Antiplatelet therapy in acute coronary syndromes: current agents and impact on patient outcomes

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Abstract: Platelets play a central role in atherothrombosis and subsequent development of acute coronary syndromes (ACS). The understanding of this process has driven a large body of evidence demonstrating the mortality and morbidity benefits of antiplatelet agents in the ACS population. As expected, however, these agents come with an intrinsically increased risk of bleeding which underlies the vast majority of their complications and adverse effects. In today’s setting of compounding comorbidities and broadening indications, finding the balance between thrombosis prevention and bleeding risk remains the challenge for all clinicians considering these medications. This article reviews the current main antiplatelet agents that are available for clinical use and outlines their impact on ACS outcome. We also outline factors which affect the response to these agents and discuss strategies to optimize clinical outcomes.

Keywords: antiplatelet, acute coronary syndromes, outcomes

Introduction
Atherosclerosis is a progressive and systemic disease process potentially resulting in grave cardiovascular, neurological, and peripheral vascular complications. Following the spontaneous rupture of an atherosclerotic plaque during an acute coronary syndrome (ACS) or controlled endothelial disruption during percutaneous coronary intervention (PCI), platelets are simultaneously exposed to numerous agonists promoting the process of thrombus formation. The platelet undergoes a morphological change through the process of thrombus formation. Initially, the platelet adheres to the damaged subendothelial matrix via binding of glycoprotein Ib/IX to von Willebrand factor. Once adhered to the subcellular matrix, the platelet is activated by collagen via further glycoprotein receptors as well as by thrombin. Finally, platelet aggregation is initiated by thromboxane A₂ and adenosine diphosphate (ADP) with subsequent release of further aggregating factors from the platelet-dense granules resulting in a procoagulant surface required for clot formation. Given their capacity to ablate these above pathways (Figure 1), antiplatelet agents have become the cornerstone of therapy in both ACS and PCI. The potential benefit on patient outcomes is proportional to the degree to which their current antithrombotic potential outweighs the associated current bleeding risk. In this review, we focus on the impact that antiplatelet agents, to date, have had on patient outcomes in ACS. We then address how clinicians and health systems can best utilize these agents to optimize patient outcomes.
Antiplatelet agents

Aspirin

Aspirin has been the mainstay of antithrombotic therapy for many years. When used in doses of 75–300 mg, aspirin irreversibly acetylates serine 530 of cyclooxygenase-1 (COX-1), thereby permanently inhibiting platelet transformation of arachidonic acid (AA) into thromboxane A₂, a potent inducer of platelet aggregation.³ This COX-1-dependent pathway appears through COX-1-independent mechanisms.⁴ Furthermore, some inhibition, suggesting that further antiplatelet effects could occur in platelet aggregation in the presence of near-complete (AA) permeability and some weak anti-inflammatory activity and promotion of nitric oxide production in platelets.⁵

Aspirin causes gastrointestinal (GI) side effects in a dose-dependent manner.⁶ It is otherwise well tolerated with only a minority of patients experiencing side effects such as asthma (2%–4%),⁷ rhinitis, urticaria, and angioedema (0.07%–0.2%).⁸ The second International Study of Infarct Survival is the seminal aspirin trial which compared placebo with 160 mg aspirin daily for the treatment of acute myocardial infarction (MI).⁹ For every 1000 patients, 1 month of at least 162 mg aspirin daily prevented 25 deaths and 10–15 nonfatal MI or strokes.¹⁰ As aspirin blocks only one of several pathways implicated in platelet activation and aggregation, it is of no surprise that the majority of cardiovascular events are not prevented by aspirin.¹¹ To further improve patient outcomes, numerous antiplatelet agents blocking COX-1-independent pathways have been developed over the last three decades leading to further significant reductions in thrombotic events across the cardiovascular disease continuum.

ADP receptor antagonists

ADP is a platelet activator released from red blood cells, activated platelets, and damaged endothelial cells, which induces platelet adhesion and aggregation.¹² Adenine nucleotides interact with P2 receptors, which are distributed in many different cell types including endothelial, smooth muscle, and epithelial cells as well as in platelets. These receptors can be subdivided into the P2X ligand-gated ion channel and the two P2Y G protein-coupled receptors (P2Y1 and P2Y12) both of which have to be coactivated for normal ADP-induced platelet aggregation to occur.¹² A well-conducted in vitro study has shown that even in conditions of near complete P2Y12 inhibition by thienopyridines, ADP is still capable of inducing platelet conformational change and residual aggregation via the P2Y1 receptor.¹³ The currently available ADP receptor antagonists i) ticlopidine, ii) clopidogrel, iii) prasugrel, and iv) ticagrelor will be discussed in detail.

Ticlopidine was the first commercially available thienopyridine-derivative ADP receptor antagonist gaining marketing approval in 1991. Its use increased significantly after numerous trials demonstrated the superiority of the combination of ticlopidine and aspirin in maintaining coronary stent patency following PCI.¹⁴,¹⁵ It is a prodrug that is metabolized in the liver into an active metabolite which irreversibly blocks the P2Y12 ADP receptor for the lifetime of the platelet (7–10 days). Clinically relevant antiplatelet activity at the standard dose (250 mg twice daily, oral) occurs at 24–48 h, peaking at 3–5 days. The unacceptably high incidence of GI side effects (30%–50% vomiting, nausea, and diarrhea) precluded the use of a higher loading dose (500 mg daily, oral).¹⁶,¹⁷ Neutropenia as a side effect of ticlopidine was first noted in phase III trials and was subsequently shown to be as high as 2.4%.¹⁸ Furthermore, ticlopidine use was associated with aplastic anemia, thrombotic thrombocytopenic purpura, agranulocytosis, and pancytopenia. These sometimes turned fatal within the first 3 months, with a median recovery time of 15 days upon cessation of agent.¹⁹ Hence, it is no surprise that ticlopidine was superseded by the second-generation thienopyridine derivative clopidogrel. A meta-analysis comparing the two agents showed that clopidogrel led to a reduction in major adverse cardiac events (MACE) including mortality, with better tolerability and a favorable side effect profile.²⁰ At present, use of ticlopidine is limited to cases of clopidogrel intolerance and in settings where the use of the newer antiplatelet agents may not be economically feasible. The use of ticlopidine requires 2-weekly blood counts during the first 3 months of therapy.
although the optimal frequency and utility of subsequent monitoring are not well defined.

Clopidogrel

Like its predecessor, clopidogrel is a prodrug that requires hepatic cytochrome P450-dependent biotransformation into an active metabolite, which irreversibly blocks the P2Y12 ADP receptor. It undergoes intestinal absorption which is unaffected by food or antacids.\(^\text{21,22}\) Clopidogrel absorption is controlled by the \(ABCB1\) gene, which exhibits its genetic polymorphism and codifies for the intestinal P-glycoprotein multidrug resistance transporter (MDR1). The impact of polymorphism at this locus on overall platelet aggregation and patient outcomes remains controversial with two well-conducted studies showing conflicting results.\(^\text{23,24}\) Once it reaches the bloodstream, 85% of the parent drug is metabolized into an inactive form. The remaining 15% is metabolized via a two-step process with the participation of several CYP450 isoenzymes. The CYP2C19 isoenzyme is involved in both steps, and recent studies have shown a strong association between allelic variations at this locus and increased cardiovascular events despite clopidogrel treatment.\(^\text{25-27}\) Not surprisingly, the pharmacodynamic response to clopidogrel shows significant interpatient variability across a normal distribution.\(^\text{28}\)

Without the administration of a loading dose, maximal platelet inhibition occurs after 3–5 days at the standard oral daily dose of 75 mg. Loading doses of 300 and 600 mg result in maximal inhibition of platelet aggregation (IPA) at 6 and 2 h, respectively.\(^\text{29}\) The minimum dose of clopidogrel required to maintain maximal platelet inhibition in most subjects is 60 mg; thus, the standard daily dose of 75 mg exposes patients to incomplete platelet inhibition if compliance is unreliable.\(^\text{30}\)

Clopidogrel has been extensively studied in both the non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI) populations. The CURE study randomized 12,562 patients suffering from NSTEMI to receive aspirin and either clopidogrel (300/75 mg) or placebo for an average of 9 months.\(^\text{31}\) Primary outcome (death, MI, or stroke at 12 months) was significantly less in the clopidogrel arm (9.3% vs 11.4%; relative risk [RR] = 0.8; \(P < 0.001\)), although at the expense of increased major (3.7% vs 2.7%; \(P = 0.001\)) and minor bleeding (5.1% vs 2.4%; \(P < 0.001\)). A subset of 2658 patients who underwent an invasive strategy was studied in PCI-CURE.\(^\text{32}\) Despite significant crossover, composite endpoints of death, MI, or urgent target vessel revascularization within 30 days were 6.1% in the control group versus 3.5% in clopidogrel arm (\(P = 0.016\)) with similar bleeding outcomes. COMMIT/CCS-2\(^\text{23}\) and CLARITY-TIMI 28\(^\text{34}\) both confirmed the superiority of dual antiplatelet therapy (DAT) over aspirin monotherapy in STEMI patients.

Rates of clopidogrel-induced neutropenia in the early trials were extremely low varying between 0%\(^\text{35}\) and 0.12%.\(^\text{31}\) Thrombotic thrombocytopenic purpura,\(^\text{36}\) suppression in all bone marrow lineages,\(^\text{37}\) and various allergic reactions\(^\text{38,39}\) have all been reported (rate < 0.1%) in association with clopidogrel use mostly occurring in the first month of therapy.

Prasugrel

The third-generation thienopyridine, prasugrel, is a prodrug whose active metabolite R-138727 irreversibly binds to the P2Y12 receptor. Its activation occurs in a two-step process with initial rapid hydrolysis to a thiolactone with a further conversion to its thiol-containing pharmacologically active metabolite R-138727 by oxidation via P450 cytochromes.\(^\text{40}\) Absorption of prasugrel is decreased by factors which increase gastric pH. Coadministration with the proton pump inhibitor (PPI) lansoprazole, however, does not alter prasugrel’s efficacy as measured by IPA.\(^\text{41}\) Furthermore, a US Food and Drug Administration (FDA) analysis suggested that antacid use did not affect prasugrel’s clinical efficacy.\(^\text{42}\)

The maximal concentration of the active metabolite is seen after 30 min of oral dosing,\(^\text{43}\) with maximal platelet inhibition occurring at 1 h with a 60-mg loading dose.\(^\text{44}\) Prasugrel was found to be ~10-fold more potent than clopidogrel in inhibiting thrombus formation and increasing bleeding time.\(^\text{45}\) This pharmacodynamic superiority is most likely a consequence of the more extensive and rapid formation of the equipotent active metabolite.\(^\text{46}\)

The TRITON-TIMI 38 compared a 60-mg loading dose of prasugrel followed by 10 mg daily dosing with standard clopidogrel dosing in high-risk ACS patients undergoing PCI. Importantly, randomization only occurred once coronary anatomy was known; hence, the study did not test the two agents as upstream therapy given in the emergency department to ACS patients prior to proceeding to cardiac catheterization.\(^\text{47}\) Prasugrel use resulted in a 19% relative risk reduction (9.9% for prasugrel vs 12.1% for clopidogrel; hazard ratio [HR] = 0.81; \(P < 0.001\)) for the composite primary efficacy endpoint of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. This benefit occurred at the expense of an increase in the rate of noncoronary artery bypass graft (CABG)-related major bleeding (HR = 1.32; 95% confidence interval [CI]: 1.03–1.68; number needed to harm [NNH] = 167; \(P = 0.03\)) and a significantly higher rate of
CABG-related bleeding in the prasugrel group (13.4% vs 3.2%; NNH = 10). Of note, the majority of the benefit was accrued in the first 3 days, and when adjudicated episodes of MI were removed from the analysis, no further separation of the Kaplan–Meier curves occurred after 30 days.48,49 Prasugrel use did not decrease all-cause mortality. A post hoc subgroup analysis by the TRITON authors identified the elderly (age >75 years), patients weighing <60 kg, and those with past history of stroke or transient ischemic attack as having unfavorable bleeding risk–benefit profiles. Currently, the FDA has approved prasugrel use for ACS patients undergoing PCI when coronary anatomy is known and likelihood of undergoing CABG is low. The clinical efficacy of prasugrel in other patient groups such as medically managed patients with unstable angina/NSTEMI is currently being evaluated in the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes trial (NCT00699998; TRILOGY ACS).

Ticagrelor
Ticagrelor is an orally administered nonthienopyridine, which directly and reversibly inhibits the P2Y12 receptor.50 Animal studies have shown that irreversible P2Y12 inhibition with ticagrelor can attenuate ADP-mediated vascular vasoconstriction51 and inhibit adenosine uptake by red cells, thereby increasing circulating ADP levels which augment the hyperemic response following arterial occlusion.52 A loading dose of 180 mg provides similar rates of platelet inhibition within 30 min that a 600-mg loading dose of clopidogrel provides at 8 h.53 Maximal IPA occurs within 2 h of dosing, with a dose of 100 mg twice daily maintaining near complete IPA and limited added inhibition from increasing doses. The half-life is ~7 h, and there is minimal residual antiplatelet effect 48 h after last dose.54 Dose-related dyspnea is a common adverse event occurring in 10%–20% of patients.54,55 Among patients experiencing dyspnea, no changes were noted in any cardiopulmonary function parameters at baseline and up to 6 weeks,56 and resulted in discontinuation in about 0.8% of patients.57 The PLATO trial showed that among 13,000 ACS patients managed with an early invasive approach, ticagrelor use resulted in a significant decrease (12.3% vs 10.2%; HR = 0.84; P = 0.0001) in the composite endpoint (death from vascular causes, MI, or stroke) at 12 months. What distinguishes ticagrelor from other antiplatelet and antithrombotic agents is that the overall mortality benefit (4.5% vs 5.9%; P < 0.001) was mainly achieved by decreasing rates of MI (2.8% vs 2.2%; P = 0.03) without increasing major non-CABG-related bleeding events using the TRITON Trial definition.58 Ticagrelor acts directly in a dose-dependent manner with a rapid onset and offset of its antiplatelet effect. These characteristics make it ideally suited to the acute setting of ACS when coronary anatomy is not known and in cohorts where semielective/urgent surgery necessitates discontinuation of antiplatelet therapy. In July 2010, the FDA Cardiovascular and Renal Advisory Committee voted 7:1 in favor of approving this medication for the indication of a troponin-positive ACS. The time for review, however, has recently been extended as the FDA was uncertain how to evaluate the lack of effect of this drug in the PLATO study in patients enrolled in sites from the USA.59

Glycoprotein IIb/IIIa inhibitors
Glycoprotein IIb/IIIa inhibitors (GPIs) are intravenous agents that inhibit fibrinogen-mediated platelet aggregation and block the expression of the prothrombotic CD40 ligand.60 Abciximab, tirofiban, and eptifibatide are the three GPIs currently available for clinical use. At optimal doses, these agents result in prompt, uniform, and very potent IPA when compared to oral antiplatelet agents.61 The major risk with their use is increased bleeding episodes, especially in certain at-risk subgroups (diabetics, chronic kidney disease, and elderly) and when inappropriate dosing occurs.61 Thrombocytopenia is associated with abciximab and tirofiban use and occurs at a frequency of 2.4% and 0.5%, respectively. It occurs within the first 24 h and is associated with adverse outcomes.62 GPI use is recommended by the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines in selected patients with NSTEMI/UA,63 STEMI,64 and those undergoing PCI.65 The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction trial compared bivalirudin (a direct thrombin inhibitor) alone with heparin plus a GPI in patients with STEMI undergoing primary PCI. Bivalirudin alone led to a significant decrease in overall mortality at 30 days (2.1% vs 3.1%; P = 0.047). This study has led many to question the clinical utility of GPIs in STEMI patients.

The Early Glycoprotein IIb/IIIa inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome trial compared routine eptifibatide use with delayed provisional use in NSTEMI in whom an invasive strategy is pursued (N = 9492). Routine use did not affect the primary composite endpoint (death, MI, recurrent ischemia necessitating urgent revascularization, or thrombotic bailout at 96 h) and resulted in a higher incidence in bleeding events and transfusions.66 The routine use of GPIs in ACS cannot be justified. Selective downstream use in high-risk ACS patients and following complicated PCI is likely to continue.
A summary of the important clinically used antiplatelet agents is shown in Table 1.

**Impact on patient outcomes**
An individual patient is best served by antiplatelet agents if the thrombotic risk significantly outweighs the resultant risk of bleeding. For any particular disease process, this critical balance depends on a myriad of factors including age, patient comorbidities, stage of disease process, pharmacogenetics, and choice of treatment modality. It is through i) maximizing adherence to therapy, ii) evaluating bleeding risk, iii) applying methods to reduce bleeding risk, iv) ensuring pharmacodynamic efficacy, and v) minimizing drug interactions that clinicians can optimize treatment outcomes with antiplatelet agents in ACS.

**Adherence**
Adherence can be viewed as a shared process where the care provider and patient work together to ensure that evidence-based treatment is administered during the patient’s hospitalization and subsequently taken regularly for the recommended duration of treatment upon discharge. Adherence to ACC/AHA guidelines during index hospitalization in ACS has been shown in numerous studies to correlate with decreased morbidity and mortality. An observational study of more than 65,000 patients demonstrated that for every 10% increase in composite adherence to nine ACC/AHA Class I recommended therapies, a 10% reduction in in-hospital mortality ensued (adjusted OR = 0.90; 95% CI: 0.84–0.97). Societal and governmental quality improvement programs, registries, and the use of standardized patient pathway medication forms have all been shown to improve care providers adherence to guidelines.

The transition period from hospital discharge to the outpatient setting is the period where the majority of patient-initiated drug discontinuation occurs. A study by Ho et al found that one in six patients delayed filling in their index clopidogrel script following drug-eluting stent (DES) implantation and subsequently went on to have long gaps between future clopidogrel refills. This group of patients was at increased risk (HR = 1.53; 95% CI: 1.25–1.87) of mortality and future cardiovascular events. Patient factors known to predict poor adherence to pharmacotherapy following ACS include insurance status, level of education, number of medications, and older age. The utility and cost-effectiveness requires targeting at-risk patients and patients who delay filling their scripts with intensive education, reminder tools, and more regular follow-up appointments, although intuitive will need to be investigated in randomized trials. A newly identified factor specifically predictive of inappropriate cessation of antiplatelet therapy is that of minor (nuisance) bleeding. Up to 28% of patients on DAT experience nuisance bleeding, resulting in high cessation rates of one (5%) or both (1%) antiplatelet agents. Of note, patients who experience a bleed and receive follow-up care from a cardiologist are more likely to maintain antiplatelet therapy than those who receive follow-up from other health professionals.

**Table 1** Summary of current antiplatelet agents approved for clinical use in the acute coronary syndromes population

<table>
<thead>
<tr>
<th>Aspirin</th>
<th>Ticlopidine</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
<th>Abciximab, tirofiban, eptifibatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Acetylsalicylic acid</td>
<td>Thienopyridine</td>
<td>Thienopyridine</td>
<td>Thienopyridine</td>
<td>Cyclopentyl-triazolo-pyridine</td>
</tr>
<tr>
<td>Route</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Block COX to prevent formation of thromboxane A2 and prostaglandins</td>
<td>Irreversible</td>
<td>Prodrug, modify P2Y12 receptor, inhibiting activation of GP IIb/IIa complex</td>
<td>Irreversible</td>
<td>Reversible</td>
</tr>
<tr>
<td>Inhibition</td>
<td>Irreversible</td>
<td>Thienopyridine</td>
<td>Thienopyridine</td>
<td>2009</td>
<td>GP IIb/IIa inhibitors 1993–&gt;</td>
</tr>
<tr>
<td>Frequency</td>
<td>Daily</td>
<td>Twice daily</td>
<td>Daily</td>
<td>Daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Time to peak effect</td>
<td>20 min</td>
<td>1–3 h</td>
<td>4–6 h</td>
<td>1 h</td>
<td>2 h</td>
</tr>
<tr>
<td>Time to peak effect</td>
<td>(150–300-mg load)</td>
<td>(250-mg dose)</td>
<td>(300-mg load)</td>
<td>(60-mg load)</td>
<td>(180-mg load)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Renal</td>
<td>Direct/none</td>
</tr>
<tr>
<td>Clearance</td>
<td>Renal</td>
<td>Renal</td>
<td>Renal</td>
<td>Renal</td>
<td>Biliary</td>
</tr>
</tbody>
</table>
| Notes: Taken from multiple sources.
Of concern is that 32% of cases of inappropriate discontinuation of antiplatelet agents were the result of a health professional’s recommendation. An observational study in a noncardiac preoperative clinic setting showed that following coronary stent implantation, the majority of patients had very poor understanding of the rationale, duration, and risk of discontinuation of antiplatelet therapy. Surgical instructions regarding antiplatelet therapy were provided in 57% of patients. Alarmingly, however, cardiology input was only documented in 17% of cases. For improved outcomes in the perioperative setting, providers of cardiovascular care must ensure adequate patient education and collaboration with other health professionals in the decision-making process of antiplatelet therapy management.

**Bleeding risk**

Antiplatelet agents prevent death, MI, and other ischemic events through their antithrombotic properties. This benefit is attenuated by an increase in bleeding risk. In PCI, it is known that with increasing levels of antithrombotic therapy, the antithrombotic beneficial effect eventually plateaus. The risk of bleeding in patients with cardiovascular disease is the result of complex interactions between baseline characteristics, comorbidities, type and stage of disease process, drug combinations, and dosing. The delicate risk/benefit balance of antiplatelet therapy is summarized in Figure 2.

In ACS, bleeding in the acute phase is a strong, stepwise independent predictor of death. This risk is more marked in the acute period (first 30 days), and in some studies, it surpasses the risk of MI. However, unlike MI, the long-term risk remains significant and persists for up to a year.

Two recent scoring systems have been validated to predict early bleeding in ACS. The Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) score used the following eight admission variables: female sex, diabetes, vascular disease, heart rate, abnormal systolic blood pressure, congestive heart failure, baseline hematocrit, and creatinine clearance to predict inpatient bleeding in ACS patients. The risk score proposed by Mehran et al relied on age, sex, creatinine clearance, hematocrit, white cell count, type of ACS presentation, and

**Figure 2** The delicate balance of an individual’s comorbidities: risk of thrombosis versus risk of bleeding.

**Abbreviations:** BMI, body mass index; CVA, cerebrovascular accident; PVD, peripheral vascular disease.
antithrombotic regimen used to predict bleeding within 30 days of presentation. A novel finding from this study was that CABG-related bleeding did not increase mortality, a finding that is likely to generate controversy about the pros and cons of initiating antiplatelet therapy prior to knowing the coronary anatomy. A bleeding obesity paradox has recently been observed where patients with mild (Class I) obesity had the lowest rates of bleeding following PCI after risk adjustment compared to underweight or severely overweight patients.

Interventions to minimize bleeding risk

Antiplatelet agents increase the risk of gastrointestinal bleeding (GIB): aspirin predominantly by promoting ulcer formation and preventing ulcer healing, whereas the thienopyridines are believed to promote bleeding at sites of existing lesions caused by nonsteroidal anti-inflammatory drugs (NSAIDs) or infection with *Helicobacter pylori*. Ancillary use of other medications such as corticosteroids and anticoagulants further compounds this risk. Of importance, GIB following ACS is independently associated with mortality. Consensus now exists that upper GI bleeding may be reduced in the setting of antiplatelet use by suppressing gastric acid production and thus promoting the healing of ulcers and erosions as well as potentially stabilizing thrombi. Histamine H₂ receptor antagonists, although suppressing acid production by up to 68%, have shown only a modest benefit in patients taking aspirin and no benefit in those on clopidogrel. The data for PPIs are far more convincing with one trial showing a 50% relative risk reduction in patients’ baseline risk of GIB (absolute risk 1.2%) and an absolute risk reduction of 2.8% per year in patients with ≥3 risk factors for GIB. These findings and other smaller studies are supported by the most recent trial and largest randomized controlled trial (RCT) which looked at clopidogrel plus omeprazole versus clopidogrel alone. In the composite outcome of overt or occult bleeding, symptomatic gastro-duodenal ulcer, or erosion, a hazard ratio of 0.34 (95% CI: 0.18–0.63) was observed in the PPI combination arm. An expert consensus document advocates the use of PPI in all patients on DAT and patients with high-risk features. Patients with a history of peptic ulcer disease should have testing for *H. pylori* and treatment when indicated. A flow diagram summarizing key clinical issues in this area is shown in Figure 3.

A wealth of evidence is accumulating supporting the superior safety of the radial approach for PCI in all groups of ACS patients, particularly regarding bleeding risk. It increases the safety of aggressive platelet inhibition in the acute periprocedural phase and minimizes bleeding and vascular access complications, without significantly increasing procedural time. Nonrandomized evidence now exists for a mortality benefit using radial compared to femoral approach for both stable and ACS patients. We await results of the randomized radial versus femoral access for coronary intervention study due for completion at the end of 2010 for definitive evidence regarding this issue (Clinical Trial: NCT01014273).

An increasing number of patients require long-term anticoagulation with warfarin predominantly for prevention of thromboembolic events in atrial fibrillation. Coexisting indications for concurrent antithrombolytic therapy such as ACS and previous PCI are common in this patient population. A recent large, Danish cohort study showed that combining clopidogrel and warfarin carries a bleeding HR of 3.08 (2.32–3.91) compared with warfarin monotherapy. Additional use of aspirin increases the bleeding HR to 3.70 (2.89–4.76). The bleeding risk, however, is grossly time independent. This concept was supported by an observational Finnish study which highlighted the importance of maintaining DAT in patients on long-term anticoagulation therapy in the first 4 weeks following PCI. Strategies to minimize the bleeding risk in this patient population include maintaining the international normalized ratio levels at the lowest possible therapeutic level and minimizing the duration of triple therapy with...

![Figure 3 Algorithm proposing an approach to cost effective utilization of PPI cotherapy for the prevention of gastrointestinal bleeding.](https://www.dovepress.com/)

**Abbreviations:** GERD, gastroesophageal reflux disease; GI, gastrointestinal; PPI, proton pump inhibitor.
the preferential use of bare metal stents (BMS).\textsuperscript{110} The use of a PPI (which will be expanded on later in this article) appears appropriate for moderate to high bleeding risk subjects that require both concomitant anticoagulation and antiplatelet therapy.

The risk of stent thrombosis in patients who undergo PCI and stent implantation decreases exponentially over time. Rates of endothelialization differ between BMS and DESs, influencing the decision about the duration of DAT. This has recently been a major concern with an increase of stent thrombosis rates seen in DES compared to BMS with an associated suggestion of increased adverse outcomes.\textsuperscript{111} This has resulted in many interventional cardiologists electing to prolong DAT in subjects following DES compared to BMS insertion. Definitive studies in this area to guide the clinician are limited; however, recent data suggest that if a patient has been clinically stable on DAT for 12 months following a DES insertion, continuation of DAT for a further 12 months compared to aspirin therapy alone is not associated with any reduction in adverse cardiovascular events.\textsuperscript{112}

Pharmacogenetics and pharmacodynamics
Consistent and effective levels of platelet inhibition are essential for obtaining optimal patient outcomes with antiplatelet therapy in ACS patients. The complex and dynamic nature of platelet function\textsuperscript{113} and the variety of targets for platelet inhibition are some of the reasons why no single platelet function test (PFT) is currently in routine clinical use.\textsuperscript{114} In a recent trial looking at six different PFTs in PCI, only three out of six tests had a modest predictive value for adverse cardiovascular events, and no test predicted bleeding complications.\textsuperscript{115} The intrinsically constant nature of interindividual allelic variation have led some to propose genetic testing as the new standard of care for individualized antiplatelet therapy.\textsuperscript{116}

Aspirin resistance has been used to describe incomplete platelet response, with prevalence estimates between 5% and 65%.\textsuperscript{10} Lack of a ‘gold standard definition’, assay variability, and the contribution of composite processes may explain this wide range.\textsuperscript{117} Two meta-analyses using studies with heterogeneous methods have suggested a nearly four-fold increase in recurrent cardiovascular events in patients poorly responsive to aspirin.\textsuperscript{118,119} The clinical utility of point of care assays for aspirin response in ACS should be tested in large randomized trials.

A large body of data supports the association of genetic polymorphisms in the hepatic cytochrome 2C19 (CYP2C19) with variable levels of the active metabolite of clopidogrel. This was subsequently shown to result in high levels of residual platelet reactivity and adverse clinical outcomes,\textsuperscript{52,66,67,71} prompting the FDA to issue a boxed warning about the diminished effectiveness in patients with loss-of-function alleles.\textsuperscript{120} Other factors, both genetic and nongenetic, most likely contribute to this clinically important phenomenon. Response to the newer P2Y12 receptor antagonists (prasugrel, ticagrelor) does not appear to be influenced by CYP2C19 allelic variation.\textsuperscript{53,121,122} The future of individualized antiplatelet therapy may involve a combination of genotypic and phenotypic testing, which will assist in guiding treatment algorithms. While the mechanisms relating to clopidogrel resistance (nonresponders) are multifactorial, the definitive treatment to counteract the associated adverse outcomes remains uncertain.\textsuperscript{123}

Drug interactions
NSAIDs are used daily by more than 30 million people worldwide.\textsuperscript{124} Their use is particularly prevalent amongst the elderly; a group also at increased risk of cardiovascular disease. Ibuprofen, the most widely used NSAID, is believed to interfere with aspirin by binding to COX-1 and attenuating its antiplatelet activity.\textsuperscript{125} This effect has also been observed with other NSAIDs,\textsuperscript{126–128} but specifically not with COX-2 selective inhibitors.\textsuperscript{129} The FDA recommends that aspirin should be taken at least 30 min before or 8 h after nonselective NSAID ingestion to preserve its efficacy.\textsuperscript{130} It is incumbent amongst all providers of care for ACS patients to realize that the use of all nonaspirin NSAIDs is associated with adverse cardiovascular outcomes.\textsuperscript{131} At-risk patients, particularly in the post-ACS and PCI setting, should be provided with education about the risks of NSAIDs (especially over the counter use), and alternative modes of analgesia should be provided wherever possible.\textsuperscript{132}

Given their broad indications and frequent coprescription, the purported interaction between PPIs and clopidogrel has generated unprecedented attention in both the lay and research community. Concomitant use of PPIs may competitively inhibit activation of clopidogrel by CYP2C19, thereby reducing its antiplatelet activity in the same way allelic variations have been reported.\textsuperscript{133} The evidence supporting this theory, however, has been conflicting and can be categorized into studies looking at pharmacodynamic and platelet function studies and those looking at clinical effect. In one study of patients who were given a high maintenance dose of clopidogrel, both omeprazole and pantoprazole were associated with reduced platelet inhibition as assessed by vasodilator-stimulated phosphoroprotein
(44% vs 23%; P = 0.04). Two other randomized trials utilizing ex vivo assays demonstrated the same attenuation with omeprazole;77,78 however, other PPIs did not seem to have the same impact in two further studies.79,80 In terms of clinical effect of interaction, large observational studies of differing size, populations, and methodologies have looked at whether patients prescribed a PPI have had increased CV events, with some reporting small but significant associations yet others reporting no difference. Whether the differences in results reflect a number of confounding factors or true clinical interaction is impossible to determine retrospectively. One of the largest observational studies randomized 13,608 patients to clopidogrel or prasugrel and found no difference between CV events in those patients on PPI compared to those who were not (regardless of which PPI was used) in either treatment arm (clopidogrel HR = 0.94; 95% CI: 0.80–1.11 and prasugrel HR = 1.00, 95% CI: 0.84–1.20).79 The only RCT published to date, as alluded to above, involved 3761 patients who were randomized to clopidogrel and omeprazole combination or clopidogrel alone.100 All patients were also on aspirin, and no difference in composite CV event rate was observed between the arms (MI, stroke, CABG, and PCI CV death). The conclusions of the study, which appear to refute any potential interaction, have been somewhat controversial given the trial was stopped before full enrollment and the low event rate resulting in broad confidence intervals.

In summary, despite being theoretically plausible and biologically measurable with platelet function testing, the clinical effect of a PPI–clopidogrel interaction is inconsistently demonstrated, of small magnitude when observed, and the only randomized trial refutes its existence. In spite of this and a recent consensus document from the ACC/AHA/AGA which reports an inability to exclude an interaction on current evidence, the FDA remains reticent to remove its black box warning on clopidogrel and has reissued its warning.134 The risk of GIB remains an important clinical problem for patients requiring DAT. The consensus statement suggests that the risk reduction with PPIs is substantial in patients with risk factors for GIB (prior bleed, advancing age, concomitant anticoagulation/steroid/NSAID, or H. pylori infection) and thus will outweigh any potential reduction in the CV efficacy of antiplatelet treatment because of a drug–drug interaction. In patients without GIB risk factors, there appears to be little incremental absolute benefit in adding PPI.

**Discussion**

The growing body of evidence highlighting the central role of platelets to the development of ACS ensures that antiplatelet therapy will continue to be the cornerstone of management for the foreseeable future. The relentless search for increasingly aggressive antithrombotic activity has resulted in increased efficacy, but it has come at the expense of increased rates of bleeding. While the quest continues, the current absence of a one-size-fits-all antiplatelet ‘panacea’ mandates an individualized approach to therapy. Evidence-based algorithms will incorporate evolving trial data assessing duration, timing, and dose of the current agents as well as the impact of new agents on thrombosis and bleeding balance. The not-so-distant future of antiplatelet therapy is destined to account for clinical phenotypes and utilize pharmacogenomics in combination with platelet function testing to individualize therapy. Regular medication reviews and education to both patients and other health care professionals will be critical in ensuring the optimal implementation and utilization of such algorithms.

**Disclosure**

None of the authors have conflicts of interest to declare in relation to this paper.

**References**


