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Review

Aspirin and clopidogrel resistance: an emerging clinical entity

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Antiplatelet therapy is a cornerstone of cardiovascular medicine. Aspirin and clopidogrel have emerged as critical therapies in the treatment of cardiovascular disease. Despite their efficacy, patients on these medications continue to suffer complications. Millions of patients are currently on low-dose antiplatelet therapy but it is unknown how many of these patients are under-treated or on the wrong medication. Aspirin and clopidogrel resistance are emerging clinical entities with potentially severe consequences such as recurrent myocardial infarction, stroke, or death. The mechanism of resistance remains incompletely defined, but there are specific clinical, cellular, and genetic factors that influence therapeutic failure. These factors range from physicians who fail to prescribe these medications despite appropriate indications to polymorphisms of platelet membrane glycoproteins. Rapid and accurate diagnosis of antiplatelet resistance also remains an issue as new bedside tests are developed. By understanding the mechanism of therapeutic failure and by improving the diagnosis of this clinical entity, a new era of individualized antiplatelet therapy may arise with routine measurements of platelet activity in the same way that cholesterol, blood pressure, and blood sugar are followed, thus improving the care for millions of people.

Introduction

Antiplatelet therapy is a cornerstone of cardiovascular medicine. Clinical trials have shown the efficacy of aspirin in both the primary and secondary prevention of myocardial infarction, stroke, and cardiovascular death.[1,2] The Antithrombotic Trialists' Collaboration found an approximately 25% reduction in stroke, myocardial infarction, or cardiovascular death.[2] The Second International Study of Infarct Survival (ISIS-2) trial demonstrated that acute aspirin use reduced mortality by 23% in acute ST-elevation myocardial infarction.[3] Aspirin was shown to be equally efficacious as thrombolytic therapy while having an additive benefit when used in conjunction with streptokinase.

The thienopyridine clopidogrel has significant antiplatelet effect by inhibiting adenosine diphosphate (ADP)-mediated platelet activation. The Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study compared clopidogrel with aspirin in a wide spectrum of patients at risk for atherothrombosis. Initial analysis revealed a statistically significant 8.7% ($P = 0.043$) relative risk reduction in stroke, myocardial infarction, or ischaemic death in patients treated with clopidogrel.[4] Further work has shown an even larger impact on high-risk populations such as patients with a previous coronary artery bypass graft, with a history of $\geq$1 ischaemic event, diabetes, hypercholesterolaemia, or with disease in multiple vascular beds.[5]

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial found that dual antiplatelet therapy with clopidogrel and aspirin in acute coronary syndromes (ACSs) reduced adverse coronary events by 20% when compared with aspirin monotherapy.[6] The PCI-CURE substudy and the Clopidogrel for the Reduction of Events During Observation (CREDO) trial investigated the use of pretreatment and long-term treatment with clopidogrel following stenting. PCI-CURE showed a 30% relative risk reduction in the primary endpoint of MI, urgent revascularization, or cardiovascular mortality at 30 days and showed further benefit from prolonged administration.[7] CREDO demonstrated a 26.9% relative risk reduction in cardiovascular risk at 1 year and also showed the efficacy of clopidogrel pretreatment in certain patients undergoing PCI.[8]

The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY-TIMI-28) study evaluated clopidogrel in conjunction with aspirin, anticoagulation, and thrombolytics in ST-elevation myocardial infarction. This study revealed a 20% relative risk reduction in death, recurrent myocardial infarction, and recurrent ischaemia in patients who received clopidogrel as opposed to placebo.[9] The Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (COMMIT/CCS-2) enrolled nearly 46 000 patients receiving aspirin and compared the use of 75 mg of clopidogrel to placebo in patients with an ST-elevation

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myocardial infarction. The results complemented that of CLARITY-TIMI-28 by showing a 9% relative risk reduction of death, myocardial infarction or stroke; the reduction in mortality alone was 7%. COMMIT/CCS-2 additionally had an upper age limit of 100 years on patient enrolment as opposed to 75 years in the CLARITY trial, thus supporting the use of clopidogrel in an older population.[10] Importantly, both trials showed the effectiveness of therapy without an increased rate of major bleeding.

In terms of primary prevention, aspirin has been evaluated in six randomized trials.[11–16] The Physicians Health Study showed a 44% risk reduction in first myocardial infarction among physicians treated with aspirin.[11] The Thrombosis Prevention Trial (TPT) revealed the utility of aspirin in men at high-risk for coronary disease,[13] whereas the Hypertension Optimal Treatment (HOT) trial demonstrated a 36% reduction of myocardial infarction in hypertensive patients treated with aspirin.[14] The Primary Prevention Project (PPP) extended the findings of these trials by showing a 56% relative reduction in cardiovascular death in men and women with one or more major cardiovascular risk factors treated with aspirin.[15] Interestingly, the underpowered British Doctors' Study found no significant benefit to aspirin therapy.[12] A meta-analysis of these five trials evaluated a combined 55 580 patients and found a 32% relative risk reduction of having a first myocardial infarction in treated patients.[17] The Women's Heath Study randomized 39 876 females to low-dose aspirin therapy and showed no significant reduction in myocardial infarction though there was a significant relative risk reduction in total and ischaemic stroke.[16] However, a subgroup analysis revealed a significant benefit in women older than 65 years of age.

On the basis of these and other studies, aspirin and clopidogrel have emerged as critical therapies in both the primary and secondary prevention of coronary artery disease. The studies underscore the importance of controlling platelet reactivity as well as systemic inflammation, and these medications provide a foundation for antiplatelet therapy in coronary disease. Importantly, the studies stimulate new questions regarding the aetiology of therapeutic failure. Millions of patients worldwide currently take low-dose aspirin. Despite its benefits, many patients continue to suffer the effects of cardiovascular disease. By understanding the mechanism of treatment failure, therapeutic regimens can be changed and thus critically alter patient outcomes.

This review of the literature was performed via PubMed and Medline using the terms 'aspirin resistance' and 'clopidogrel resistance.' In addition, relevant journals were handsearched for recently presented data from national cardiology conferences.

Mechanisms of failed therapy

Aspirin works by irreversibly acetylating the cyclooxygenase (COX)-1 enzyme, thus suppressing thromboxane A_2.[18] Thromboxane A_2 serves as a potent agonist of platelet aggregation, and aspirin prevents thrombus formation via this mechanism. However, its antiplatelet effect is not uniform in all patients[19] and its inhibition of platelet aggregation is subject to inter-individual and intra-individual variability.[20] This unpredictable response to aspirin can be attributed to clinical, cellular, and genetic factors.[21]

Clinical causes of aspirin resistance can range from patient non-compliance to physicians who display aspirin resistance, that is, physicians who fail to prescribe aspirin appropriately (*Figure 1*).[21,22] Alternatively, patients may take aspirin but not absorb it, or may have interactions because of other medications. Ibuprofen, for example, can adhere to the COX-1 binding site of aspirin, and may via steric hindrance prevent aspirin from exerting its antiplatelet effect and limit its cardioprotective function.[23] The dose

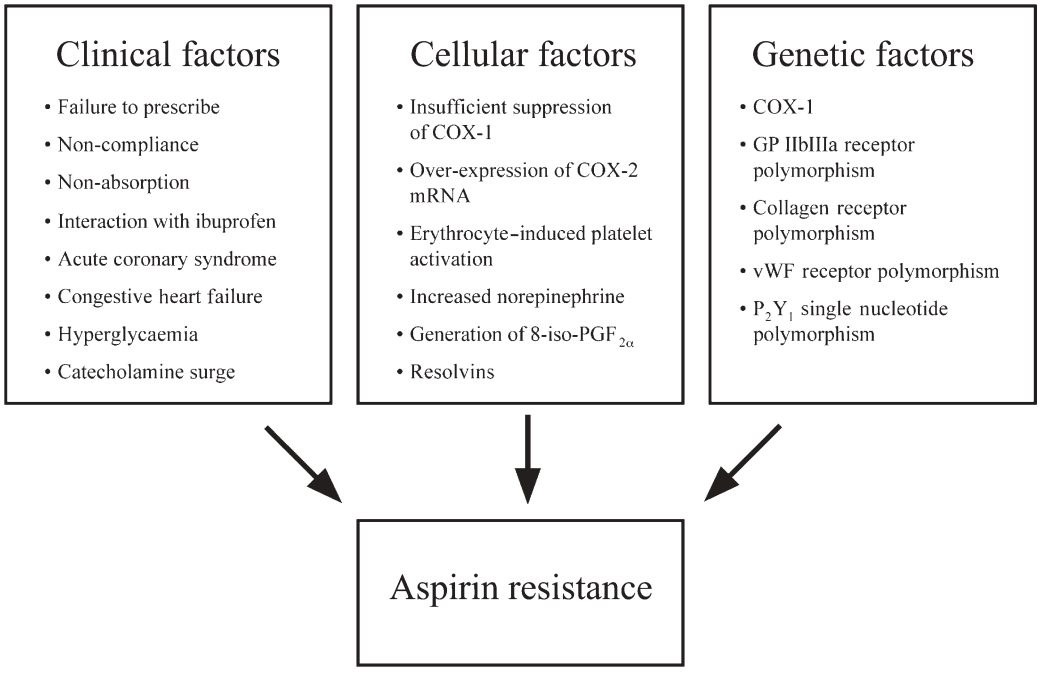

Figure 1. Mechanisms of aspirin resistance. [adapted from *Journal of the American College of Cardiology*, 43, Bhatt, DL. Aspirin resistance: more than just a laboratory curiosity, 1128, 2005].

of aspirin may contribute to uninhibited platelet activity depending on the weight and age of patients.[24]

In addition, ACSs and congestive heart failure are associated with increased platelet reactivity.[25] Hyperglycaemia may decrease the effectiveness of antiplatelet therapy by increasing reactive oxidant species,[26] whereas hypercholesterolaemia may blunt aspirin's effect on thrombin.[27,28] Exercise and the catecholamine surge associated with stress can also affect platelet responsiveness.[29]

Cellular factors influencing aspirin efficacy include inadequate suppression of platelet COX-1. In addition, aspirin resistance has been attributed to COX-2 mRNA over-expression by platelets and endothelial cells, though this remains controversial.[30,31] 8-iso-PGF_2 generation by catalysed arachidonate peroxidation may also cause aspirin resistance by binding thromboxane receptors.[32] Resolvins, a family of bioactive omega-3 fatty acid metabolites, mediate the inflammatory response and are generated via COX-2 acetylation by aspirin.[33] A deficiency of these products could also influence therapeutic failure.

Genetics also play a role in patient response to aspirin as polymorphisms of platelet membrane glycoproteins such as P1 (A1/A2) have been associated with an attenuated response to aspirin.[34,35] Polymorphisms of von Willebrand Factor (vWF) or the collagen receptor gene have also been postulated to cause aspirin resistance.[36,37] Single nucleotide polymorphisms of the *P_2Y_1* gene also can affect response to aspirin.[38] Despite these findings, the impact of polymorphisms on aspirin response remains controversial.[39]

Clopidogrel resistance may also be because of clinical, cellular, and genetic factors. Clopidogrel is a prodrug that is converted in the liver by cytochrome P450 3A4 (CYP3A4) into its active metabolite. It inhibits platelet aggregation by irreversibly binding to the P_2Y_{12} ADP receptor on the platelet surface. Similar to aspirin, clopidogrel therapy may fail owing to patient non-compliance or because physicians may not prescribe it. In addition, there may be variability in absorption[40] with associated under-dosing in patients and possible drug–drug interactions.[41] A recent study correlated the level of angina class with platelet inhibition by clopidogrel and found that patients with higher Braunwald angina class had lower inhibition of platelet aggregation.[42]

A recent analysis has raised the possibility of an interaction between atorvastatin and clopidogrel.[43] Analysis of the CREDO trial, found that this was not clinically significant and that the benefit of clopidogrel was similar with all statins regardless of the metabolic mechanism.[44] Other data, from the Plavix for Reduction of New Thrombotic Occurrences (PRONTO) study and the Interaction of Atorvastatin and Clopidogrel Study (Interaction) have shown that statins including atorvastatin do not interfere with platelet inhibition by clopidogrel.[45,46] Additional studies investigating the use of high-dose clopidogrel (600 mg) with statins has shown a lack of interaction between the agents.[47,48]

Cellular mechanisms of clopidogrel resistance may be because of inter-individual differences in P_2Y_{12} receptors and the number of receptors an individual possesses, varying the levels of ADP release, or platelet activation via alternative pathways. Notably, the degree of platelet responsiveness in patients treated with clopidogrel has been found to follow a normal bell-shaped curve (*Figure 2*).[49] Two small studies investigated the use of a 300 mg loading dose of clopidogrel immediately after stenting and found highly variable levels of responsiveness among individuals.[50,51] The durability of platelet inhibition by clopidogrel has also been studied showing the sustained antiplatelet effect of clopidogrel after 5 days, but also a significant heterogeneous response to the medication.[52] In terms of genetics, the H2 haplotype of the P_2Y_{12} receptor was associated with a more substantial down-regulation of platelet cyclic AMP because of ADP, which potentially could lead to a greater risk of thrombotic events.[53,54] A recent study noted, however, that the H2 haplotype did not adversely affect platelet inhibition by high-dose clopidogrel.[55] Eventually, analysis of the human genome may reveal previously undefined mechanisms of platelet resistance as well.

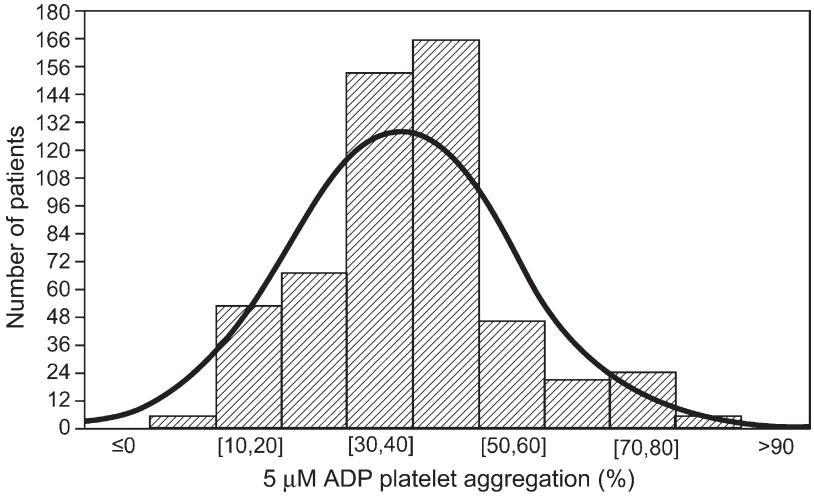

Figure 2. Variability in platelet responsiveness to clopidogrel among 544 individuals. Distribution of 5 μM of ADP-induced residual platelet aggregation in 544 patients after receiving clopidogrel therapy. [Reprinted from *Journal of the American College of Cardiology*, 45, Serebruany, Victor L., Steinhubl, Steven R., Berger, Peter B., Malinin, Alex I., Bhatt, Deepak L., Topol, Eric J. Variability in Platelet Responsiveness to Clopidogrel Among 544 Individuals, 247, 2005, with permission from the American College of Cardiology Foundation].

Aspirin and clopidogrel resistance may also be caused because platelet reactivity is mediated via the thromboxane A2 and ADP-pathways. A sufficient stimulus for platelet aggregation (i.e. thrombin) may in fact overcome the inhibition of these pathways. In addition, human platelets have a variable response to agonists such as ADP, epinephrine, and others.[56] Similarly, platelets exhibit variable responsiveness to drug-related inhibition as well.[57] Acquired forms of aspirin response variability also play a role in terms of ACSs and systemic inflammation.[58,59]

Defining resistance

As the mechanisms of aspirin and clopidogrel resistance are becoming clearer, defining these clinical entities remains a challenge. In its broadest sense, resistance refers to the continued occurrence of ischaemic events despite adequate antiplatelet therapy and compliance. The lack of a standard definition of resistance as well as the lack of a standard diagnostic modality has hampered the field in identifying and treating this clinical entity. Attempts have been made to develop a more meaningful definition with the goal of correlating laboratory tests with clinical outcomes, but there is no current definition which unifies the biochemical and clinical expression of failed treatment.[60–65] Rates of aspirin resistance range from 5 to 45% of the population depending on the study and the method of determining therapeutic failure.[66–69] Rather than attempting to characterize patients as simply resistant or sensitive to a medication, however, therapeutic resistance is more likely a continuous variable similar to blood pressure. By shifting the paradigm of diagnosis from a specific value to this notion of a continuous variable, the physiology of treatment failure may be better elucidated and thus better managed. In the meantime, a clear and consistent characterization of antiplatelet resistance is necessary.

In terms of diagnostic testing, light transmittance aggregometry is the current gold standard for determining platelet function. Unfortunately, this technique is labour intensive and requires the assay to be performed in a laboratory, thus preventing bedside assessment. In addition, differences in technique and proficiency between laboratories can make data from varying institutions difficult to interpret.[70,71]

The platelet function analyzer (PFA)-100 (Dade-Behring, Deerfield, IL), and the VerifyNow Rapid Platelet Function Assay (RPFA)-ASA (Accumetrics, San Diego, CA) have been designed as point-of-care tests to allow ease of use and widespread distribution (*Table 1*). The PFA-100 test has variable correlation with the historical gold standard of light-transmittance aggregometry and requires further study in order to determine its clinical relevance.[72,73] The VerifyNow RPFA-ASA assay has shown excellent correlation with optical aggregometry using whole blood but requires investigation into the clinical impact of resistance (defined as an aspirin resistance unit or ARU of >550) and the rate of subsequent cardiovascular events.[74] Urinary levels of 11-dehydro-thromboxane B_2 have also been utilized to study aspirin inhibition of thromboxane generation though it is not known whether the persistent elevation in urinary thromboxane B_2 levels is because of uninhibited platelet COX-1 activity or by COX-1 independent sources of thromboxane generation.[63,75,76]

What are the consequences of aspirin or clopidogrel resistance?

Eikelboom *et al.*[76] measured urinary 11-dehydro thromboxane B_2 levels in patients on aspirin from the Heart Outcomes Prevention Evaluation (HOPE) study. Patients in the highest quartile of urinary 11-dehydro thromboxane B_2 levels had a 1.8 times higher risk of myocardial infarction, stroke, or cardiovascular death than patients in the lowest quartile ($P = 0.009$). Gum *et al.*[66] performed a randomized prospective trial of 326 patients on aspirin and no other antiplatelet agents. Aspirin sensitivity was tested by optical platelet aggregation, considered the gold standard in determining platelet response. Of those studied, 17(5%) patients were found to be aspirin-resistant and in follow-up had

Table 1 Laboratory assays for aspirin and clopidogrel resistance

Lab method	Pros	Cons
Light transmittance aggregometry	Considered gold standard Monitors aspirin, thienopyridines, and IIB/IIIA inhibitors	Time-consuming Cannot be run at bedside Variable results depending on reagents used
Platelet Function Analyzer (PFA)-100	Allows for bedside analysis Easy to use and rapid Whole blood assay	Depends on vWF and haematocrit Monitors only aspirin (not thienopyridines or IIB/IIIA inhibitors)
VerifyNow Rapid Platelet Function Assay	Allows for bedside analysis Easy to use and rapid Whole blood assay Monitors aspirin, thienopyridines,[a] and IIB/IIIA inhibitors	
Urinary 11-dehydrothromboxane B2	COX-1 dependent	Indirect measure Not platelet-specific Depends on renal function Monitors only aspirin (not thienopyridines or IIB/IIIA inhibitors)

[a]Rapid Platelet Function Assay is now FDA approved for clopidogrel.

a nearly three-fold increased risk of death, myocardial infarction, or CVA ($P = 0.03$).[66]

More recently, Chen *et al*. investigated the effect of aspirin resistance on myonecrosis after non-urgent percutaneous coronary intervention (PCI) among 151 patients pretreated with 300 mg of clopidogrel >12 h prior to PCI and 75 mg the morning of the PCI. The point-of-care VerifyNow RPFA test was utilized to determine therapeutic responsiveness. Twenty-nine patients (19.2%) were found to be aspirin-resistant with an increased risk of myonecrosis (51.7% vs. 24.6% as assessed by troponin elevation, $P = 0.006$) following non-urgent PCI, despite pretreatment with aspirin.[77]

Clopidogrel resistance has been studied in patients with acute myocardial infarction confirming the inter-individual variability of platelet inhibition by clopidogrel. Matetzky *et al*.[78] analysed 60 patients with acute ST-segment myocardial infarction who underwent primary PCI and were subsequently placed on clopidogrel. Patients were divided into quartiles of responsiveness to clopidogrel measured by the percent reduction of ADP-induced platelet aggregation. The patients who were least responsive to therapy determined by aggregometry were 25% more likely to have a recurrent cardiovascular event during a 6-month follow-up when compared with patients in the other three quartiles of platelet responsiveness ($P = 0.007$). In addition, clopidogrel use post-PCI for stable angina has been evaluated, with a higher rate of subacute stent thrombosis found in clopidogrel non-responders.[79]

On the basis of these studies, the risk of therapeutic failure to antiplatelet therapy is concerning. Patients are at increased risk for cardiovascular complications including death, myocardial infarction, and cerebrovascular accidents. Thus, the need for additional investigation into the clinical consequences of these laboratory findings remains vital, as the data presented earlier must be reproduced in larger datasets. Given the consequences of therapeutic failure, the question thus turns to how a clinician can effectively treat resistance to antiplatelet agents.

Treating aspirin and clopidogrel resistance

The treatment for failed antiplatelet therapy is as yet undefined. An initial approach would be to correct the clinical factors that may cause therapeutic resistance. Physicians must ensure proper patient compliance while also minimizing drug–drug interactions. In addition, optimal control of glucose levels and cholesterol levels can reduce platelet reactivity.

Currently, there is no good evidence that increasing aspirin dose would be useful.[2] Data from Blockage of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trial and the CURE trial actually indicate an increased risk of serious bleeding associated with high aspirin doses.[67,80] However, it remains possible, though unproven, that increased doses of aspirin may overcome aspirin resistance in an individual patient. The addition of clopidogrel to aspirin is logical given its distinct mechanism of action. The Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study revealed modest superiority of clopidogrel monotherapy over aspirin monotherapy,[4] while also showing an increased benefit in high-risk patients.[68] In terms of dual antiplatelet therapy, aspirin resistant patients have platelets that are more sensitive to ADP.[81] The CURE and CREDO trials support this notion as they revealed the additive clinical benefit of clopidogrel to aspirin.

Beyond the use of aspirin in conjunction with clopidogrel, the options for medical therapy remain limited. Consideration can be given to increasing maintenance doses or loading doses of clopidogrel.[82,83] The Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty (ARMYDA-2) study showed the benefit of 600 mg of clopidogrel when compared with 300 mg of clopidogrel as pretreatment in reducing periprocedural myocardial infarction in patients undergoing PCI.[84] The utility of increasing the dose of clopidogrel has been further supported by the recent findings in the Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation, and Ongoing Necrosis (ALBION) trial.[85] Additionally, the Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect trial (ISAR-CHOICE) has been recently published and showed a greater and faster degree of platelet inhibition with a 600 mg versus a 300 mg loading dose of clopidogrel.[86]

Alternative thienopyridine agents are also possibilities as CS-747, also known as prasugrel (LY640315)[87] and non-thienopyridine P_2Y_{12} inhibitors such as the intravenous agent cangrelor[88–90] and the oral ADP antagonist AZD6140 are still under investigation. CS-747 has already been investigated in a large phase-2 study, Joint Utilization of Medications to Block Platelets Optimally—Thrombolysis in Myocardial Infarction 26 (JUMBO-TIMI-26), and was found to have low rates of clinical bleeding.[91] Other studies have shown the potential benefit of cangrelor as an adjunct to fibrinolysis in acute myocardial infarction as well as in facilitated angioplasty.[92,93] In addition, cangrelor has potent platelet inhibition which may be greater than clopidogrel, has a short plasma half-life, does not require hepatic activation, and is a direct antagonist of the P_2Y_{12} receptor.[94] AZD6140 is an oral P_2Y_{12} antagonist which blocks platelet aggregation more completely than clopidogrel and also does not require hepatic metabolism for activation.

Looking to the future

As the understanding of antiplatelet resistance improves, more options become available for diagnosing and treating this clinical entity. The need for larger trials that correlate clinical outcomes data with laboratory assessment of platelet aggregability has been underscored by the adverse results seen in patients with aspirin or clopidogrel resistance (*Table* 2).[66,76,78,95] Such efforts are currently underway as part of the Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management, and Avoidance (CHARISMA) Trial. This randomized, international, double-blinded, placebo controlled trial will follow 15 603 patients who receive either clopidogrel and aspirin or placebo and aspirin for high-risk primary or secondary prevention.[96,97] The primary endpoints will be vascular death, myocardial infarction, or stroke. In a substudy, DNA samples will be obtained from patients and can help identify single nucleotide polymorphisms that may contribute to aspirin or clopidogrel resistance. Also in a substudy, urinary 11-dehydro thromboxane B_2 levels will be checked, thus prospectively

Table 2 Future trials

CHARISMA	Investigates the additive benefit of clopidogrel to aspirin for high-risk primary or secondary prevention
Substudy	DNA samples will be obtained to help identify single nucleotide polymorphisms contributing to aspirin and clopidogrel resistance
Substudy	Urinary 11-dehydro thromboxane B2 levels will be checked to assess the clinical risk associated with aspirin resistance and whether clopidogrel decreases this risk
RESISTOR	Investigates the use of the VerifyNow assay in determining patient response to aspirin and clopidogrel and whether non-responders have benefit with IIB/IIIA inhibitors
TRITON-TIMI 38	Evaluates prasugrel compared with clopidogrel in patients with ACS undergoing PCI

assessing whether clopidogrel added to aspirin attenuates the clinical risk associated with aspirin resistance.

Another study, the Research Evaluation to Study Individuals who Show Thromboxane or P_2Y_{12} Receptor resistance (RESISTOR) trial, will investigate the use of clopidogrel in addition to aspirin prior to elective angioplasty. The trial will utilize the VerifyNow Rapid Platelet Function Analyzer to identify patients as responders or non-responders and then randomize patients to the intravenous glycoprotein IIb/IIIa inhibitor eptifibatide plus unfractionated heparin or unfractionated heparin alone.

The JUMBO-TIMI-26 trial has prompted a phase-3 evaluation of prasugrel vs. clopidogrel in patients with ACSs undergoing PCI. This study, entitled TRITON-TIMI-38, will have a target enrolment of 13 000 patients and have a primary composite endpoint of cardiovascular death, myocardial infarction, or stroke.[91] The DISPERSE2 study was a phase IIb study that investigated the efficacy of two different doses of AZD6140 (90 mg or 180 mg twice daily) compared to 75 mg of clopidogrel once daily in patients with non-ST elevation myocardial infarction. Results showed similar rates of bleeding in all groups and no significant difference in the composite endpoint of cardiovascular death, stroke, or recurrent ischemia. Based on this finding, further studies may be forthcoming regarding this new agent.[98]

As more is learned about the variable response to antiplatelet drugs, the need for accurately assessing inter-individual response to such therapy increases. Millions of patients take low-dose aspirin for thromboprophylaxis today. How many are taking the wrong dose or the wrong drug? Given the wide range of possible aspirin resistance from 5 to 45%, a large population is at risk for inadequate or incorrect therapy. While the terms aspirin and clopidogrel resistance remain broadly defined, they represent valid biochemical entities with potentially very significant clinical consequences. The future may soon be realized with routine measurements of platelet activity in the same way that cholesterol, blood pressure, and blood sugar are followed to help guide therapy. A new era of individualized antiplatelet therapy may arise with differing doses and differing therapeutic agents provided for the millions of patients receiving these treatments. However, ongoing and future trials will be necessary to validate this approach.

Conflict of interest: T.H.W. and E.J.T. have no conflicts of interest to report. D.L.B. has received honoraria for educational lectures and/or served on scientific advisory boards for AstraZeneca, Bristol Myers Squibb, Eli Lilly, Millennium, Sanofi Aventis, Schering Plough, and The Medicines Company.

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