplatelet therapy need to be balanced against the risk of intracranial hemorrhage. In-stent thrombus, recurrent stenosis, and delayed stent occlusion are potential risk factors for recurrent stroke.

In patients treated with acute carotid or intracranial stenting, dual antiplatelet therapy is often administered in the acute setting to maintain stent patency. Intravenous aspirin is often used and has been shown to reduce platelet aggregation and thromboxane B2 synthesis more rapidly than oral aspirin.[29] Although there are no head-to-head comparison studies, achieving peak concentration with intravenous aspirin is faster

than oral or any other formulation.[29] If intravenous aspirin is not available, aspirin can be administered as a suppository per rectum or orally through an orogastric or nasogastric tube. As for the second antiplatelet, use of clopidogrel, prasugrel, ticagrelor, or a glycoprotein IIb/IIIa inhibitor have all been described.

Patients undergoing stenting for ipsilateral carotid artery occlusion or stenosis during mechanical thrombectomy can be hemodynamically unstable or have organ dysfunction, which can affect the bioavailability of aspirin or clopidogrel via delayed gastric emptying, reduced hepatic reserve, splanchnic blood flow, plasma proteins for binding, body fat stores, reduced microsomal enzyme activity, and redistribution of total body water.[20] Other factors such as anatomic variation, pathophysiology (atherosclerotic versus dissection of otherwise normal vessel), presence of tandem lesions, and stent type can affect platelet aggregation and response.

Other Neurointerventions

The use of antiplatelet drugs in treatment of cerebral aneurysms primarily applies for patients with unruptured aneurysms and retreatment of recurrent aneurysms.

The standard approach to minimize thromboembolic complications of aneurysm coiling has been procedural anticoagulation with unfractionated heparin. Advances to help address the technical limitations of coiling wide-necked aneurysms have included intracranial stents, flow-diverting stents, and intra-aneurysmal occlusion devices. Stent-assisted treatment of an intracranial aneurysm enables higher coil packing densities and helps prevent coil herniation into the parent artery.[28] In flow diversion, the stent design facilitates blood flow past the aneurysm neck along the parent vessel to its branches.

Because of the inherent nature of any stenting procedure, platelet activation and aggregation is induced by instrumentation of the vessel, exposure of the underlying endothelial matrix, and the stent or stentlike device itself. Platelet activation induces thrombus formation and release of inflammatory mediators. In addition, plasma proteins including fibrinogen can also bind and initiate the coagulation cascade.[30] The extent to which platelets aggregate depends on the composition of the stent or device, its surface area, and direct shear stress.[28,30] In patients with a coil, the process of detachment can induce thrombus formation, as the generated positive charges attract blood products and platelets to the site of implantation.[31]

To date, there are no trials to guide antiplatelet treatment in the aforementioned settings,[28] and guidelines acknowledge these limitations.[3,32]

For intracranial stent deployment and stent-like devices, neurointerventionalists usually recommend treatment with aspirin and clopidogrel for 7 to 10 days or loading with aspirin and clopidogrel before an elective procedure.[3,32] Platelet testing may or may not be performed. There is significant variation in clinical practice nd it is partly dependent on the device used and the result achieved. Some clinicians continue dual therapy for 3 to 12 months after the procedure, and then aspirin is continued for life.[3,28,32]

In the setting of flow diversion, testing for clopidogrel resistance is often performed, as the results may be helpful to predict thromboembolic or hemorrhagic complications.[33,34] If the patient is found to be resistant to clopidogrel, treatment is switched to an alternative agent. If the patient is hyperresponsive to clopidogrel, its administration may be changed to every other day instead of daily. After flow diverter implantation, current clinical practice is to continue aspirin and clopidogrel (or an alternative agent in the setting of resistance) for 6 months and then aspirin indefinitely.[26,28,33,34]

Pharmacodynamic Interactions

Another important factor that is known to affect response to aspirin and clopidogrel is interaction with other drugs. Studies have shown that concomitant treatment with nonsteroidal antiinflammatory drugs (eg, ibuprofen, naproxen, and indomethacin) could directly compete with aspirin's antiplatelet effect by blocking COX-1.[35] Because aspirin and clopidogrel can increase the risk of gastrointestinal bleeding, proton pump inhibitors such as omeprazole or esomeprazole are often coprescribed. This is significant, as proton pump inhibitors work by suppressing acid release in the stomach and reduce aspirin bioavailability through the enzyme gastrointestinal esterase.[20] Proton pump inhibitors are competitive inhibitors of cytochrome P450 (*CYP*) 2C19, and this is relevant, as clopidogrel is dependent on this enzyme for conversion to its active form in the liver.[36] Some studies have shown that the interaction between clopidogrel and proton pump inhibitors is associated with a higher risk of cardiovascular events.[14] In the United Kingdom and the United States, regulatory experts advise against the concurrent use of clopidogrel and omeprazole.[37,38]

It is suggested that lipophilic statins (simvastatin, atorvastatin, and fluvastatin) also compete with clopidogrel for conversion to its active form by *CYP3A4*, but randomized trials in stroke have shown benefit when they are administered together.[39] Similarly, concurrent treatment with dihydropyridine calcium channel blockers, for example, amlodipine, has been shown to decrease the platelet inhibition effect of

clopidogrel, but the effects on TIA and ischemic stroke are not validated.[39]

Pharmacogenetics

It is estimated that up to 30% of the variability in response to antiplatelet treatment can be explained by genetic factors.[35] Common genetic polymorphisms identified with aspirin resistance include the platelet COX-1 and COX-2 genes, glycoprotein receptors (P1A1/A2), collagen (Ia/IIa), von Willebrand factor (vWF; Ib), fibrinogen (glycoprotein IIb/IIIa), the enzyme uridine diphosphate glucuronyltransferase (UGTIA6∗2) and in patients with diabetes, ADRA2A, TXBA2R, and PLA2G7 (Table 1).[40] Clopidogrel resistance has been linked to polymorphisms in genes involved in hepatic metabolism (*CYP3A4*, *CYP1A2*, *CYP2C19*), intestinal absorption (ABCB1), P glycoprotein gene (C3435ST subtype), and platelet surface receptors ($P2Y_1$ and $P2Y_{12}$).[14] The putative mechanisms of how these genes lead to aspirin resistance is unclear, as some studies have shown reduced response to treatment, while others have shown no association.[41] Similar results have been reported with clopidogrel, but studies have associated polymorphism with higher risk of atherosclerosis, platelet aggregation, and cardiovascular events.[41]

CYP2C19 is one of the superfamily members of *CYP450*, the enzyme that is involved in converting clopidogrel to its active metabolite in the liver. *CYP2C19* polymorphisms include loss-of-function (LOF) and increased function alleles, which yield 5 phenotypes: ultrarapid, rapid, normal, intermediate, and poor metabolizers (Table S1).[42] Patients with *CYP2C19* polymorphism who are intermediate and poor metabolizers of clopidogrel have been shown to have significantly low levels of the active drug with reduced inhibition of platelet aggregation.[43]

The population frequency of the *CYP2C19* allele varies, with LOF reported in ≈15% of White and African American people and ≈35% in Asians.[40] The most common LOF alleles are *CYP2C19∗2* and *CYP2C19∗3*, and less common include *CYP2C19∗4*, ∗5, ∗6, ∗7, and ∗8. In acute stroke and TIA, *CYP2C19∗2* LOF is the most commonly studied and associated with poor response to treatment and risk of major vascular events.[40]

Genotype-Guided Antiplatelet Treatment and Response in Minor Stroke/TIA

Compared with acute coronary syndrome,[44] there are few trials assessing the association between genotype-guided antiplatelet treatment and outcomes in acute stroke or TIA. There are no large-scale trials of aspirin, and only recently, studies conducted in China, the United States, and Europe have investigated the interaction of *CYP2C19* LOF genotype and outcomes in nondisabling stroke/TIA. In the CHANCE (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) trial, treatment with clopidogrel plus aspirin compared with aspirin reduced the risk of recurrent stroke in patients who were noncarriers of the *CYP2C19* LOF allele (∗2 or 3) but not in carriers.[45] In CHANCE, 2933 participants were genotyped using point-of-care genetic testing, and 58.8% of participants were found to be carriers of LOF alleles (∗2 or ∗3).[42] When stratified by *CYP2C19* genotype and risk of recurrent stroke, the hazard ratios (95% CIs) of the clopidogrel-plus-aspirin group for stroke recurrence was 1.00 (0.70–1.42), 0.63 (0.41–0.97), 0.62 (0.40–0.96), and 0.52 (0.31–0.88) among LOF carriers at low risk, LOF carriers at high risk, noncarriers at low risk, and noncarriers at high risk, respectively.[42] There was no significant difference in bleeding between carriers and noncarriers of the LOF alleles in the clopidogrel-plus-aspirin group (2.3% versus 2.5%) or aspirin (1.4% versus 1.7%; P=0.78).[42]

In contrast, a substudy of POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke Trial) conducted in the United States and Europe found no interaction with LOF carrier state and outcomes.[46] Potential explanations include the lower number of gene carriers of *CYP2C19* in POINT, lower-than-expected number of recurrent strokes, higher loading dose of clopidogrel in POINT, and less tobacco use, which is associated with less efficacy with clopidogrel or racial and ethnic differences.[46]

A recent meta-analysis assessed the prevalence of resistance to clopidogrel in ischemic stroke and/or TIA and the association with outcome and genetic basis of on-treatment response variability.[47] In 21 studies including 4312 patients, the pooled prevalence of clopidogrel resistance was 28% (high heterogeneity I^2=88.2%).[47] The studies varied in patient demographics, dose of clopidogrel, and timing of administration. There was significant heterogeneity in the platelet function tests used to determine resistance, and the definition of high platelet reactivity also varied.[47] Across 8 studies (1887 patients) with data on recurrent stroke, major vascular risk, and functional outcome, patients with the *CYP2C* 19∗2 or ∗3 LOF gene or carriers were at higher risk for recurrent stroke compared with those who were not (relative risk=2.09 [95% CI, 1.61–2.70]; low heterogeneity I^2=27.4%).[47]

Clinical Implications of Other Genetic Variations of Clopidogrel and Response

It is unclear whether genetic variants other than *CYP2C19* LOF are associated with risk of recurrent stroke or bleeding in minor stroke or TIA. It is estimated that the increased function *CYP2C19*∗17 gene, which increases *CYP2C19* expression, is observed in ≈30% of the population in the United States.[48,49] The clinical relevance of *CYP2C19*∗17 is unclear as a higher risk of bleeding and lower risk cardiovascular events have been reported in some but not in all observational studies.[40] Similarly, the effects of variation in genes affecting the absorption (ABCB1) of clopidogrel and conversion to its active form (carboxylesterase-1 and paraoxonase-1) merit exploration, and routine testing is not recommended for prescribing.

Two advantages of genetic testing are that the patient's genotype does not change over time and testing can be performed before treatment. Another advantage is that in patients with LOF alleles, medication type or dosing can be modified to alter the risk of vascular events. The disadvantages are that the process of testing is time consuming, requires expertise in the interpretation of the results, and is expensive. Moreover, it is not possible to test for patient compliance.

Antiplatelet Resistance Through Alternate Platelet Activation Pathways

Mechanisms that activate platelets through COX-1– or $P2Y_{12}$-independent pathways are associated with resistance to aspirin or clopidogrel. For example, upregulation of the COX-2 enzyme in inflammation, infection (eg, pneumonia), and atherosclerosis lead to thromboxane production (eg, monocytes, macrophages, and endothelial cells), causing increased platelet reactivity.[11,14] This would be relevant in patients with diabetes, as antiplatelet resistance combined with increased levels and activity of prothrombotic clotting factors is associated with a higher risk of cardiovascular events.[50] Although improving glycemic control could increase platelet inhibition,[50] the effects on clinical outcomes in acute ischemic stroke andTIA are unclear. Other factors that are associated with platelet activation through alternate pathways include smoking, hypercholesterolemia, obesity, hypertension, congestive heart failure, and catecholamine release in response to exercise, stress, and sepsis.[11,20,51]

Increased Platelet Turnover

The average plasma half-life of aspirin is ≈20 minutes and ≈8 hours for clopidogrel. Both aspirin and clopidogrel bind irreversibly to platelets, and therefore the duration of inhibition relates to platelet life span, typically 5 to 10 days.[52] Increasing the number of uninhibited platelets from increased bone marrow turnover in conditions such as bleeding or after platelet transfusions could negate their effects.[11,14]

Role of vWF

vWF is responsible for platelet adhesion to endothelium through platelet glycoprotein Ib receptors. vWF levels are frequently elevated in acute ischemic stroke, and high levels may impair the effect of antiplatelet drugs by increasing platelet adhesion.[53] Evidence also suggests that the level of ADAMTS-13, an endogenous proteinase that cleaves vWF, is increased in acute stroke, and an imbalance in the ratio of ADAMTS-13:vWF is associated with volume/size of brain infarction and functional outcome.[54]

Sex and Race orEthnic Differences in Platelet Function and Response to Antiplatelets

There is substantial evidence that pharmacokinetics and pharmacodynamics to antiplatelets vary according to sex.[55] From a biological perspective, this can be explained in the differences in the structure of blood vessels and vessel walls between men and women as well as hormonal effects (estrogen, progesterone, or androgens) on platelets, which in turn affects activation and response.[56] Compared with men, women have higher platelet counts and increased platelet reactivity at baseline and after treatment with aspirin and clopidogrel.[55,57] Prior work has also shown that despite higher salicylate concentration and COX-1 inhibition, the effect of aspirin on platelets reduces over time in women but remains stable in men.[56] This has clinical implications, as aspirin is reported to be more effective in acute stroke in women than in men. Likewise, aspirin is more protective in treatment of myocardial infarction (MI) in men. As for bleeding, meta-analyses have shown that there is no difference,[58] but observational data report higher rates of bleeding in men taking aspirin.[59]

Racial and ethnic differences in platelet function and response have been identified as independent risk factors of poor prognosis in coronary artery disease, and this may apply to acute ischemic strokeTIA.[60] A study testing the effect of race and ethnicity on platelet response found that patients of White descent had moderate response for epinephrine and ADP-induced aggregation, while African Americans responded strongly.[61] A recent genome-wide association study identified genetic loci associated with ADP-induced platelet aggregation which probably explains why African American patients have strong

platelet response.[62] Evidence also suggests that during ischemia, African Americans have higher platelet–fibrin clot strength, shorter time to thrombus formation, and risk of poor outcome.[60] This could be because of potentiation of platelet activation pathways independent of COX and $P2Y_{12}$ and a more thrombogenic and dysfunctional endothelium, suggesting that aspirin and clopidogrel may not be that effective.[63]

Patients of Hispanic ancestry are reported to have increased platelet counts, with specific loci identified in genome-wide studies. This has been associated with abnormal platelet activation and aggregation.[60]

Platelet Function Tests

General

Evaluation of platelet function to guide antiplatelet treatment may translate into tailored patient care that lowers risk of recurrent stroke without increasing the risk of bleeding. Various tests are available: Some are laboratory based (eg, LTA), while others are performed at point of care (eg, platelet function analyzer-100 system [PFA-100], VerifyNow test, impedance aggregometry). Each platelet function test has a particular purpose. Tests such as PFA-100 provide a global assessment of platelet function from activators to inhibitors, while others measure individual pathways or drug-specific action (eg, LTA–arachidonic acid). In general, tests that are directly related to the inhibition of COX-1 or P2Y12 receptor (LTA with arachidonic acid as agonist), VerifyNow Aspirin and VerifyNow P2Y12, are reported to show lower resistance rates compared with nonspecific assays (PFA-100).[64] Recently, 1 study showed that the platelet function analyzer-200 (PFA-200) could be useful to predict the risk of major vascular events in patients treated with clopidogrel, but this needs to be validated in larger studies.[65] Table 2 summarizes a list of platelet function tests and their advantages and disadvantages.

Preanalysis Considerations

As in all laboratory procedures, the reliability and reproducibility of platelet function tests is known to be affected by the technique of blood collection (eg, duration of tourniquet application), sample transport, and sample preparation.[66] Samples should be analyzed within 2 hours of collection, as storage beyond 2 hours can trigger platelet damage. Evidence also suggests that smoking; a high-cholesterol diet; exercise; caffeine; drugs such as antibiotics, anticoagulants, and selective serotonin reuptake inhibitors; timing of blood tests; and patient posture may affect test results.[66]

Prevalence of Antiplatelet Resistance and Practical Considerations

The prevalence of antiplatelet resistance based on platelet function tests varies and is assay and agonist dependent.[67] In a comparison study, aspirin resistance was reported at ≈60% with PFA-100, 10% to 52% using LTA with different concentrations of arachidonic acid as agonist, 23% with urinary 11-dehydrothromboxane-B2 assay, 18% with whole-blood aggregometry, 7% with VerifyNow test for aspirin, and 4% LTA with standard arachidonic acid as agonist.[68] The rate of clopidogrel resistance is also assay dependent.[14] In a head-to-head study comparing different antiplatelet assays in patients on clopidogrel 150 mg, the resistance of clopidogrel was 13% with LTA and ADP as agonist, ≈40% with vasodilator-stimulated phosphoprotein assay, and 33% with VerifyNow $P2Y_{12}$.[69]

Two reasons for the variation in antiplatelet resistance is the use of nonstandardized tests and a lack of definition. For example, in 1 study, 7 different thresholds were used to define aspirin resistance using the PFA system.[14] One other explanation is the inconsistency in the type of platelet function test that is used. For example, a review of 19 studies of flow diversion in cerebral aneurysms found that only 6 studies used the same platelet function test and the rest did not.[70] Another reason is timing of testing in relation to the index stroke or TIA. Third, individual antiplatelet resistance has been shown to vary over time. Therefore, a patient who is "resistant" to aspirin or clopidogrel at time point may respond at another period.[71] This is because the use of aspirin and clopidogrel, particularly long term, is associated with platelet aggregation through activation of alternate pathways. Another reason is that increasing the drug dose may alter the test result. Finally, platelet function tests are not identical, and there is high intra- and interassay variability.

Clinical Significance

A systematic review including 20 studies (4989 patients) in ischemic stroke or TIA found that the prevalence of resistance detected by platelet function tests significantly varied: 3% to 65% with aspirin, 8% to 56% with clopidogrel, and 1.8% to 35% with aspirin combined with clopidogrel.[72] When assessed by the relationship with outcomes, patients on aspirin or aspirin and clopidogrel with high platelet reactivity (reactivity is a measure of response; high platelet reactivity indicates low response) on platelet function tests were at 2-fold increased risk of recurrent stroke, MI, or death during follow-up compared with those without. Furthermore, the risk of severe stroke was higher (odds ratio,

Table 2. . Techniques of Platelet Function Assays

Basis	Platelet to platelet aggregation						Activation-dependent signaling	Thrombus formation under flow
Name of test	Impedance aggregometry	Light transmission aggregation	Platelet function analyzer (PFA-100)	VerifyNow system	Multiple electrode aggregometry	Thromboelastography platelet mapping	Flow cytometry	Global thrombosis test
Method	Electrical impedance	Turbidimetry	Occlusion of an aperture coated with agonists	Light transmission–based optical detection assay	Impedance	Viscoelastic test	Fluorescence intensity	Labeled platelets passed through a flow chamber under shear stress with assessment of adhesion and aggregation in real time
Medium of assessment	Whole blood	Platelet-rich plasma	Whole blood	Whole blood	Whole blood	Whole blood	Whole blood	Whole blood
Where can test be performed?	Laboratory	Laboratory	Point of care or laboratory	Point of care	Laboratory	Point of care	Specialized/research laboratory	Specialized/research laboratory
Advantages	Assesses platelet function under more physiological conditions; can be performed in patients with thrombocytopenia or von Willebrand disease; no sample processing required; diagnostic method	"Gold standard"; different platelet pathways can be assessed; used in most number of antiplatelet resistance studies	Simple, quick to perform; low sample volume; high shear; minimal sample preparation required	Simple, quick, point of care; no sample preparation required	Point-of-care assay; highly sensitive for aspirin resistance; duplicate	Simple test; quick to use; many clinical areas already use thromboelastography for other indications	Small sample volume; high accuracy; good correlation with light transmission aggregometry; can be used for multiple applications	Global platelet method; requires small volume
Disadvantages	Limited by hematocrit	Poor reproducibility; variation in response affected by age, race, and concentration of agonist; time consuming; requires manual processing; less representative of in vivo conditions	Dependent on von Willebrand factor, hematocrit; no instrument adjustment	No instrument adjustment; expensive; single cartridge use; less representative of in vivo conditions	Few resistance studies to date; less reproducible	Requires training of staff to use as a point-of-care device	Requires flow meter and sample preparation; expensive; not standardized; highly specialized and not routinely available for clinical use	Lack of clinical studies; very highly specialized and not widely available; requires rapid access to a confocal microscope and advanced facilities for sample processing. Lack of standardization for technique
Monitoring of aspirin	Yes	Yes	Yes	Yes (with arachidonic acid or propyl gallate cartridge)	Yes	Yes	No	Yes
Monitoring of clopidogrel	Yes	Yes	Yes (with P2Y12 cartridge for PFA-200 analyzer)	Yes (with pending adenosine diphosphate cartridge)	Yes	Yes	Yes	Yes

2.65 [95% CI, 1.00–7.01]) with antiplatelet resistance irrespective of treatment.[72]

In patients undergoing neurointervention, the effect of aspirin resistance was assessed in retrospective, small, single-center studies, and 1 prospective trial.[28,34] The results showed that ≈4% to 21% of patients were resistant, but there was no association with clinical outcome. Potential explanations for the observed results were that many patients were not compliant with treatment and the dose of aspirin was incorrect.[34]

Compared with aspirin, there are data on the link between clopidogrel resistance and response. Some studies in stenting for carotid artery stenosis and coil embolization of cerebral aneurysms reported an association between high platelet reactivity and stent thrombosis, while others did not.[34,70] Other authors used surrogate markers such as the presence of infarction on follow-up magnetic resonance scanning of the brain, which strongly correlates with treatment resistance.[73] Asai et al also reported that the number of infarcts detected by magnetic resonance imaging increased (39% versus 21%) as resistance to clopidogrel increased, a finding that was confirmed in a prospective clinical trial.[74,75] However, the effect on functional outcome was not known, and this needs to be assessed prospectively.

Platelet Function Tests to Predict Bleeding in Neurointervention

The causes and pathogenesis of major bleeding after neurointervention in patients are usually heterogeneous. Aside from known risk factors, low platelet reactivity is also suggested to contribute.[76] There is interest in predicting the risk of bleeding in patients with *CYP2C19* polymorphism using platelet function tests but this is debated.[34,77]

Two studies in neurointervention attempted to define the threshold as a percentage of platelet inhibition using the VerifyNow $P2Y_{12}$, and the values were similar (≥72% and 74%, respectively).[34,76] Analysis has shown that these thresholds have good predictive value, but it is difficult to recommend percentage of inhibition on its own as a measure of platelet response.[34,76] This is because the test is directly dependent on baseline platelet function and little is known on the relationship with clinical outcomes.[76]

It is also suggested that testing for the magnitude of platelet inhibition in patients on clopidogrel could be useful to predict the risk of bleeding.[34,78] However, it is important to highlight that periprocedural treatment with heparin is common, and this could be a key confounding factor.[26,28,34] In addition, trauma or traction on the treated vessel by the stent/device, variation in global or regional cerebral blood flow, or dynamics during the procedure can modulate the risk of bleeding regardless of the individual's platelet response.[28,70]

Irrespective of *CYP2C19* status, the thresholds for bleeding using platelet function tests are debated because of variation in standards to define severity, timing, follow-up assessments, and adjudication in studies.[77]

Commentary and Perspectives

It is important to highlight that the majority of the data on antiplatelet resistance testing come from patients with coronary artery disease. Although the risk factors for acute stroke and MI are similar, it is essential to consider that the pathophysiology is different: Only 50% of ischemic strokes are caused by rupture of an atherosclerotic plaque with subsequent platelet aggregation, whereas ≈90% of MIs are caused by plaque rupture alone.[20]

Recent guidelines have attempted to address the variation in platelet function testing and suggest that thresholds should be determined by the testing laboratory, rather than adopting from published studies.[66] Guidelines also suggest that testing multiple samples of patients in 1 laboratory could avoid misinterpretation.[66]

There is emerging evidence that testing for surface platelet expression of P-selectin (CD62P) correlates with other measures of platelet function tests in acute stroke and TIA.[79] Data from the TARDIS (Triple Antiplatelets for Reducing Dependency After Ischemic Stroke) trial (n=689) showed that both aspirin and clopidogrel reduced P-selectin expression on platelets and ≈25% of patients had high on-treatment platelet reactivity.[80] A single-center study found that 11% of 62 patients with a history of recent stroke or TIA who were resistant to clopidogrel (higher levels of surface platelet expression of P-selectin) were more likely to have a recurrent stroke compared with those who had no recurrence.[79] It is important to highlight that testing for P-selectin was feasible remotely with storage and transportation across multiple hospital sites in the United Kingdom.[79,80]

In conclusion, the spectrum of the pathophysiology of TIA and acute stroke is heterogeneous, and with an aging population and rising incidence, the risks of complications or fatal outcomes are only anticipated to increase.[1] Acute treatment including intervention is rapidly evolving with new studies and technology innovation, and to prevent thromboembolic events, more antiplatelets will be used. A tailored strategy using platelet function tests would be ideal,[81] but the present evidence indicates that well-designed, prospective, randomized trials are needed before they are incorporated into routine clinical practice. Apart from assessment of risk of ischemia and bleeding, future work

should include outcomes including neurological deterioration, death, disability, mood, cognition, and quality of life.

Management of Antiplatelet Resistance

Current clinical practice in managing patients with resistance to aspirin or clopidogrel is to switch one antiplatelet for another, increase the dose, or use a combination. However, it is not known if these measures are effective, safe, or cost-effective, including individualized treatment based on platelet function tests in TIA and secondary prevention of ischemic stroke.

Some studies suggest that a higher dose of aspirin could lower resistance but 1 large review of secondary prevention showed no difference in the number of vascular events (MI, stroke, or death) with aspirin 500 to 1500 mg compared with 75 to 325 mg.[82] By comparison, a higher dose of clopidogrel (1200 mg) and maintenance (150 mg) is associated with more platelet inhibition in patients with *CYP2C19* LOF polymorphism, but whether this translates to better functional outcome or increased risk of bleeding in ischemic stroke or high-risk TIA is unknown.

Another approach to manage antiplatelet resistance is to use a different formulation, for example, enteric-coated aspirin, but as highlighted, bioavailability may be reduced compared with plain or regular preparations. Some experts suggest switching aspirin to clopidogrel on the basis of clinical failure to prevent recurrent ischemic stroke/TIA.[11,35,40] However, it is not known whether this is effective, as patients with aspirin resistance could be resistant to clopidogrel as well.[35]

Recent studies have shown that it is feasible to test for antiplatelet resistance using point of care (eg, VerifyNow $P2Y_{12}$) and adjust treatment in patients undergoing carotid stenting.[83] It is suggested that a longer duration, that is, 6 months with aspirin and clopidogrel, could lower resistance, but the potential benefits need to balanced against the risk of intracranial hemorrhage (≈1.5% each year).[31] Indirect evidence from 1 large secondary prevention stroke trial[84] supports this approach, but this needs to be validated prospectively.

There is emerging evidence that patients with aspirin or clopidogrel resistance may respond to other thienopyridines (eg, ticagrelor or prasugrel). Ticagrelor is a nonreversible antagonist of $P2Y_{12}$ and because it is not dependent on enzyme activation, may be less susceptible to drug interactions. Moreover, ticagrelor is associated with more platelet inhibition through increasing plasma level of adenosine.[85] However, the clinical effects are not known. There is significant heterogeneity in the prevalence of resistance to ticagrelor but the estimates might be less compared with clopidogrel.[20] Increasing age and diabetes are associated with high platelet reactivity, and smokers are reported to have less platelet reactivity.[86] Compared with clopidogrel, the bioavailability of ticagrelor is affected by pharmacogenetics, but variation in the soluble carrier organic anion transporter family member $1B_1$) and $UG72DB_7$ (uridine diphosphate glucuronsyltransferase family 2 member B_7) genes can affect levels of the active form of the drug.[87]

Recently, investigators conducted a trial in China comparing ticagrelor with clopidogrel for the secondary prevention of stroke in ischemic stroke or TIA in *CYP2C19* LOF carriers. Of the 6412 patients enrolled, 3205 were assigned to ticagrelor and 3207 to clopidogrel.[88] Stroke occurred within 90 days in 191 patients (6.0%) in the ticagrelor group and 243 patients (7.6%) in the clopidogrel group (hazard ratio, 0.77 [95% confidence interval, 0.64–0.94]; P=0.008).[88] There were no significant differences in major bleeding between the 2 groups.

Like clopidogrel, prasugrel is a prodrug, and activation to its active form requires intestinal esterase and to a lesser extent *CYP2C19* and *CYP2C9*. In patients with ischemic heart disease, genetic polymorphism studies of *CYP2C19* and *CYP2C9* have shown no effect on the pharmacokinetics and pharmacodynamic effects of prasugrel.[89,90] One explanation is that the activity of other hepatic CYP enzymes are able to compensate for reduced activity of *CYP2C19* or *CYP2C9*.[91] Potential mechanisms of resistance to prasugrel are similar to clopidogrel and include reduced or noncompliance with treatment, reduced bioavailability, and increased platelet turnover.[90] In addition, it is reported that prasugrel resistance is associated with variation in *CYP2C9* alone or in combination with *CYP2B6* reduced function genotypes. Supportive evidence comes from analysis of a trial in MI where carriers of *CYP2B6* were more likely to have cardiovascular events than noncarriers.[90] It is unclear whether other genotype polymorphisms are associated, but concomitant use of *CYP3A4* inhibitors is implicated in prasugrel resistance.[92]

Prasugrel has been tested in acute stroke and recently in patients undergoing neurointervention.[93,94] Some experts do not recommend prasugrel in treatment of ischemic stroke or TIA given the risk of intracranial hemorrhage.[95]

Although the prevalence of resistance to prasugrel and ticagrelor is reported to be less compared with clopidogrel, it is not insignificant.[96] Analyses suggest that ticagrelor may be more effective than prasugrel, but studies have varied in the method of platelet function test, timing of testing, and definition of platelet reactivity.[96] Prospective studies are needed to assess the safety and clinical efficacy of prasugrel or ticagrelor in patients with ischemic stroke/TIA who are resistant.

As a phosphodiesterase-3 inhibitor of platelets, cilostazol has a different mechanism of action compared with aspirin or clopidogrel. It is also known to protect vascular endothelium, improve endothelial function, and inhibit inflammation.[97] The metabolism of cilostazol is complex, involving many CYP enzymes. There are 11 active metabolites, and 1, dehydrocilostazol, is more potent than cilostazol itself; this is important when taking into account the pharmacokinetic effects. Cilostazol has been used for stroke prevention in Japan and South Korea since the 1980s and was first approved in the United States in 1998 for treating symptomatic peripheral arterial disease.[98] Studies have shown that in acute stroke, cilostazol is noninferior to aspirin but in combination, tends to increase the antiplatelet effect in patients with aspirin resistance.[99,100] A recent systematic review showed that combining cilostazol and clopidogrel could be more effective in preventing recurrent stroke in patients with clopidogrel resistance undergoing carotid artery stenting without increasing the risk of bleeding.[12] However, these results need to be validated prospectively, particularly in patients who are hyperresponders to clopidogrel who may be at higher bleeding risk.[12]

The precise mechanism of resistance to cilostazol is unclear, but *CYP2C19* and *CYP3a5* polymorphisms can affect its conversion to its active form.[101] This suggests that dose adjustment of cilostazol is indicated in poor metabolizers of *CYP2C19*, but studies have not accounted for its metabolites and their pharmacokinetics.[101] It is also important to highlight that research into cilostazol has mainly been conducted in Far East Asia, which raises the issue of generalizability of the results, and there are few data on resistance to treatment in acute stroke/TIA, including neurointervention, adjustment based on platelet function testing, and prognosis.[101]

FUTURE DIRECTIONS AND CONCLUSION

Growing evidence indicates that assessing patients with ischemic stroke and TIA for antiplatelet resistance could be important, as poor response may be associated with an increased risk of recurrent vascular events. While individualized treatment by measuring the effects of antiplatelet resistance would be ideal, there are several unresolved issues in the translation of platelet function tests to routine clinical practice. Platelet function testing needs to be easily available, reliable, inexpensive, and not labor intensive. Given that there is no single test or standard definition, future trials could measure in vivo platelet activity using nonspecific tests and drug-specific inhibition from time to treatment. Identifying patients at high risk of recurrent stroke or major vascular events (ie, those with ipsilateral atherosclerotic stenosis) and comparing treatment complications (eg, bleeding) would be of interest. Platelet function tests have been assessed in commonly used drugs such as aspirin and clopidogrel, but its utility with emerging agents such as ticagrelor, prasugrel, or cilostazol needs to be tested prospectively.

It is important to highlight that patients with cerebrovascular disease are usually older with fragile vascular beds, so testing specific response to treatment could help to determine the "therapeutic window" of maximum platelet inhibition in those at high risk of recurrence while minimizing the risks of bleeding. This could also include comparisons by stroke etiology (eg, atherosclerosis versus small-vessel disease), location (intracranial versus extracranial), stroke severity, treatment (intervention versus no intervention), dose (high versus low), method of revascularization, stent type, timing (early versus late; before versus after), sex (female versus male), and population (Far East versus Europe).

The results of this review highlight that treatment modification based on genetic testing is safe and feasible in poor metabolizers of clopidogrel, but whether this translates to other ethnicities (non-Chinese) and other genetic variations associated with treatment resistance merits exploration in further studies. This could further lead to discovery of other genetic polymorphisms, new risk variants, and improvement in technologies, which facilitate interpretation. Future studies of gene mapping the brain itself and cellular components including neurons, glia, axons/white matter, endothelium, and arteries could examine why some patients are at risk of recurrent stroke or major vascular events or vary in response to treatment.

While platelet function testing and genetics could have a future role in optimizing acute stroke/TIA treatment, it is important to highlight that measures focusing on compliance, smoking cessation, selecting the right formulation, avoidance of drug interaction, and controlling vascular risk factors remain important to substantially reduce the risk and severity of recurrent stroke or major vascular events.

ARTICLE INFORMATION

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APPENDIX

The following search teams were used to identify the relevant articles for this narrative review:

Ischemic stroke, transient ischemic attack, stroke, antiplatelets, aspirin, clopidogrel, prasugrel, ticagrelor, dual antiplatelets, genomics, genetics, gene, race, variant, ethnicity, ancestry, phosphodiesterase inhibitor, neurointervention, clipping, coiling, stent, radiology, cerebral aneurysm, bleeding, hemorrhage, ischemic, ischemia, infarct, brain, flow diverting, intracranial, endovascular, neuroendovascular, blood, platelet, reactivity, cytochrome P450 enzyme, percutaneous intervention, response, platelet function test, pharmacogenetics, pharmacodynamics, nonresponse, treatment, point of care, genomics, genetics, translational, platelet aggregation, inhibitors, platelet aggregation inhibitors, vascular disorders, critical care, intensive, carotid, thrombectomy, thrombolysis, angioplasty resistance, function, outcome, study, randomized, trial, clinical trial, systematic review, and meta-analysis.

Supplemental Materials

Supporting Information.

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