Aspirin and clopidogrel provide significant clinical benefit in patients with cardiovascular disease. However, given the complexity of platelet activation, it is not surprising that aspirin or clopidogrel prevent a small proportion of cardiovascular events. Of late, the terms aspirin and clopidogrel “resistance” have entered the physicians’ lexicon, and infer a lack of therapeutic response and a single underlying mechanism, which is misleading. The incidence of “resistance” detected in studies varies with the definition applied and assay used to measure response. Rather than true resistance, however, there is a variable response that reflects the unique pharmacology and pharmacokinetics of each drug, the clinical significance of which remains to be established.

True “aspirin resistance” implies that cyclooxygenase-1 is less sensitive to inactivation by aspirin. Despite 95% inhibition of serum thromboxane B2 by aspirin, residual platelet aggregation is detected in some cases, the clinical significance of which is unknown. Heritable factors directly and indirectly related to platelet cyclooxygenase may influence aspirin response. In contrast to aspirin, the response to clopidogrel is highly variable and reflects the bioavailability of the active metabolite and not “resistance” of the receptor to inhibition.

Introduction
Aspirin and clopidogrel “resistance” are terms that have entered the lexicon of physicians without there being much evidence for (1) a single mechanism as envisaged by the phrase or (2) a lack of response despite adequate bioavailability, which the phrase implies. Drug dosing is often based on the population response, where a dose is selected that balances therapeutic (usually clinical) effect and risk in the population. By definition, some individuals will not respond to the dose selected. There is an additional aspect when addressing aspirin and clopidogrel in that they are each specific for just one of myriad potential platelet agonists. On the other hand, arterial thrombosis is a complex phenomenon involving multiple agonists. Not surprisingly therefore, aspirin or clopidogrel prevent only a proportion of events. Whether one considers the pharmacologic or the clinical response, there are many reasons for the failure of individuals to respond as expected. For aspirin and clopidogrel, those reasons differ, reflecting their unique pharmacology and pharmacokinetics.

Platelet Activation and Coronary Thrombosis
Coronary thrombosis is initiated by platelet activation in response to plaque rupture or vascular injury, although there is also evidence of genetically enhanced platelet activity in patients with the disease. Platelets adhere to areas of injury through engagement of adhesion receptors (including glycoproteins VI, IB/IX/αIIbβ3) with adhesive proteins (collagen, von Willebrand factor, and fibrinogen, respectively), triggering activation and shape change. Secondary platelet activation is triggered by soluble agonists released or generated as a consequence of platelet activation, including thromboxane (TXA2) and adenosine diphosphate (ADP) or the formation of thrombin locally. The adherent platelets are activated, a downstream consequence of which is induction of a high-affinity binding site for fibrinogen in the quiescent GPαIIbβ3. Additional platelets aggregate to the adherent platelet layer through cross-linking of fibrinogen to adjacent platelets, creating a platelet mass that acts as a scaffold for coagulation.

Platelet Cyclooxygenase
Nearly all platelet agonists induce thromboxane formation as a consequence of phospholipase-mediated release of membrane arachidonic acid and its subsequent metabolism by the enzyme, cyclooxygenase (COX). The only isoform of COX in platelets is COX-1, which converts arachidonic acid to the intermediary endoperoxide, which in turn is metabolized to the final product, TXA2, by the enzyme thromboxane synthase. TXA2 is released from platelets and activates a surface membrane G-protein-coupled receptor, the TP-receptor. Activation of the TP receptor induces further platelet activation, amplifying the original stimulus and reinforcing the platelet aggregation. In the case of weak agonists (low concentrations of collagen, thrombin and ADP, epinephrine), formation of thromboxane is essential for full, irreversible platelet aggregation, and the response is susceptible to aspirin. More potent agonists like thrombin induce full platelet aggregation independently of TXA2 and are not susceptible to aspirin.

Platelet ADP
ADP is released from platelet-dense granules upon activation and, like thromboxane, reinforces the platelet response to weak agonists. ADP activates the purinergic receptors P2Y1 and P2Y12 that are expressed by platelets. Full platelet response depends on the activation of both receptors and includes platelet shape change, aggregation, forma-
tion of thromboxane and expression of surface tissue factor. ADP is rapidly metabolized and, indeed, at low concentrations, the platelet activation is reversible. At high concentrations of ADP, platelet aggregation is irreversible. Hereditary absence of the P2Y12 receptor results in a mild bleeding diathesis and unstable platelet aggregate formation.

The Pharmacology of Aspirin
Aspirin (acetylsalicylate) is hydrolyzed more rapidly in alkaline conditions to the inactive salicylate. As it has a low pKa, it is absorbed in the stomach and appears in the blood within 10 minutes, with peak plasma concentrations seen at 30 to 40 minutes. Aspirin is metabolized by esterases in blood and in the liver and has a half-life of 15 minutes. The bioavailability of regular, soluble aspirin (that is, the amount detected systemically) is 50%, but this is lower for controlled-release preparations. The major metabolite, salicylate has a half-life of 3 to 6 hours depending on the dose and, unlike aspirin, can be detected in plasma and urine long after the active drug has been eliminated. Given its instability, it is difficult to measure aspirin in biological samples, particularly when given in low doses. Studies with low dose, controlled-release aspirin have found platelet inhibition prior to any detectable aspirin in the systemic circulation. This arises as aspirin exerts its effect on platelets in the portal or presystemic circulation and is subsequently removed by the liver. Thus, inhibition of platelets is often used as a surrogate measure of aspirin bioavailability.

The target for aspirin is COX, of which there are two isoforms, COX-1 and COX-2. COX-1 is ubiquitously expressed and is the only isoform in platelets, where it generates TXA2. COX-1 is also expressed in vascular endothelium, where it generates prostacyclin (PGI2), the major cyclooxygenase product of these cells. COX-2 is an inducible gene and is found at sites of inflammation and in many cancers. COX-2 is largely absent in healthy subjects, but is nevertheless expressed in sufficient amounts to generate PGI2.

Aspirin is a nonselective COX inhibitor, inhibiting both isoforms. Yet, at low dose in humans, aspirin is relatively selective for platelet COX-1. The explanation lies in both the irreversible effect of aspirin on the enzyme and the slow turnover of COX-1 in platelets. Aspirin acetylates a serine in the substrate pocket of the enzyme and consequently through bulk action alters the positioning of the substrate arachidonic acid, preventing its metabolism to the endoperoxide. In the case of COX-1, the enzyme is inactivated and as the reaction is irreversible, no thromboxane is generated for the lifetime of the platelet (about 10 days). (In the case of COX-2, the enzyme is converted to a lipooxygenase.) This is because platelets have a low capacity to generate protein (they are anucleate), and so new platelets must be generated to restore cyclooxygenase activity. Thus, following a single 100-mg dose of aspirin, the ability of whole blood to generate TXA2 recovers in parallel with the appearance of new platelets and achieves pre-treatment levels at 8 to 10 days. Maintenance of the effect requires only a small dose of aspirin, as low as 40 mg daily. Thus, despite its rapid inactivation in the body, aspirin has a long-term effect on platelets that can be maintained by just once-a-day administration. The model assumes a low platelet turnover. Where platelet turnover is increased, higher doses of aspirin may be required.

Measuring Aspirin’s Effect
In platelets, COX-1 generates TXA2, which in turn is rapidly and nonenzymatically converted to the inactive TXB2. TXB2 is metabolized enzymatically to a range of products, the most abundant being 11-dehydro-TXB2 and 2,3-dinor-TXB2, both of which are excreted in urine. Aspirin’s inhibition of COX-1 is best assessed directly by measuring the capacity of platelets to generate TXB2. Nonanticoagulated blood is incubated at 37°C for at least 45 minutes to induce maximum platelet activation and release of the substrate for metabolism to TXB2. Aspirin reduces this assay of serum TXB2 by at least 95% when adequately dosed. Measures of plasma TXB2 are less informative. The levels are so low that it is difficult to discern a reduction, and what is measured is often an artefact of platelet activation during sampling. Aspirin also reduces urinary thromboxane metabolites, but as these are not solely derived from platelet TXB2, the assay is less informative about the degree of platelet inhibition.

As an alternative strategy, the effect of aspirin can be estimated by assays of platelet activity, usually platelet aggregation in response to agonists such as arachidonic acid, epinephrine and collagen. The response to more potent agonists like thrombin is less dependent on platelet cyclooxygenase and is unaffected. More recently, bedside assays have been developed that provide a more rapid assay of platelet function and have been used to detect inadequate response to aspirin (see Table 1). These include the PFA-100, in which a sample of blood is forced through a capillary containing both collagen and a platelet agonist (e.g., epinephrine) and the time to cessation of flow (caused by platelet aggregation) is the measure of platelet activity. Aspirin prolongs the closure time, and thus the PFA-100 has been used to assess the response to aspirin in patients.

Variation in the Response to Aspirin
All drugs show variation in response, which is not surprising given the heterogeneity of the population. (The most common reason is variation in pharmacokinetics reflecting the heterogeneity in volume of distribution [weight, fat] and/or drug metabolism.) The response to drugs is normally distributed in most cases, so that by definition some patients fall into the lower extreme end of response. For aspirin this is largely irrelevant, as doses as low as 30 mg daily effectively inactivate platelet cyclooxygenase. There are, nevertheless, circumstances where low doses of aspirin may prove inadequate, such as when platelet turnover is increased (for example, following surgery or in myelopro-
The Rising Tide of "Aspirin Resistance"

In recent times, there has been a flood of papers suggesting that there are patients who are "resistant" to aspirin (Table 1). Of course, aspirin is a relatively weak antithrombotic agent in that it reduces the risk of serious cardiovascular events by little more than 20% (it is higher, perhaps 40% to 50% in higher-risk diseases, such as acute coronary syndrome). Here, the explanation is largely related to the complexity of the disease, primarily coronary thrombosis. Coronary thrombosis arises from vascular injury, either long-standing or acute plaque disruption, where platelets adhere to the vessel wall, thereby triggering a cascade of events reinforced by the generation of thromboxane. Many platelet activation pathways are implicated, include adhesion-mediate outside-in signaling, shear-induced activation of adhered platelets, the local formation of thrombin, and the release of platelet agonists, including TXA₂, ADP and growth arrest–specific (GAS) gene 6. Aspirin influences just one of these pathways and not surprisingly has a limited effect. Few, if any, of the patients failing to respond clinically to aspirin are "resistant" to the drug.

That said, there may be circumstances where aspirin in regular doses may not have the desired platelet inhibition. The target for aspirin is >95% inhibition of serum TXB₂, as at lower levels of inhibition, sufficient TXA₂ is generated to support platelet aggregation to some extent. Several studies have shown that this is achieved at a dose of regular aspirin of 75 mg daily in virtually every case. At more than 95% inhibition of serum TXB₂, there is near complete inhibition of platelet aggregation to weak agonists. Whether suppression of this residual degree of platelet activity translates into a greater clinical benefit is doubtful, as the clinical response to aspirin across large-scale studies is not dose related at doses greater than 75 mg daily.

"True Aspirin Resistance"

True aspirin resistance implies that the target, cyclooxygenase, is less sensitive to inactivation by aspirin. In one study, Maree and colleagues examined serum TXB₂ and platelet aggregation to arachidonic acid in patients with coronary artery disease on aspirin and related

Table 1. Prospective studies of variable platelet response to aspirin and clinical events.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Patients (no.; % female; mean age, y)</th>
<th>Aspirin dose (mean follow-up period)</th>
<th>Aspirin resistance assay (prevalence)</th>
<th>Clinical outcome associated with aspirin resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grotemeyer et al¹⁶ (1993)</td>
<td>Prior CVA (180; 41; 58)</td>
<td>500 mg TID (2 y)</td>
<td>Platelet reactivity test (33%)</td>
<td>OR 14.53 (5.16-40.9); P &lt; .0001 Risk of stroke, MI or vascular death</td>
</tr>
<tr>
<td>Mueller et al¹⁷ (1997)</td>
<td>Intermittent claudication (100; 30; 62.5)</td>
<td>100 mg/d (1.5 y)</td>
<td>Corrected whole blood aggregometry*</td>
<td>87% higher risk of lesion reclosure post peripheral vascular angioplasty (P = .009)</td>
</tr>
<tr>
<td>Eikelboom et al¹⁸ (2002)</td>
<td>High cardiovascular risk (976; 15.8; 67)</td>
<td>Unspecified (5 y)</td>
<td>Urinary 11-dehydro TXB₂ (quartile comparison)</td>
<td>Upper versus lower quartile OR 1.8 (1.2-2.7) Risk of MI, CVA or cardiovascular death</td>
</tr>
<tr>
<td>Gum et al¹⁹ (2003)</td>
<td>Stable coronary artery disease (328; 22.4; 62)</td>
<td>325 mg/d (1.86 y)</td>
<td>Optical aggregometry (5.2%)†</td>
<td>OR 3.12 (1.1-8.9) Risk of MI, CVA, all cause death</td>
</tr>
<tr>
<td>Chen et al²⁰ (2004)</td>
<td>Non-urgent PCI (151; 24.5; 64)</td>
<td>80-325 mg (24 h)</td>
<td>Ultegra rapid platelet function assay-ASA 19.2%‡</td>
<td>OR 3.29 (1.42-7.59); P &lt; .01 Risk of myonecrosis post PCI (CK-MB = 16 U/L)</td>
</tr>
<tr>
<td>Poston et al²¹ (2006)</td>
<td>Patients undergoing off-pump coronary artery bypass grafting (225; 34; 69)</td>
<td>325 mg/d (30 d)</td>
<td>Thromboelastography§</td>
<td>Early SVG thrombosis - 45% ASA resistant versus patent SVG 20% ASA resistant; P &lt; .05</td>
</tr>
<tr>
<td>Ohmori et al²² (2006)</td>
<td>Prior cerebral infarct or ischemic heart disease (140; 53.7; 75.4)</td>
<td>81 mg (1 y)</td>
<td>Optical aggregometry (collagen) PA-20 platelet aggregation analyzer (quartile comparison)</td>
<td>HR 7.98; P = .008 Risk of cardiovascular events if upper quartile (optical aggregometry) HR 7.76; P = .007 Risk of cardiovascular events (PA-20 analysis)</td>
</tr>
</tbody>
</table>

Adapted from Maree and Fitzgerald, with permission.¹

Abbreviations: TID, three times a day; OR, overall response; MI, myocardial infarction; CVA, cerebrovascular accident; ASA, aspirin; PCI, percutaneous coronary intervention; CK-MB, creatine kinase isoenzyme MB; HR, hazard ratio

Resistance defined as persistent aggregation to ADP and collagen.

†Resistance defined as mean aggregation ≥70% with 10 μM ADP and mean aggregation of ≥20% with 0.5 mg/mL arachidonic acid.

‡Propyl gallate agonist, resistance defined as ≥550 aspirin response units.

§Resistance defined as 2 of 3 assays positive.
this to polymorphisms in the COX-1 gene. The response to aspirin was related to the haplotype (the pattern of variants in an individual), without a clear explanation, as only one variant was predicted to affect the structure of the protein. Whether other variants (possibly linked to the known variants) exist has yet to be addressed, requiring resequencing of the gene in a large population. Others associated aspirin resistance, determined by the PFA-100 point-of-care platelet function assay (collagen and epinephrine cartridge) with increased expression of three vitamin D–binding protein isotypes. In effect, genetic variation in any platelet-signaling component, whether directly targeted by a drug or not, has the potential to influence drug response. This is borne out by a recent study of healthy volunteers showing that both baseline platelet function and persistent platelet activation in the presence of aspirin largely reflected signaling via COX-1–independent pathways and that this was an inherited trait. Not surprisingly, platelet activity and bleeding time response to antiplatelet therapy are to some extent inherited.

**Aspirin and Nonsteroidal Antiinflammatory Drugs**

There is one circumstance in which the pharmacologic response to aspirin may be impaired, namely when a nonsteroidal anti-inflammatory drug (NSAID) has been administered prior to aspirin. This has been reported primarily with ibuprofen, a nonselective cyclooxygenase inhibitor. Ibuprofen inhibits COX-1 in part through binding to the arginine-120 at the mouth to the substrate-binding site. The drug has a long plasma half-life (4-6 hours) and therefore inhibits the enzyme for several hours. In so doing, ibuprofen prevents aspirin from accessing the target serine in the active site. As aspirin is rapidly inactivated to form salicylate, and therefore is active for a relatively short period, it fails to inactivate the enzyme. Ibuprofen is a reversible inhibitor of COX-1 and washes out, leaving the enzyme uninhibited. In effect, prior dosing with ibuprofen blocks the inhibition by aspirin. There is evidence of a higher than expected event rate in patients on aspirin who take NSAIDs regularly, which is consistent with the hypothesis that NSAIDs interfere with the action of aspirin. However, other mechanisms may be responsible, as there is growing evidence that some NSAIDs are associated with a higher rate of cardiovascular events even in patients not on aspirin.

**Clinical Studies of “Aspirin Resistance”**

Many studies have examined the response to aspirin in patients with cardiovascular disease and have reported “aspirin resistance” in as many as 33% of subjects. Given what has been outlined above, this is a surprisingly high frequency. The explanation lies in the definition, which is often based on an arbitrary level of platelet activity and on assays that are not solely measuring platelet cyclooxygenase activity. For example, while the closure time of the PFA-100 (often used in studies) and platelet aggregation to agonists are to some extent dependent on platelet thromboxane formation, other platelet activation pathways that are insensitive to aspirin are undoubtedly involved.

Studies based on serum TXB$_2$ are few and in general report a very low rate of “aspirin resistance.” Several studies have examined urinary excretion of 11-dehydro-TXB$_2$ and report incomplete suppression of this index of whole-body thromboxane formation. Moreover, the continued excretion of 11-dehydro-TXB$_2$ was related to subsequent cardiovascular events. The assay does not solely measure thromboxane generated by platelets, but also detects thromboxane generated by other tissues. Indeed, there is good evidence that atherosclerotic plaque can generate thromboxane and this may explain its continued generation and contribution to disease progression.

**Clinical Outcome and Aspirin Resistance**

There have been few studies examining the outcome of patients demonstrating “aspirin resistance,” and all have their flaws. In many cases, the assay used measured residual platelet activity and not the primary response to aspirin. Small studies have explored the clinical utility of point-of-care platelet function assays. All are case-control studies or prospective comparisons between groups and are not randomized. The likelihood of a randomized study capable of discriminating the benefit of complete suppression of platelet cyclooxygenase being adequately powered is low, given how many studies were required to show a beneficial effect of aspirin in the first place.

**Pharmacology of Clopidogrel**

Clopidogrel is one of a series of compounds developed as antagonists of P2Y$_{12}$. These compounds inhibit platelet aggregation to a range of agonists in addition to ADP, as the response to many agonists is in part dependent on the release of ADP from platelet dense granules. Strong agonists, such as thrombin, are, however, unaffected by clopidogrel. The platelet response to ADP and glycoprotein inhibitors is highly dependent on the con-
centration of the agonist. At low concentrations, the response to ADP is highly dependent on the generation of thromboxane and is inhibited by aspirin. Higher concentrations of ADP induce full and irreversible platelet aggregation that is insensitive to aspirin but is inhibited by up to 90% in the presence of a P2Y12 antagonist. Thus, the assay is an effective means of assessing the response to clopidogrel. Other point-of-care assays are sensitive to P2Y12 antagonism. The PFA100, for example, can be designed to examine the response to ADP, and the time to closure is prolonged in patients on clopidogrel. 

**Variation in the Response to Clopidogrel**

Inhibition of platelet aggregation to ADP by clopidogrel is highly variable and shows a normal distribution, with an average of 40% to 50% inhibition. This wide variation in response reflects several issues, including poor compliance with medication, variable absorbance of the parent drug and variability in formation of the active metabolite. Clopidogrel is activated by CYP3A4, one of a series of cytochrome P450 enzymes involved in drug metabolism. The activity of the enzyme varies widely in the population, as has been reported for other cytochrome P450 enzymes, with the result that the activity of clopidogrel is similarly heterogeneous. In part, this may reflect genetic variation in the enzyme although coadministration of drugs that are metabolized by the enzyme and environmental factors may influence the activation of clopidogrel. Not surprisingly, therefore, there is a wide variation in the platelet response to clopidogrel when a standard daily dose is administered. Thus, platelet aggregation to high concentrations of ADP can show minimal inhibition or marked suppression in patients on clopidogrel. The response is dose dependent and is augmented by the addition of a P2Y12 antagonist or the active clopidogrel metabolite in vitro. This suggests that the variability in response reflects the variable bioavailability of the active metabolite and not “resistance” of the receptor to inhibition by the drug.

### Table 2. Studies of variable platelet response to clopidogrel with clinical correlation.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Patients (no.,% female; mean age, y)</th>
<th>Clopidogrel dose (mean follow-up period)</th>
<th>Clopidogrel resistance assay (prevalence)</th>
<th>Clinical outcome associated with clopidogrel resistance (assay results in stent thrombosis studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobley et al (2004)</td>
<td>Patients undergoing PCI (50; 20; 58)</td>
<td>75 mg daily maintenance 300 mg loading clinician’s discretion 6/12</td>
<td>Optical aggregometry 1 μmol/L ADP; &lt;10% average platelet inhibition (30%)</td>
<td>No correlation with major adverse clinical events</td>
</tr>
<tr>
<td>Matetzky et al (2004)</td>
<td>Patients undergoing primary PCI for acute STEMI (60; 20; 58)</td>
<td>300 mg load post PCI, then 75 mg daily × 3/12 (6 mo)</td>
<td>Optical aggregometry 5 μmol/L ADP (1st quartile comparison to remainder)</td>
<td>Recurrent cardiovascular events (40% vs 6.7%; P = .007)</td>
</tr>
<tr>
<td>Gurbel et al (2005)</td>
<td>Patients undergoing PCI (192; 44; 61)</td>
<td>300 mg or 600 mg loading, 75 mg daily (6 mo)</td>
<td>Optical aggregometry 5 and 20 μmol/L ADP TEG hemostasis analyzer (upper quartile comparison to remainder)</td>
<td>Ischemic events (upper quartile) ADP aggregation (63 ± 12% vs 56 ± 15%, P = .02) Clot strength (74 ± 5 mm vs 65 ± 4 mm, P &lt; .001) Time to fibrin generation (4.3 ± 1.3 min vs 5.9 ± 1.5 min, P &lt; .001)</td>
</tr>
<tr>
<td>Barragan et al (2003)</td>
<td>Stent thrombosis (&lt;30 d) vs no stent thrombosis (48 [16 cases]; 26; 67)</td>
<td>Clopidogrel 75 mg twice daily or ticlopidine 250 mg twice daily</td>
<td>Flow cytometric assay VASP phosphorylation (% platelet reactivity)</td>
<td>Platelet reactivity in patients with stent thrombosis vs no stent thrombosis (63.28% ± 9.56% vs 39.8 ± 10.9%; P &lt; .0001)</td>
</tr>
<tr>
<td>Aizenberg et al (2005)</td>
<td>Stent thrombosis vs no stent thrombosis (32 [10 cases]; 85; 58)</td>
<td>300 mg load after PCI, then 75 mg daily × 3/12</td>
<td>Coaxial cylinder shearing device Shear-induced platelet aggregation</td>
<td>Shear 200 S⁻¹ (40.9 ± 12.2% vs 18.2 ± 18%, P = .013) Shear 4000 S⁻¹ (57.4 ± 16.4% vs 23.4 ± 21.2%, P = .009)</td>
</tr>
<tr>
<td>Gurbel et al (2005)</td>
<td>Stent thrombosis vs no stent thrombosis (120 [20 cases]; 43; 63)</td>
<td>75 mg daily ± 300 mg loading</td>
<td>Optical aggregometry 5 and 20 μmol/L ADP P2Y₁₂ reactivity ratio by VASP phosphorylation Flow cytometry assay of GPIIb/IIIa expression (upper quartile comparison to remainder)</td>
<td>5 μmol/L ADP aggregation (49 ± 4% vs 33 ± 2%, P &lt; .05) 20 μmol/L ADP aggregation (65 ± 3% vs 51 ± 2%, P &lt; .001) P2Y₁₂ reactivity ratio (69 ± 5% vs 46 ± 9%; P = .03) Mean fluorescence intensity for stimulated GPIIb/IIIa expression (138 ± 19 vs 42 ± 4; P &lt; .001)</td>
</tr>
<tr>
<td>Buonamici et al (2007)</td>
<td>Stent thrombosis vs no stent thrombosis (804 [25 cases]; 25; N/A)</td>
<td>600 mg loading, 75 mg daily (6 mo)</td>
<td>Optical aggregometry 10 μmol/L ADP; aggregation ≥70% (13%)</td>
<td>Definite/probable stent thrombosis In responders vs non-responders 16/699 (2.3%) vs 9/105 (8.6%); P &lt; .001</td>
</tr>
</tbody>
</table>

Adapted from Maree and Fitzgerald, with permission.  
Abbreviations: PCI, percutaneous coronary intervention; ADP, adenosine diphosphate; STEMI, ST segment elevation myocardial infarction; VASP, vasodilator-stimulated phosphoprotein
**Drug Interactions and Clopidogrel**

As with other drugs that are metabolized by members of the cytochrome P450 enzyme family, clopidogrel demonstrates drug interactions. Thus, drugs that inhibit or induce the enzyme alter the response to clopidogrel. One class of drugs that are particularly relevant in this respect is the “statins” or HMG CoA reductase inhibitors. In vitro, the addition of the lipophilic statin atorvastatin at an equimolar concentration to clopidogrel suppresses the latter’s activation by 90%. Similarly, co-administration of atorvastatin suppresses the antiplatelet effect of clopidogrel. Evidence of a clinically significant interaction, however, has not been demonstrated in two studies of lower-risk patient cohorts.

**Clinical Studies of “Clopidogrel Resistance”**

As with aspirin, many studies have examined the response to clopidogrel and outcomes in patients with cardiovascular disease using a variety of approaches (Table 2). While there is reasonable agreement of the target for aspirin response (>95% suppression of serum TXB2), this is more difficult to define for clopidogrel given the variable level of response and an “average” reduction of platelet aggregation to ADP of 40% to 50%. Thus, the target for suppression of platelet aggregation to ADP is not defined and may in any event be revised as new P2Y12 antagonists become available that are capable of a far higher level of receptor blockade and inhibition of ADP-induced platelet aggregation.

**Conclusion**

“Resistance” to aspirin and clopidogrel reflects a variety of mechanisms that can largely be explained by the pharmacokinetics and pharmacodynamics of the drugs. There are no assays of aspirin resistance that are definitively linked to clinical outcome, so that routine testing is not recommended.

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